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Sodium Bicarbonate Prescription and Extracellular Volume Increase: Real-world Data Results from the AlcalUN Study

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Oral alkalization with sodium bicarbonate ($NaHCO_3$) or citrate is prescribed for conditions ranging from metabolic acidosis to nephrolithiasis. Although most nephrologists/urologists use this method routinely, extracellular volume (ECV) increase is the main feared adverse event reported for $NaHCO_3$. Thus far, no trial has specifically studied this issue in a real-world setting. AlcalUN (NCT03035812) is a multicentric, prospective, open-label cohort study with nationwide (France) enrollment in 18 (public and private) nephrology/urology units. Participants were adult outpatients requiring chronic (>1 month) oral alkalization by either $NaHCO_3$-containing or no-$NaHCO_3$-containing agents. The ECV increase (primary outcome) was judged based on body weight increase (ΔBW), blood pressure increase (ΔBP), and/or new-onset edema at the first follow-up visit (V1). From February 2017 to February 2020, 156 patients were enrolled. After a median 106 days of treatment, 91 (72%) patients reached the primary outcome. They had lower systolic (135 (125, 141) vs. 141 (130, 150), $P = 0.02$) and diastolic (77 (67, 85) vs. 85 (73, 90), $P = 0.03$) BP values, a higher plasma chloride (106.0 (105.0, 109.0) vs. 105.0 (102.0, 107.0), $P = 0.02$) at baseline, and a less frequent history of nephrolithiasis (32 vs. 56%, $P = 0.02$). Patients experienced mainly slight ΔBP (< 10 mmHg). The primary outcome was not associated ($P = 0.79$) with the study treatment (129 received $NaHCO_3$ and 27 received citrate). We subsequently developed three different models of propensity score matching; each confirmed our results. Chronic oral alkalization with $NaHCO_3$ is no longer associated with an ECV increase compared to citrate in real-life settings.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Oral alkalization with sodium bicarbonate ($NaHCO_3$) is beneficial for patients with chronic kidney diseases or nephrolithiasis. Clinical studies have reported an extracellular volume (ECV) increase from secondary outcomes in selected populations. However, no trial has specifically studied this issue in a real-world setting.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is $NaHCO_3$ chronic oral treatment associated with ECV increase in a real-world setting?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Using meaningful clinical endpoints (body weight, blood pressure, and edema), the fact that the alkalizing agent contained or did not contain $NaHCO_3$ was not associated with any ECV increase in a real-world setting. Furthermore, patients taking $NaHCO_3$ did not have higher levels of ECV increase than those taking citrate, even after powerful statistical adjustments.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ $NaHCO_3$ is inexpensive, well-tolerated, and widely available. Thus, it could be used more broadly, even in a population at high risk of ECV increase (such as patients with chronic kidney disease).

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INTRODUCTION

Acid-base homeostasis is tightly controlled by the kidneys.[1] Several conditions, ranging from nephrolithiasis to metabolic acidosis, require interventions that include an alkalizing agent. Approximately 15% of patients with chronic kidney disease (CKD) exert a low blood bicarbonate concentration, which worsens with the decrease of glomerular filtration rate (GFR) and concerns up to one-third of patients[2] with an estimated GFR (eGFR) below 30 mL/min/1.73 m^2. Moreover, metabolic acidosis can also coexist with a blood bicarbonate concentration within the normal range in patients with[3] or without CKD.[4] Overt metabolic acidosis (as well as acid retention) has been shown to be a key independent factor for worsening CKD progression[5] and overall survival.[6] Experimental and clinical studies have also reported close relationships with hyperkalemia, muscle waste, osteopenia, clinical outcomes (such as asthenia), and quality of life.[7]

Thus, modifying the natural history of CKD by correcting metabolic acidosis is an important, widely used therapeutic strategy. Oral alkalization can be achieved with medications containing either potassium/sodium citrate or sodium bicarbonate ($NaHCO_3$). Both are available by prescription or over-the-counter.[8] $NaHCO_3$ is also commercially available as alkaline-enriched water.[9] $NaHCO_3$ supplementation has been linked to a slowdown of GFR decline, as well as to better renal survival.[10,11] Potassium citrate administration prevents new episodes of nephrolithiasis.[12] However, the effects of alkalizing agents on other outcomes (related to bone and muscle, for instance) are still a matter of debate, as recent randomized placebo-controlled trials have failed to show any improvement.[13,14]

Despite its beneficial effects, oral alkalization by $NaHCO_3$ has been linked to adverse events, such as gastrointestinal disorders[13] and poor blood pressure (BP) control due to extracellular volume (ECV) overload.[10] This is of particular importance in patients with CKD who are at a higher risk of ECV increase and for whom ECV control is thus a therapeutic target. Few open-label studies have reported detrimental effects on ECV and have been included in meta-analyses.[10,11] However, these results were based on secondary outcomes, and a recent double-blinded randomized controlled trial reported no effect on ECV.[15] To date, no prospective clinical trial has assessed ECV as a primary outcome during chronic oral alkalization.

METHODS

Study design and population

The AlcalUN study was a multicenter (18 centers), nationwide (France), prospective cohort study. Patients were included from February 2017 to February 2020. We performed a study from a clinical point-of-view; in such, we decided to focus our inclusion criteria, not on medical background, but on the decision-making process. The inclusion criteria were (i) age 18 years old or older at the date of inclusion, (ii) coverage by health insurance, and (iii) requirement of chronic (> 1 month) oral alkalization prescribed by a nephrologist or a urologist. The exclusion criteria were (i) refusal to participate in the study and/or (ii) loss to follow-up. The medication was chosen by the physician in charge of the patient. The intervention consisted of routine clinical oral alkalization by $NaHCO_3$, sodium or potassium citrate, and/or any other oral alkalizing agent.

