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Title

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Abstract

Oral alkalization with sodium bicarbonate ($NaHCO_3$) or citrate is prescribed for conditions ranging from metabolic acidosis to nephrolithiasis. While 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 02/2017 to 02/2020, 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 increases in blood pressure (ΔBP<10 mmHg). The primary outcome was not associated (*p*=0.79) with the study treatment (129 received $NaHCO_3$, 27 received citrate). We subsequently developed 3 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.

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 1/3 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 to 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 02/2017 to 02/2020. 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 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. 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, 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 3 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, body mass index (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. 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 [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 (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 $NaHCO_3$, while 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 S21**).

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, while 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 S32A**). We found similar results with DBP (**Figure S32B**). 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, while 2 did not (**Figure S32C**).

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, while 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 2 groups, we developed 3 different models of propensity score matching (**Figure 2**); even if we found a good fit between matched patients (**Figure 2A-C**) in all 3 models (**Table S2**), we did not find any difference in terms of primary outcome (**Figure 2D-F**).

While 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 (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 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 endpoint, 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). Similarly, even if proof-of-concept data exist(27), prospective studies have failed to demonstrate a positive effect on muscle function(13, 14). Nonetheless, a recent randomized controlled study using a no-$NaHCO_3$ alkalizing agent showed beneficial effects on muscle strength(28), while another showed beneficial effects of $NaHCO_3$ on vascular function(29). Unfortunately, we did not collect information on muscle function in our study. The other purpose of alkalizing patients with CKD is to decelerate GFR decline(10, 11, 30). The inability to excrete daily acid load is tightly linked to poor kidney function(31, 32) and decreased survival(33). 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(34, 35). Thus, the composition of the alkalizing agent is not important(35, 36). 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 either $NaHCO_3$ and/or potassium citrate. A recent meta-analysis showed that potassium intake could facilitate sodium excretion(37). 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(38) which is an important determinant in the adaptation to ECV variations. Plasma chloride is also linked to the response to diuretics(39), as well as to death and cardiovascular outcomes(40). 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 history of nephrolithiasis to be linked to ECV increase after initiating alkalizing therapy. The link between kidney stones and blood pressure is well known(41): 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 9 (31%) and 6 (30%), respectively, who had CKD (p>0.99). So, 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 3 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 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 than 50% of the physicians disagreed with the gold standard(42). 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 $NaHCO_3$ *versus* sodium chloride(43). It appears that the most important factor is in fact the associated anion (bicarbonate *versus* chloride) rather than the sodium(44) or potassium(45) itself. This is probably related to a β-intercalated cell fluid retention effect (through the pendrin/NDCBE complex), as shown in animal models(46, 47). Some authors have argued that, under a liberal diet (i.e., with a normal chloride sodium intake), $NaHCO_3$ is related to ECV increase(48, 49). 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.

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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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.F., A.B., L.G., S.C., and J.P.B. designed the research; J.B., L.F., M.B., L.D.F., 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., C.O., and J.P.B. analyzed the data; J.B., L.F., M.B., L.D.F., H.A., T.D.H., V.G., A.B., L.G., S.C., G.S., L.B., R.C., Y.L., F.L., R.N.H.S., C.O., and J.P.B. revised the manuscript.

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Figure legends

Figure 1. The 3 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.** Body weight increased (lighter blue circle, Δ>0) in 52 patients during the AlcalUN study. Of them, 50/52 patients (96%) experienced increases of more than 0.5 kg (medium blue circle proportional to this population, Δ>0.5), while 42/52 (81%) experienced increases of more than 1 kg (deep blue circle proportional to this population, Δ>1). **C.** Systolic blood pressure increased (lighter red circle, Δ>0) in 53 patients during the AlcalUN study. Of them, 38/53 patients (72%) experienced increases of more than 5 mmHg (medium red circle proportional to this population, Δ>5), while 24/53 (45%) experienced increases of more than 10 mmHg (deep red circle proportional to this population, Δ>10). **D**. Diastolic blood pressure increased (lighter green circle, Δ>0) in 55 patients during the AlcalUN study. Of them, 32/55 patients (58%) experienced increases of more than 5 mmHg (medium green circle proportional to this population, Δ>5), while 17/55 (31%) experienced increases of more than 10 mmHg (deep green circle proportional to this population, Δ>10).