Outcomes

The main objective was to assess whether an increase in ECV in patients requiring chronic alkalization would be associated with oral alkalization with $NaHCO_3$ in a real-life setting. Hence, we *a priori* stated the primary outcome to reflect the increased ECV at the first follow-up visit (V1) as judged by a composite criterion including body weight (BW) increase, systolic BP (SBP) increase, diastolic BP (DBP) increase, and/or clinically relevant new-onset edema. We chose to use the absolute variation (Δ) for each component without prespecifying any threshold. The baseline characteristics were collected the day of the prescription of the treatment (V0). For each patient, an increase in any one of these four components was sufficient to reach the primary outcome. The secondary outcomes were changes in the following biological outcomes at V1: plasma sodium, potassium, chloride, bicarbonate, protein concentrations, eGFR, urine output, sodium, chloride, and protein excretions. The biological parameters were analyzed onsite. The eGFR was estimated with the Modification of Diet in Renal Disease (MDRD) formula.[16] The following covariates were systematically collected at V0: sex, age, medical history of chronic heart failure, CKD, renal dialysis, kidney transplantation, hypertension, nephrolithiasis, chronic gastrointestinal disorder, or any other medical condition and treatment with a renin-angiotensin-aldosterone blocker, a diuretic, any other antihypertensive medicine, steroids, or a low-salt diet (i.e., reported daily intake < 6 g of sodium chloride).

Statistics

Due to the lack of published data about our real-life composite primary outcome, we were not able to anticipate a minimum number of subjects to enroll. We decided *a priori* to include more than 100 subjects over a maximum of 3 years of enrollment. At the end of the study, we conducted a case-control study and compared patients who reached the primary outcome to those who did not. A multiple logistic regression (stepwise analysis) was conducted to identify the baseline factors that could explain why the cases reached the primary outcome. We selected all nonredundant variables that reached sufficient importance ($P < 0.20$) in the univariate analysis (namely body mass index (BMI), SBP, DBP, history of nephrolithiasis, low-salt diet, plasma sodium and chloride concentrations at V0, history of kidney transplantation, and plasma potassium at V0), along with age, sex, history of hypertension, eGFR, treatment with diuretics, time between visits, and adherence

to treatment. Effects were entered step-by-step into the model when P values were < 0.20 and were removed when P values were > 0.05. Discrimination ability was evaluated by calculating the area under the receiver operating characteristic curve (AUROC); sensitivity, specificity, positive, and negative predictive values were calculated only for parameters with AUROC > 0.800. As all the characteristics did not follow a normal distribution (Kolmogorov-Smirnov test), we used nonparametric tests and summarized the data using medians and interquartile ranges or frequencies, as appropriate. Values were compared by two-tailed Mann–Whitney or Fisher's exact tests when appropriate using RStudio (Integrated Development Environment for R. RStudio, PBC, Boston, MA; URL http://www.rstudio.com/). Venn diagrams were designed using a publicly available website, http://bioinformatics.psb.ugent.be. We considered a P value < 0.05 to be significant in all cases. For paired analyses, we used two-tailed Wilcoxon matched-pairs signed-rank tests.

Propensity score matching

To further explore the possibility of hidden bias, we undertook additional analyses of three matched cohorts of $NaHCO_3$-treated patients generated using propensity score matching[17,18] compared with No-$NaHCO_3$-treated patients. Propensity scores were estimated using logistic regression with the group as the dependent variable on the following covariates: model 1 included all variables with a P value ≤ 0.10 in univariate analysis (namely hypertension, CKD, nephrolithiasis, other antihypertensive medicine, and steroids as a surrogate for kidney transplantation) comparing patients based on their exposure (NaHCO3 or No-$NaHCO_3$ containing alkalizing agent); model 2 included all variables (namely age, BMI, hypertension, chronic heart failure, eGFR, diuretics, steroids as a surrogate for kidney transplantation, and low-salt diet) that we considered clinically relevant to influence the outcome; and model 3 included fewer variables (age, BMI, hypertension, and eGFR). Matching was performed using the MatchIt package.[17] Patients were matched on a 1:1 basis on the logit of the propensity score with nearest neighbor matching without replacement and with an optimal caliper of 0.04.[18]

Informed consent and ethics approval

The study was conducted in accordance with the international rules established by the Helsinki Declaration of 1975 (as revised in 1983) and received approval by the ethics committee of the HIA Sainte Anne, Toulon, France (438/HIA.S.A./SMC). Data were collected in accordance with the French regulatory board (ref. 2004299v0). According to the French regulation and the ethics committee, written consent was not required, but each participant gave their informed consent before enrollment, after being given and having read and understood a full disclosure letter.

Clinical trial registration

This trial is registered under NCT03035812.

RESULTS

Participants

We enrolled 156 participants, 127 of whom had at least one follow-up visit (V1). Their characteristics are presented in **Table 1**; we included mostly men (57%), with a median age of 64 years (53, 73). More than two-thirds of the cohort had hypertension; the median SBP and DBP were 136 (125, 145) and 80 (70, 88) mmHg, respectively, and were controlled by the use of antihypertensive medications in 26 to 54% of the cohort. Edema was observed in 17 patients, but the ECV was judged as increased in only 12. In addition to hypertension, CKD was the second most important

Table 1 Characteristics of participants at baseline

	Participants (n = 127)
Clinical data	
Age, y	64.0 [53.0, 73.0]
Gender women, n (%)	54 (43)
BMI, kg/m^2	28.7 [23.5, 33.1]
SBP, mmHg	136 [125, 145]
DBP, mmHg	80 [70, 88]
Edema, n (%)	17 (14)
Extracellular volume, n (%)	
Decreased	3 (2)
Normal	112 (88)
Increased	12 (10)
Medical history	
Hypertension, n (%)	87 (69)
Chronic heart failure, n (%)	8 (6)
Chronic kidney disease, n (%)	79 (62)
Kidney transplantation, n (%)	29 (23)
Nephrolithiasis, n (%)	49 (39)
Chronic bowel disorder, n (%)	11 (9)
Biology at inclusion	
Plasma sodium, mEq/L	140.0 [138.0, 141.0]
Plasma potassium, mEq/L	4.50 [4.10, 4.85]
Plasma chloride, mEq/L	106.0 [104.0, 108.0]
Plasma bicarbonate, mEq/L	19.4 [17.6, 24.8]
eGFR, mL/min/1.73m^2	42.3 [25.7, 70.6]
Plasma proteins, g/L	70.0 [65.9, 74.0]
Daily urine output, L/day	1.85 [1.50, 2.20]
Daily sodium excretion, mmol/day	135 [99, 206]
Urine pH, UpH	5.30 [5.00, 6.00]
Urine protein-to-creatinine ratio, mg/g	225 [85, 805]
Ongoing medications	
RAAS inhibitor(s), n (%)	58 (46)
Diuretics, n (%)	33 (26)
Other antihypertensive medicine, n (%)	69 (54)
Steroids, n (%)	23 (18)
Low-salt diet, n (%)	43 (34)
Study treatment	
Alkaline-enriched water, n (%)	41 (32)
$NaHCO_3$ pills, n (%)	68 (54)
Potassium citrate, n (%)	36 (28)
Duration of treatment prescribed, days	90 [90, 120]

In the AlcalUN study, patients received either sodium bicarbonate ($NaHCO_3$)-based treatment or an alkalizing treatment that did not contain any $NaHCO_3$. The categorial data are presented as n and percentages (%) while the quantitative data are presented as median [IQR]. The reported values for blood pressure are the ones measured at each physician's office. Edema was assessed clinically by the investigators, as well as reported extracellular volume assessment. The glomerular filtration rate was estimated (eGFR) by the MDRD formula. Low salt diet was reported by the investigators.
BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

(62%) medical condition. Fifteen participants had both CKD and nephrolithiasis (**Figure S1**). The median blood bicarbonate concentration was 19.4 (17.6, 24.8) mmol/L, with a median eGFR of 42.3 (25.7, 70.6) mL/min/1.73 m^2. The study treatment (alkalizing agent) was prescribed for a median duration of 90 (90, 120) days; 107 participants were prescribed $NaHCO_3$, whereas 20 received a treatment that did not contain any $NaHCO_3$. Patients received either $NaHCO_3$ pills (n = 68) and/or alkaline-enriched water (n = 41). Among the 36 patients who received potassium citrate, 16 received both alkaline-enriched water and potassium citrate (**Figure S2**).

Primary outcome

First follow-up visit (V1) occurred after a median of 105 (71, 184) to 107 (82, 154) days (**Table 2**). The composite primary outcome was reached in 91 cases (72%). At V0, SBP (135 (125, 141) vs. 141 (130, 150) mmHg, P = 0.02) and DBP (77 (67, 85) vs. 85 (73, 90) mmHg, P = 0.03) were slightly lower in cases than in controls. ECV was judged the same at baseline, with no more edema in cases than in controls. The medical background was very similar between groups, except for nephrolithiasis, which was less frequently reported in cases (32%) than in controls (56%, P = 0.02). None of the baseline treatments differed between groups. The proportions of patients who received $NaHCO_3$-containing alkalizing agents were very similar between groups (84% and 86%, P = 0.79). The daily prescribed doses of $NaHCO_3$ were also very similar (P = 0.46). At V0, plasma chloride concentration was the only biological parameter that differed between groups; cases had slightly higher values (106.0 (105.0, 109.0) mmol/L) than controls (105.0 (102.0, 107.0) mmol/L, P = 0.02). We wondered whether using different thresholds for ΔBW, ΔSBP, and ΔDBP would change our results: using a ΔBW > 0.5 kg, ΔSBP > 5 mmHg, and ΔDBP > 5 mmHg (PO2), we found 81 (64%) patients who reached the primary outcome; using a ΔBW > 1.0 kg, ΔSBP > 10 mmHg, and ΔDBP > 10 mmHg (PO3), we found 69 (54%) patients who reached the primary outcome. As for the initial primary outcome, reaching PO2 or PO3 was not associated to the treatment. By a stepwise analysis, we identified SBP, history of nephrolithiasis, and plasma sodium concentration to be independently associated with the primary outcome. We could not find any specific threshold to be helpful in clinical practice; none of them had enough sensitivity and specificity to be clinically relevant, either alone or combined.

As expected, SBP, DBP, and BW increased only in cases, and new-onset edema was observed only in cases as well. Most of the cases (57) had more than one criterion to reach the primary outcome (**Figure 1a**). Most of the patients who experienced a BW increase (**Figure 1b**) had a ΔBW > 1 kg, whereas most of the patients did not experience a ΔSBP (**Figure 1c**) or a ΔDBP (**Figure 1d**) > 10 mmHg. The proportion of patients who had an SBP > 140 mmHg was similar between V0 and V1 (**Figure S3a**). We found similar results with DBP (**Figure S3b**). Finally, the clinical evaluations of the extracellular volume were similar in both cases and controls (**Table 2**); physicians reported 11 patients to have clinically increased their ECV between V0 and V1, and out of these, 9 reached the primary outcome, whereas 2 did not (**Figure S3c**).

Secondary outcomes

Adherence to treatment, as judged by clinicians, was very similar. Even if the plasma bicarbonate concentration was similar (P = 0.82) between groups (22.5 (20.0, 25.0) and 23.0 (18.8, 25.0) mmol/L in cases and controls, respectively), the cases experienced a greater change (increase) in plasma bicarbonate concentration (9.2 (0.0, 20.5)) than controls (0.0 (0.0, 4.0)%, P = 0.01). Interestingly, the only other biological parameter that significantly differed between the groups was the plasma protein concentration; cases experienced a greater increase (1.4 (−1.5, 5.5)) than controls (0.0 (0.0, 0.0)%, P = 0.02). Of note, urine pH was similar in both groups.