Figure 2. Results from 3 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).

Supplementary information titles

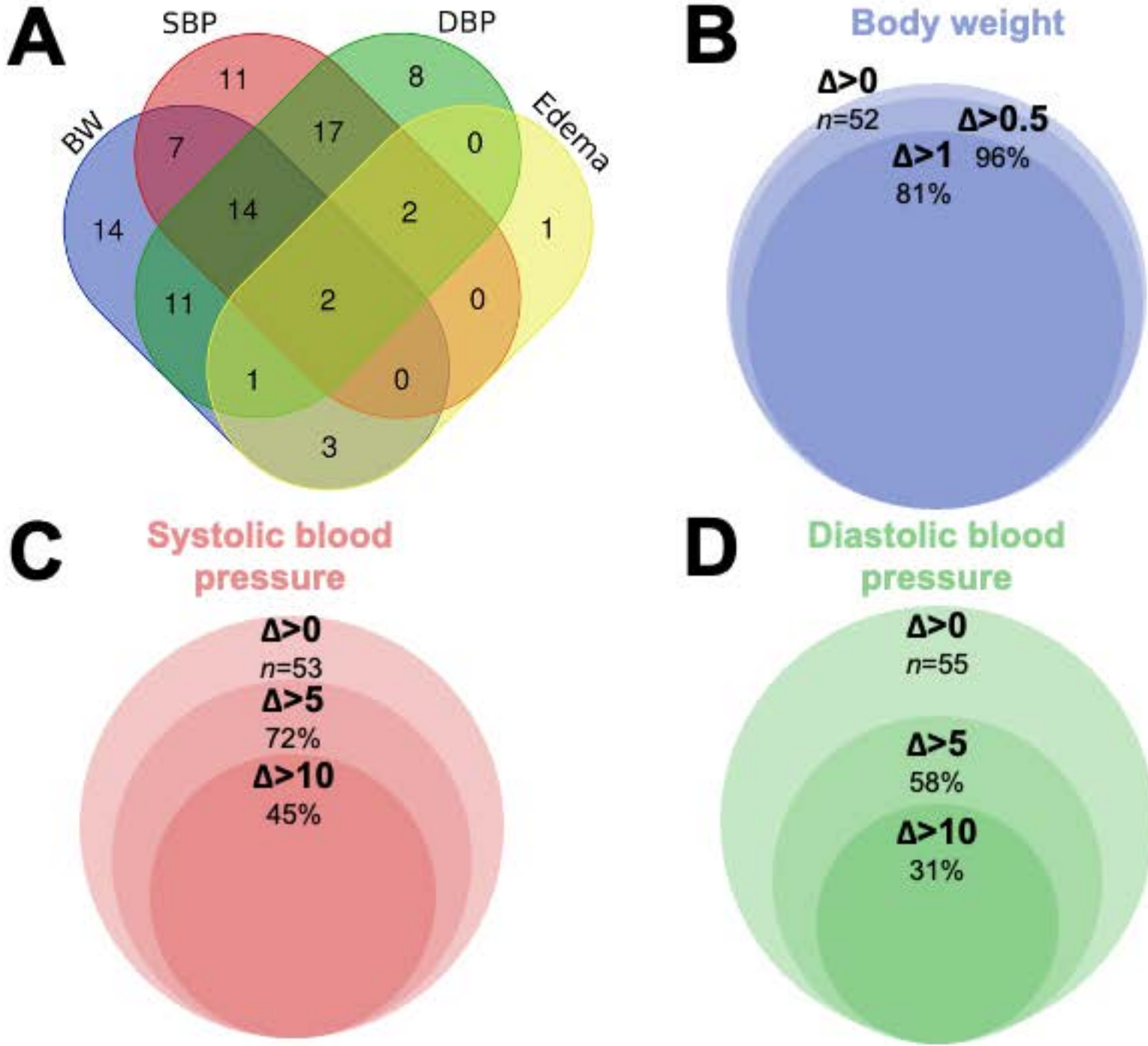
Figure S1. Shared comorbidities within groups of treatment. ~~Prescriptions of active treatments during the AlcalUN study.~~

Figure S2. Prescriptions of active treatments during the AlcalUN study.