Propensity score matching

We next conducted an analysis no longer based on comparing cases and controls but rather comparing patients who received $NaHCO_3$-containing agents ($NaHCO_3$ group) vs. those who received an agent that did not contain any $NaHCO_3$ (No-$NaHCO_3$ group). We did not find any significant differences when comparing baseline demographics between the $NaHCO_3$ and No-$NaHCO_3$ groups (**Table 3**). Even if the initial clinical parameters did not significantly differ, only patients from the $NaHCO_3$ group experienced edema and were the only ones with a clinically increased ECV at V0. More patients in the $NaHCO_3$ group had a medical history of hypertension, CKD, and/or kidney transplantation, whereas more patients in the No-$NaHCO_3$ group had a history of nephrolithiasis. Baseline biology reflected the undergoing medical conditions; patients in the $NaHCO_3$ group had a lower eGFR, a higher protein-to-creatinine ratio, a higher plasma potassium concentration, and a more severe metabolic acidosis (i.e., lower plasma bicarbonate concentration) than their counterparts. Taken together, these data indicate that at the time of inclusion, enrolled patients from the $NaHCO_3$ group were at a higher risk of increased ECV than those from the No-$NaHCO_3$ group. In the $NaHCO_3$ group, 76 reached the primary outcome, which was a similar (P = 0.79) proportion (71%) to that observed in the No-$NaHCO_3$ group, in which 15 (75%) reached the primary outcome. Using PO2 and PO3 thresholds, we found no differences between groups of treatment (**Table S1**). To better compare the two groups, we developed three different models of propensity score matching (**Figure 2**); even if we found a good fit between matched patients (**Figure 2a-c**) in all three models (**Table S2**), we did not find any difference in terms of primary outcome (**Figure 2d-f**).

Although 42 (39%) and 10 (50%) patients in the $NaHCO_3$ and No-$NaHCO_3$ groups, respectively, experienced BW increases between visits, the paired (between V0 and V1) individual comparison did not find any significant differences between groups; the median changes were 0.0 (−1.0, +2.0) and +0.3 (−2.3, +1.4) kg in the $NaHCO_3$ and No-$NaHCO_3$ groups, respectively (P = 0.66). Similarly, the paired comparison for SBP showed no difference; the median changes were 0.0 (−3.0, +7.8) and −2.0 (−9.0, +9.0) mmHg in the $NaHCO_3$ and No-$NaHCO_3$ groups, respectively

Table 2 Clinical and biological characteristics of participants who reached the primary outcome (cases) and of those who did not (controls)

	Cases (*n* = 91)	Controls (*n* = 36)	*P* value
Time between visits, days	107 [82, 154]	105 [71, 184]	0.740
Clinical data at baseline			
Age, y	64.00 [51.50, 73.50]	64.00 [53.75, 71.50]	0.934
Gender women, *n* (%)	38 (42)	16 (44)	0.939
BMI, kg/m^2	27.6 [23.1, 32.2]	29.9 [26.1, 34.8]	0.065
SBP, mmHg	135 [125, 141]	141 [130, 150]	0.020
DBP, mmHg	77 [67, 85]	85 [73, 90]	0.026
Edema, *n* (%)	11 (12)	6 (17)	0.561
Extracellular volume, *n* (%)			0.688
Decreased	3 (3)	0 (0)	
Normal	80 (88)	32 (89)	
Increased	8 (9)	4 (11)	
Medical history			
Hypertension, *n* (%)	63 (69)	24 (67)	0.833
Chronic heart failure, *n* (%)	6 (7)	2 (6)	1
Chronic kidney disease, *n* (%)	60 (66)	19 (53)	0.223
Kidney transplantation, *n* (%)	24 (26)	5 (14)	0.163
Nephrolithiasis, *n* (%)	29 (32)	20 (56)	0.016
Chronic bowel disorder, *n* (%)	8 (9)	3 (8)	1
Biology at baseline			
Plasma sodium, mEq/L	140.0 [138.0, 142.0]	139.0 [137.0, 140.0]	0.091
Plasma potassium, mEq/L	4.50 [4.23, 4.90]	4.40 [4.00, 4.80]	0.101
Plasma chloride, mEq/L	106.0 [105.0, 109.0]	105.0 [102.0, 107.0]	0.021
Plasma bicarbonate, mEq/L	19.0 [17.4, 24.0]	20.5 [18.0, 25.0]	0.422
eGFR, mL/min/1.73m^2	37.5 [25.7, 65.5]	46.2 [28.8, 78.4]	0.210
Plasma proteins, g/L	70.0 [65.8, 73.8]	71.0 [67.0, 74.0]	0.513
Daily urine output, L/day	1.80 [1.50, 2.05]	2.00 [1.51, 2.28]	0.478
Daily sodium excretion, mmol/day	134 [99, 194]	161 [105, 230]	0.793
Urine pH, UpH	5.30 [5.00, 6.00]	5.25 [5.00, 5.83]	0.652
Urine protein-to-creatinine ratio, mg/g	225 [85, 816]	226 [108, 427]	0.928
Ongoing medications			
RAAS inhibitor(s), *n* (%)	39 (43)	19 (53)	0.330
Diuretics, *n* (%)	23 (25)	10 (28)	0.824
Other antihypertensive medicine, *n* (%)	50 (55)	19 (53)	0.846
Steroids, *n* (%)	17 (19)	6 (17)	1
Low-salt diet, *n* (%)	35 (39)	8 (22)	0.098
Study treatment			0.794
$NaHCO_3$-containing agent, *n* (%)	76 (84)	31 (86)	
No-$NaHCO_3$-containing agent, *n* (%)	15 (16)	5 (14)	
Daily $NaHCO_3$ prescribed, mmol/kg/d	0.34 [0.21, 0.58]	0.44 [0.26, 0.56]	0.458
Daily HCO_3^- prescribed, mg/day	1453 [1089, 2905]	1513 [1453, 3697]	0.306
Daily Na^+ prescribed, mg/day	547 [411, 1095]	586 [547, 1440]	0.301
Adherence to treatment, *n* (%)			0.916
> 75%	66 (73)	25 (74)	
50-75%	13 (15)	4 (11)	