Figure S3. Meaningful components of the primary outcome.

Table S1. Different thresholds of components of the primary outcome in patients by groups of treatment.

Table S2. The 3 propensity score matching models show no difference.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DBP
BW
Edema
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14
14
2
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11
2
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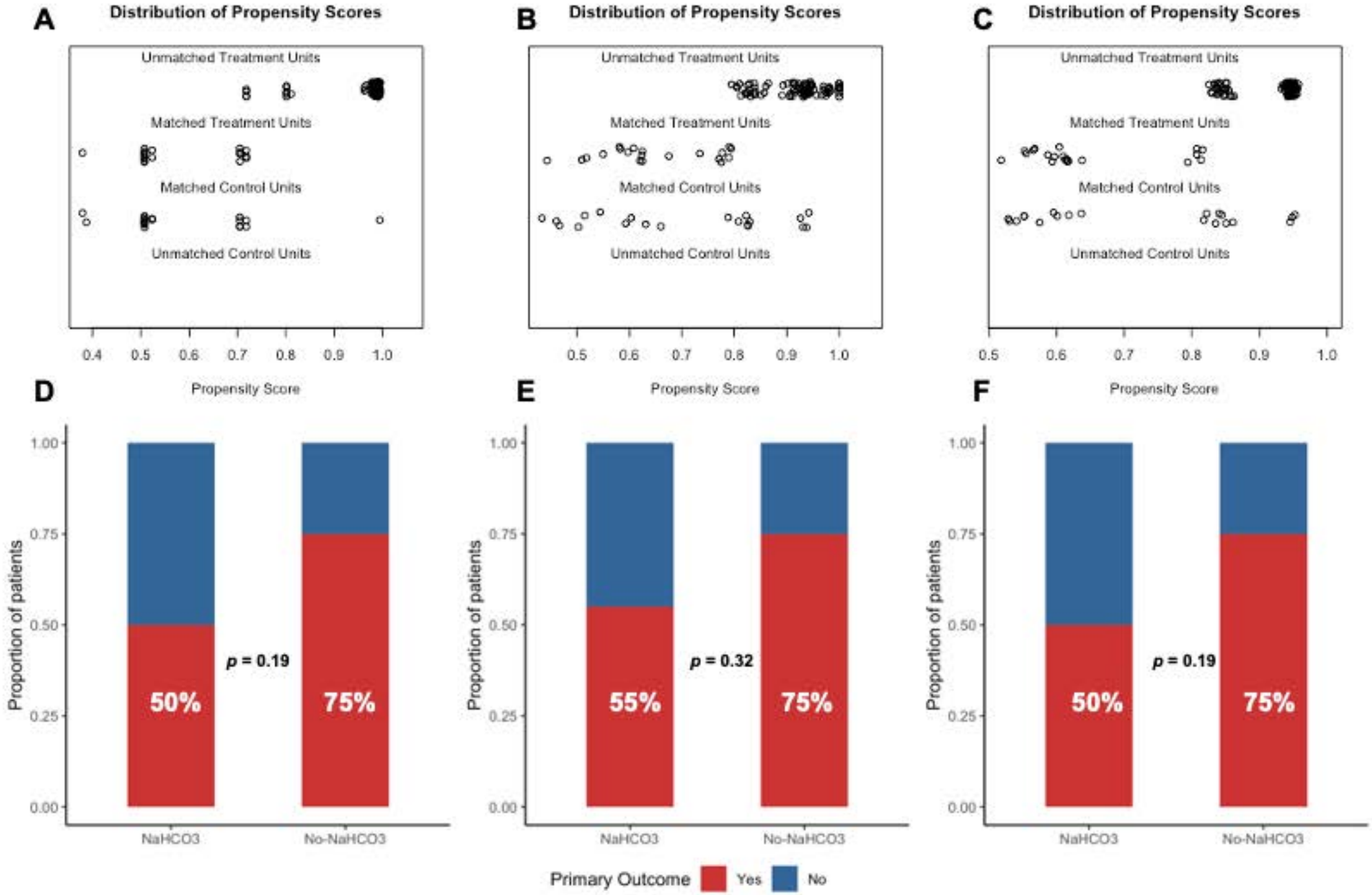
1
0
3
B
Body weight
Δ>0
n=52
Δ>0.5
96%
Δ>1
81%
C
Systolic blood pressure
Δ>0
n=53
Δ>5
72%
Δ>10
45%
D
Diastolic blood pressure
Δ>0
n=55
Δ>5
58%
Δ>10
31%


A
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Unmatched Treatment Units
Matched Treatment Units
Matched Control Units
Unmatched Control Units
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Propensity Score
B
Distribution of Propensity Scores
Unmatched Treatment Units
Matched Treatment Units
Matched Control Units
Unmatched Control Units
0.5
0.6
0.7
0.8
0.9
1.0
Propensity Score
C
Distribution of Propensity Scores
Unmatched Treatment Units
Matched Treatment Units
Matched Control Units
Unmatched Control Units
0.5
0.6
0.7
0.8
0.9
1.0
Propensity Score
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Proportion of patients
1.00
0.75
0.50
0.25
0.00
50%
75%
p = 0.19
NaHCO3
No-NaHCO3
E
Proportion of patients
1.00
0.75
0.50
0.25
0.00
55%
75%
p = 0.32
NaHCO3
No-NaHCO3
F
Proportion of patients
1.00
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0.00
50%
75%
p = 0.19
NaHCO3
No-NaHCO3
Primary Outcome
Yes
No

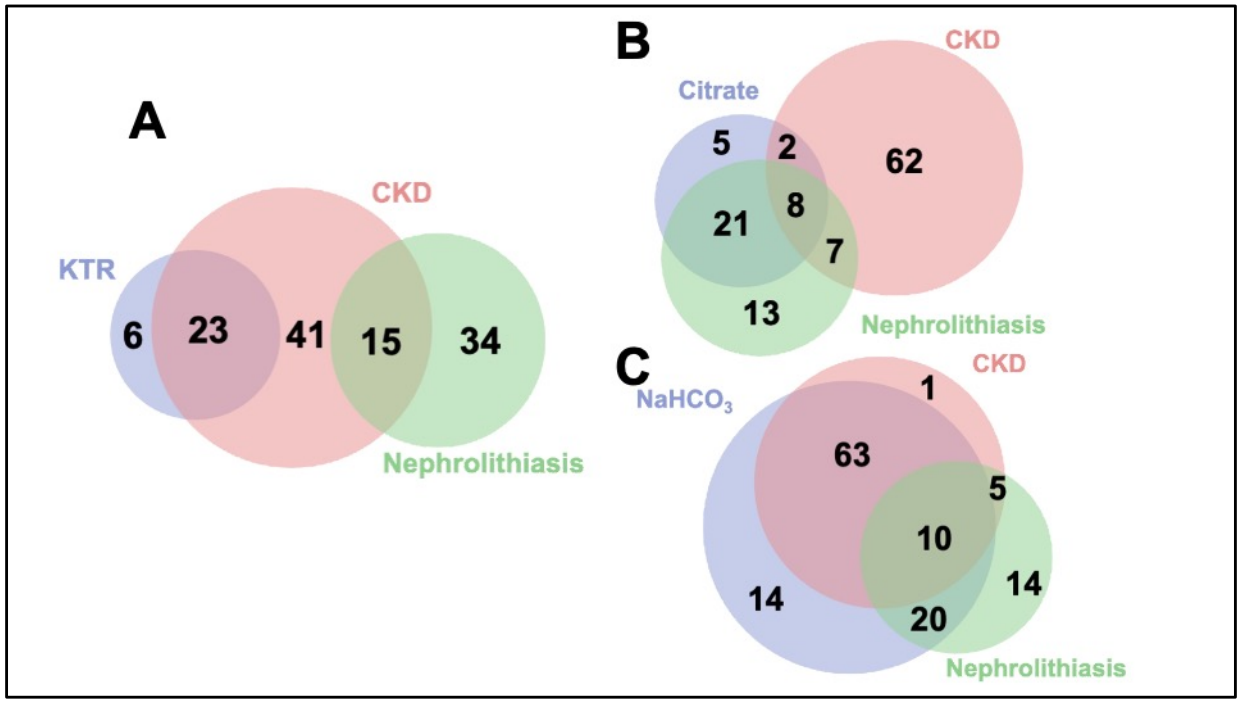