(Continued)

Table 2 (Continued)

	Cases (*n* = 91)	Controls (*n* = 36)	*P* value
25-50%	5 (6)	3 (9)	
< 25%	5 (6)	2 (6)	
Evolution under treatment			
SBP, mmHg	135 [124, 151]	137 [130, 149]	0.882
DBP, mmHg	80 [72, 87]	76 [70, 88]	0.470
Edema, *n* (%)	17 (19)	6 (17)	1
Extracellular volume, *n* (%)			1
Decreased	0 (0)	0 (0)	
Normal	80 (88)	32 (89)	
Increased	11 (12)	4 (11)	
Extracellular volume change, *n* (%)			0.558
Has decreased	2 (2)	2 (6)	
Is same	80 (88)	31 (89)	
Has increased	9 (10)	2 (5)	
Plasma sodium, mmol/L	140.0 [139.0, 142.0]	139.0 [137.0, 141.0]	0.016
Plasma potassium, mmol/L	4.50 [4.20, 4.90]	4.30 [4.10, 4.80]	0.254
Plasma chloride, mmol/L	105.0 [103.0, 107.3]	103.0 [101.0, 106.0]	0.099
Plasma bicarbonate, mmol/L	22.5 [20.0, 25.0]	23.0 [18.8, 25.0]	0.815
Plasma bicarbonate change, %	9.2 [0.0, 20.5]	0.0 [0.0, 4.0]	0.007
Plasma proteins, g/L	71.0 [68.0, 75.0]	70.7 [64.8, 74.0]	0.554
Plasma proteins change, %	1.4 [−1.5, 5.5]	0.0 [0.0, 0.0]	0.024
Plasma creatinine change, %	0.0 [−6.7, 15.3]	0.0 [0.0, 4.8]	0.513
Daily urine output, L/day	1.72 [1.52, 2.00]	1.98 [1.67, 2.28]	0.135
Daily sodium excretion, mmol/day	155 [103, 192]	168 [119, 227]	0.524
Urine pH, UpH	6.00 [5.00, 6.25]	6.00 [5.62, 6.00]	0.954
Urine protein-to-creatinine ratio, mg/g	273 [91, 845]	271 [74, 421]	0.560

In the AlcalUN study, the primary outcome was a composite criterion including: body weight (BW) increase, systolic blood pressure (SBP) increase, diastolic BP (DBP) increase, and/or clinically relevant new-onset edema. Patients received either a sodium bicarbonate ($NaHCO_3$)-containing alkalizing agent or potassium citrate. The categorial data are presented as *n* and percentages (%) while the quantitative data are presented as median [IQR]. Edema was assessed clinically by the investigators. Low salt diet was reported by the investigators' prescriptions. The reported values for BP are the ones measured at each physician's office. The glomerular filtration rate was estimated (eGFR) by the MDRD formula. Adherence to treatment was reported by physician's evaluation.
BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

(P = 0.22). Similar results were found for DBP; the median changes were 0.0 (−6.0, +6.0) and +4.0 (−3.0, +7.0) mmHg in the $NaHCO_3$ and No-$NaHCO_3$ groups, respectively (P = 0.32). Finally, we did not find any evidence for a significant increase in ECV in the $NaHCO_3$ group compared to the No-$NaHCO_3$ group.

DISCUSSION

The first series of 40 alkali-treated patients was published nearly a century ago.[19] $NaHCO_3$ is mainly prescribed to treat metabolic acidosis during CKD, as reflected in the enrollment during our real-life study. In our study, 76 (60%) patients received alkalization because of metabolic acidosis, following the latest Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[20] Several lines of evidence have shown the strong relationship between acid-base status and bone metabolism.[21–24] Thus far, however, no interventional study has clearly demonstrated the effect of such an intervention on a clinically relevant end point, most likely because, in some studies,[14] therapy was initiated while the blood bicarbonate concentration was still within the normal range. Small, randomized trials have recently reported improvements in surrogate markers.[25,26] The other purpose of alkalizing patients with CKD is to decelerate GFR decline.[10,11,27] The inability to excrete daily acid load is tightly linked to poor kidney function[28,29] and decreased survival.[30] We did not find any difference in terms of eGFR, mainly because of the short duration of our study. Overall, alkalizing therapy has shown substantial beneficial effects in the CKD population and should be encouraged.