Figure S1. Shared comorbidities within groups of treatment. A. At the inclusion, 79 participants had chronic kidney disease (CKD), 29 were kidney transplant recipients (KTR) and 49 had nephrolithiasis. Fifteen patients had both CKD and nephrolithiasis, while 23 had both CKD and KTR. **B.** During the study, 36 participants received potassium citrate as an alkalizing agent (citrate). Of these, 10 had CKD, 29 had nephrolithiasis, and 8 had both CKD and nephrolithiasis. **C.** During the study, 107 participants received sodium bicarbonate as an alkalizing agent ($NaHCO_3$). Of these, 73 had CKD, 30 had nephrolithiasis, and 10 had both CKD and nephrolithiasis.

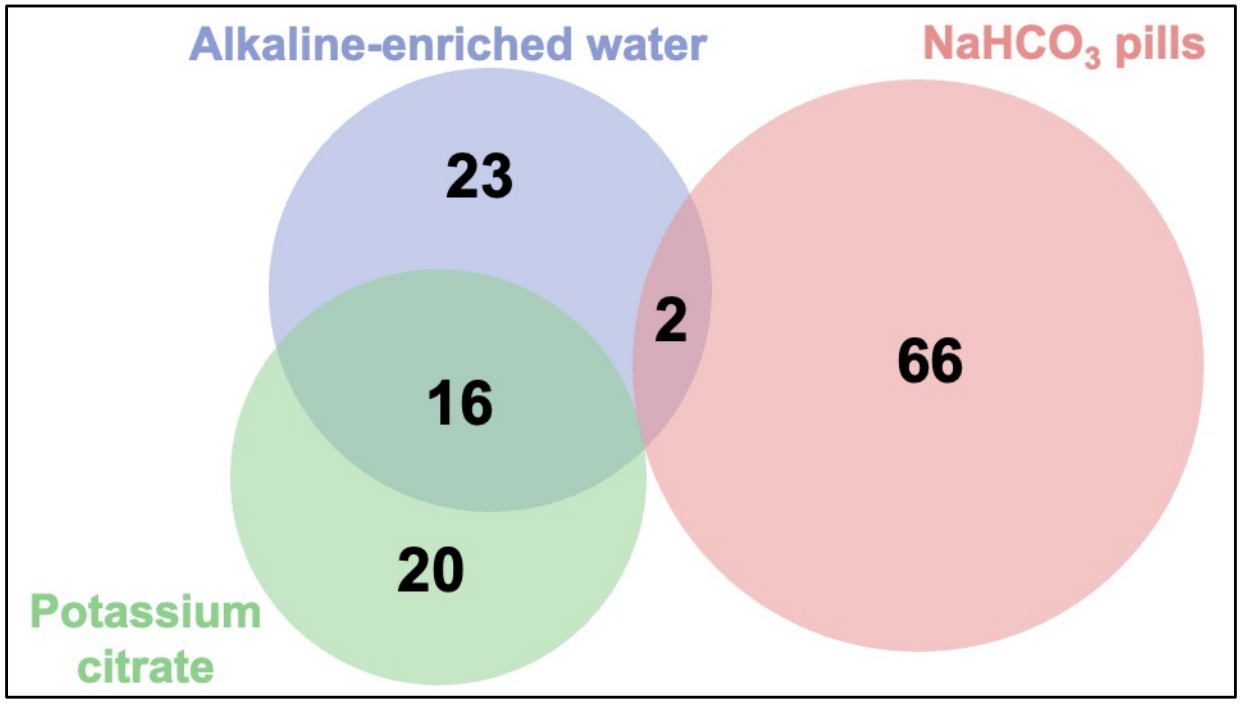

Figure S2. Prescriptions of active treatments during the AlcalUN study. At the inclusion, 41 (32%) of the participants were prescribed alkaline-enriched water as treatment. Among them, 16 (39%) were also prescribed potassium citrate or sodium bicarbonate ($NaHCO_3$ pills) in 2 (5%) cases. Sixty eight (54%) patients were prescribed $NaHCO_3$ pills, whom 66 (97%) were prescribed as the sole therapy. Finally, 36 (28%) patients were prescribed potassium citrate, whom 20 (56%) were prescribed as sole therapy.