As also reflected by our real-life enrollment, the other important purpose of alkalizing therapy is to prevent recurring episodes of nephrolithiasis.[31,32] Thus, the composition of the alkalizing agent is not important.[32,33] We clearly show that whether the alkalizing agent contains $NaHCO_3$ is not associated with a clinically relevant increase in ECV. Our study included patients with

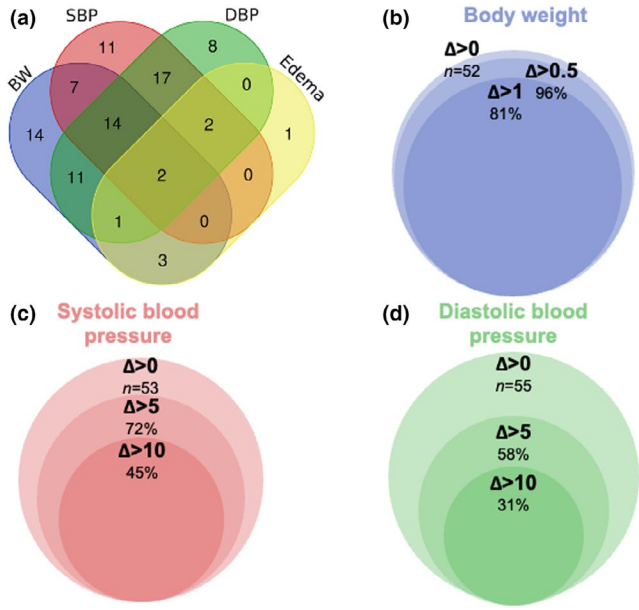

Figure 1 The three major components of the extracellular volume (ECV) increase. (**a**) The ECV increase was assessed by a composite primary outcome; within the participants with at least one follow-up visit, patients reached the primary outcome by increases in body weight (BW) in 52 (41%) patients, systolic blood pressure (SBP) in 53 (42%) patients, diastolic blood pressure (DBP) in 55 (43%) patients, and new-onset edema in 9 (7%) patients. (**b**) BW increased (lighter blue circle, $\Delta > 0$) in 52 patients during the AlcalUN study. Of them, 50 of 52 patients (96%) experienced increases of more than 0.5 kg (medium blue circle proportional to this population, $\Delta > 0.5$), whereas 42 of 52 (81%) experienced increases of more than 1 kg (deep blue circle proportional to this population, $\Delta > 1$). (**c**) SBP increased (lighter red circle, $\Delta > 0$) in 53 patients during the AlcalUN study. Of them, 38 of 53 patients (72%) experienced increases of more than 5 mmHg (medium red circle proportional to this population, $\Delta > 5$), whereas 24 of 53 (45%) experienced increases of more than 10 mmHg (deep red circle proportional to this population, $\Delta > 10$). (**d**) DBP increased (lighter green circle, $\Delta > 0$) in 55 patients during the AlcalUN study. Of them, 32 of 55 patients (58%) experienced increases of more than 5 mmHg (medium green circle proportional to this population, $\Delta > 5$), whereas 17 of 55 (31%) experienced increases of more than 10 mmHg (deep green circle proportional to this population, $\Delta > 10$).

either $NaHCO_3$ and/or potassium citrate. A recent meta-analysis showed that potassium intake could facilitate sodium excretion.[34] Even if our patients taking both potassium citrate and $NaHCO_3$ showed a lower proportion of the primary outcome (6/16; i.e., 37.5%), interestingly, those taking potassium citrate alone had a higher proportion of primary outcome (75%, $P = 0.04$), which was similar in patients taking $NaHCO_3$ alone (77%, $P > 0.90$).

We identified a higher plasma chloride concentration to be associated with the primary outcome. It is possible that plasma chloride concentration better reflect the metabolic acid-base status: plasma bicarbonate concentration is influenced by both metabolic and ventilatory acid-base status. To further explore this point, we would have required a blood arterial gas analysis, which is not the clinical routine in the population of our study. On the other hand, here, the acid-base status does not seem to be independently associated to the outcome. Plasma chloride could also reflect the hydration of the intracellular compartment, as does plasma sodium (that tends to be higher in cases than in controls in our study): higher plasma chloride/sodium concentrations would indicate a lower intracellular volume, usually associated to a lower ECV (to note, SBP and DBP were significantly lower in cases than in controls); therefore, it is easier to show an increase, moving from a lower state than from a normal or "increased" volume. Furthermore, plasma chloride concentration could reflect cardiac output,[35] which is an important determinant in the adaptation to ECV variations. Plasma chloride is also linked to the response to diuretics,[36] as well as to death and cardiovascular outcomes.[37] Finally, even if plasma chloride concentration is an interesting biomarker, it cannot be considered as clinically relevant due to a huge overlap between cases and controls.

We also identified the history of nephrolithiasis to be linked to ECV increase after initiating alkalizing therapy. The link between kidney stones and BP is well known[38]: even if pathophysiology is not totally understood, inflammation and oxidative stress are involved; it is possible that nephrolithiasis be part of a syndrome in which ECV volume control is also impaired, as during metabolic syndrome. Out of the 49 patients with a history of nephrolithiasis, 29 (59%) reached the primary outcome. Comparing the prevalence of CKD in this population to the one in those who did not reach the primary outcome and had a history of nephrolithiasis, we found nine (31%) and six (30%), respectively, who had CKD ($P > 0.99$). Therefore, CKD is not a risk marker for increasing ECV in patients with a history of nephrolithiasis. Further studies are required to investigate the link between nephrolithiasis and ECV control.

Moreover, considering the imbalance regarding baseline characteristics, we performed three different propensity-score matching analyses that did not show any difference between groups; second, this imbalance was in fact disadvantageous toward the $NaHCO_3$ group. Patients in the $NaHCO_3$ group were more prone to increase their ECV. Thus, we conclude it is very unlikely that any difference between groups could have been masked by either our recruitment or the clinical heterogeneity of the $NaHCO_3$ group.

One limitation lies in not recruiting patients treated by other alkalizing therapies, such as sodium citrate; this lack of enrollment primarily reflects how rarely these therapies are prescribed in real life.[8] Thus, we focused our efforts on comparing the impact of $NaHCO_3$ on ECV because it was supposed to be an adverse event limiting its prescription, as this concern was already raised in the KDIGO guidelines.[20] Even if our population received a $NaHCO_3$ dose in the lower range of these recommendations, we did not find more primary outcomes in patients receiving higher doses than in those receiving lower doses, and the doses were sufficient to significantly increase blood bicarbonate concentrations. Most of previous studies on this topic did not report any difference in terms of BP[13,14] or BW.[14] The meta-analyses of those secondary outcomes did not show any significant modification of either BP or BW[10,11]; however, one reported a significant worsening (that included increasing treatment) of hypertension and/or edema.[10] More recently, the latest randomized placebo-controlled BASE pilot trial did not show any difference in terms of BW or BP.[15] Other adverse events, such as cardiac, gastrointestinal, musculoskeletal, and

Table 3 Clinical and biological characteristics of participants at inclusion

	$NaHCO_3$ group (n = 107)	No-$NaHCO_3$ group (n = 20)	P value
Demographics			
Age, y	65 [53;73]	60 [45;67]	0.160
Gender women, *n* (%)	63 (59)	10 (50)	0.470
BMI, kg/m^2	28.9 [23.8;33.1]	26.2 [21.7;32.6]	0.480
Clinical data			
SBP, mmHg	137 [128;145]	132 [120;143]	0.240
DBP, mmHg	80 [70;88]	79 [69;88]	0.900
Edema, *n* (%)	17 (16)	0 (0)	0.070
Medical history			
Hypertension, *n* (%)	80 (75)	7 (35)	0.001
Chronic heart failure, *n* (%)	8 (7)	0 (0)	0.350
Chronic kidney disease, *n* (%)	73 (68)	6 (30)	0.002
Kidney transplantation, *n* (%)	29 (27)	0 (0)	0.007
Nephrolithiasis, *n* (%)	30 (28)	19 (95)	<0.001
Chronic bowel disease, *n* (%)	9 (8)	2 (10)	0.680
Ongoing medications			
RAAS inhibitor(s), *n* (%)	51 (48)	7 (35)	0.340
Diuretics, *n* (%)	30 (28)	3 (15)	0.280
Other antihypertensive medicine, *n* (%)	62 (58)	7 (35)	0.090
Steroids, *n* (%)	22 (21)	1 (5)	0.120
Low salt diet, *n* (%)	39 (36)	4 (20)	0.200
Biology at inclusion			
Plasma sodium, mEq/L	140.0 [138.0;141.0]	139.5 [138.0;141.3]	0.850
Plasma potassium, mEq/L	4.60 [4.25;4.90]	4.10 [3.98;4.43]	0.003
Plasma chloride, mEq/L	106.0 [105.0;109.0]	104.5 [103.0;106.0]	0.006
Plasma bicarbonate, mEq/L	19.0 [17.0;21.1]	25.0 [24.0;27.0]	<0.001
eGFR, mL/min/1.73 m^2	35.8 [24.5;62.5]	79.8 [56.1;104.7]	<0.001
Plasma proteins, g/L	70.0 [65.0;74.0]	71.0 [69.7;75.5]	0.160
Urine protein-to-creatinine ratio, mg/mmol	31.3 [9.8;96.3]	11.9 [8.1;18.9]	0.020
Urine pH, UpH	5.13 [5.00;6.00]	5.38 [5.00;5.77]	0.740

In the AlcalUN study, patients received either sodium bicarbonate-based treatment (and were allocated to the $NaHCO_3$ group) or an alkalizing treatment that did not contain any $NaHCO_3$ (and were allocated to the No-$NaHCO_3$ group). The categorial data are presented as *n* and percentages (%) whereas the quantitative data are presented as median [IQR]. Edema was assessed clinically by the investigators. Low salt diet was reported by the investigators' prescriptions. The reported values for blood pressure are the ones measured at each physician's office. The glomerular filtration rate was estimated (eGFR) by the MDRD formula.
BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range; $NaHCO_3$, sodium bicarbonate; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

nervous system disorders, have been reported, especially in the elderly population.[13]

All the data used in previous studies were collected from secondary outcomes. However, herein, we report the results from a real-world study specifically designed to follow up on ECV in a clinically relevant setting; as components of the primary outcome, we chose systolic/diastolic BP, BW and new-onset edema. Those outcomes appeared to be more clinically relevant while treating patients experiencing metabolic acidosis and/or nephrolithiasis. One assumption is that the lack of difference we observed could be due to the low reliability of our measurement of ECV; as an example, at inclusion, BP was slightly lower in cases than in controls, so those with the lower BP would have, by a regression to the mean, a higher reading at V1. Moreover, the use of the same scale for BW measurement was not required in our study, as we were not influencing the day-to-day practice of clinicians. Even if they did not use the same scale, this would be the data they take into account in their interpretation of ECV. All of this suggests that parts of the composite primary outcome would not necessarily capture clinically relevant information. We *a priori* considered that our composite primary outcome would be a good surrogate marker of the ECV, but when we asked clinicians whether the ECV increased during the follow-up based on clinical judgment, they were in agreement with our primary outcome in less than 10% of cases (9/91 patients had an ECV judged as increased). This discrepancy has been shown before in the context of hyponatremia; more

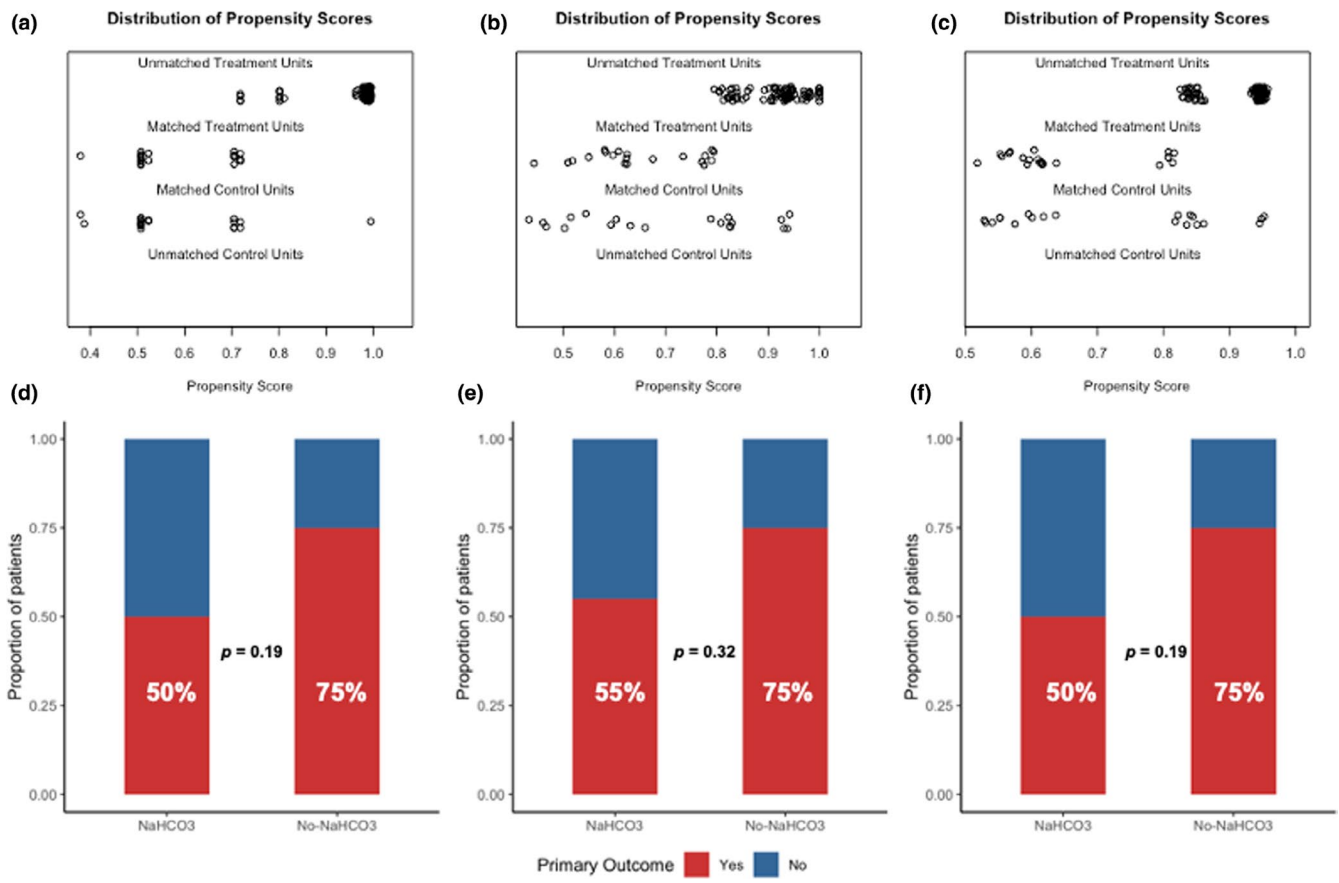

Figure 2 Results from three different propensity score matching analyses do not show any differences. (**a-c**) The distributions of the propensity scores between the 20 matched treated ($NaHCO_3$) and 20 control (No-$NaHCO_3$) patients show good fits using model 1 (**a**), model 2 (**b**), and model 3 (**c**). (**d-f**) The proportions of patients who reached the composite primary outcome were not different between the 2 groups after matching with model 1 (**d**), model 2 (**e**), or model 3 (**f**) Fisher's exact test. [Colour figure can be viewed at wileyonlinelibrary.com]

than 50% of the physicians disagreed with the gold standard.[39] We were not able to use any objective measure of ECV (such as dual-X absorptiometry); therefore, we chose to use real-life markers that matter for physicians to make therapeutic decisions in the daily clinic. This, combined with the fact that we assessed it as a primary outcome, is the strength of our study. Even if a lack of difference does not necessarily mean a lack of association, we had a high sensitivity (i.e., 72% of our cohort reached the primary endpoint); *post hoc* analyses that included different meaningful thresholds also did not show any differences.

A small study previously reported no significant increase in ECV when comparing very short-term intravenous infusion of $NaHCO_3$ vs. sodium chloride.[40] It appears that the most important factor is in fact the associated anion (bicarbonate vs. chloride) rather than the sodium[41] or potassium[42] itself. This is probably related to a β-intercalated cell fluid retention effect (through the pendrin/NDCBE complex), as shown in animal models.[43,44] Some authors have argued that, under a liberal diet (i.e., with a normal chloride sodium intake), $NaHCO_3$ is related to ECV increase.[45,46] When we compared, within the subgroup of patients who received $NaHCO_3$ alone, those under a low-salt diet ($n = 38$) to the others ($n = 53$), we did not find any difference in terms of primary outcome (84% vs. 72%, $P = 0.21$). Significantly, the first report (in 1930) of the use of a combination of $NaHCO_3$/potassium citrate reported the disappearance of edema (i.e., a decrease in ECV) in 36 out of 40 patients rather than an increase.[19]

Altogether, our data clearly demonstrate no specific increase in ECV when using $NaHCO_3$ (compared to potassium citrate) in the clinical practice of alkalizing patients in the nephrology/urology setting. This outcome argues for a wider use of $NaHCO_3$, which is safe even in a high-risk population of patients with impaired kidney function.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS
J.B., L.F., M.B., R.N.H.S., C.O., and J.P.B. wrote the manuscript. J.B., L.F., L.d.L., A.B., L.G., S.C., and J.P.B. designed the research. J.B., L.F., M.B., L.d.L., H.A., T.D.H., V.G., A.B., L.G., S.C., G.S., L.B., R.C., Y.L., C.O., and J.P.B. performed the research. J.B., L.F., M.B., F.L., C.O., and J.P.B. analyzed the data.

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