Table S21. The 3 matched sub-groups show no difference.

	Overall	$NaHCO_3$ group	No-$NaHCO_3$ group	*p*	*SMD*
Model 1					
n	38	19	19		
Chronic kidney disease, n(%)	10 (26.3)	4 (21.1)	6 (31.6)	0.71	0.241
Hypertension, n(%)	14 (36.8)	7 (36.8)	7 (36.8)	0.9	<0.001
Nephrolithiasis, n(%)	36 (94.7)	18 (94.7)	18 (94.7)	0.9	<0.001
Other antihypertensive medicine, n(%)	13 (34.2)	7 (36.8)	6 (31.6)	0.9	0.111
Steroids, n(%)	2 (5.3)	1 (5.3)	1 (5.3)	0.9	<0.001
Distance, median [IQR]	0.51 [0.51, 0.71]	0.51 [0.51, 0.71]	0.51 [0.51, 0.71]	0.9	0.004
Primary outcome, n(%)	25 (65.8)	10 (52.6)	15 (78.9)	0.17	0.577
Model 2					
n	30	15	15		
Age, years	64.50 [53.25, 70.25]	65.00 [44.50, 72.00]	63.00 [56.00, 67.50]	0.9	0.199
BMI, kg/m^2	28.35 [24.53, 32.64]	28.33 [25.78, 30.62]	28.44 [23.69, 32.96]	0.85	0.128
Chronic kidney disease, n(%)	11 (36.7)	5 (33.3)	6 (40.0)	0.9	0.139
Hypertension, n(%)	14 (46.7)	7 (46.7)	7 (46.7)	0.9	<0.001
Chronic heart failure, n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0.9	<0.001
Diuretics, n(%)	4 (13.3)	2 (13.3)	2 (13.3)	0.9	<0.001
Steroids, n(%)	3 (10.0)	2 (13.3)	1 (6.7)	0.9	0.224
Low salt diet, n(%)	5 (16.7)	2 (13.3)	3 (20.0)	0.9	0.180
Distance, median [IQR]	0.82 [0.61, 0.90]	0.82 [0.62, 0.87]	0.82 [0.62, 0.88]	0.82	0.013
Primary outcome, n(%)	20 (66.7)	9 (60.0)	11 (73.3)	0.70	0.286
Model 3					
n	32	16	16		
Age, years	64.50 [54.75, 68.00]	64.50 [53.00, 67.25]	64.00 [57.00, 68.75]	0.73	0.200
BMI, kg/m^2	28.24 [23.25, 32.47]	27.44 [23.25, 30.04]	29.85 [23.27, 32.82]	0.50	0.148
Hypertension, n(%)	13 (40.6)	6 (37.5)	7 (43.8)	0.9	0.128
Chronic kidney disease, n(%)	13 (40.6)	7 (43.8)	6 (37.5)	0.9	0.128
Distance, median [IQR]	0.83 [0.61, 0.85]	0.83 [0.61, 0.85]	0.83 [0.61, 0.85]	0.82	0.017
Primary outcome, n(%)	23 (71.9)	11 (68.8)	12 (75.0)	0.9	0.139

The models 1, 2, and 3 allowed matching 19, 15, and 16 patients from each groups. The standardized mean difference (SMD) was improved in every component of each model, with regard to basal values. Finally, regardless of the model used (1, 2 or 3), the distance between

patients is highly similar between the sodium bicarbonate treated ($NaHCO_3$) group and the No-$NaHCO_3$ group. After matching, there is no difference in terms of proportion of patients who reached the primary outcome either. BMI: body mass index.

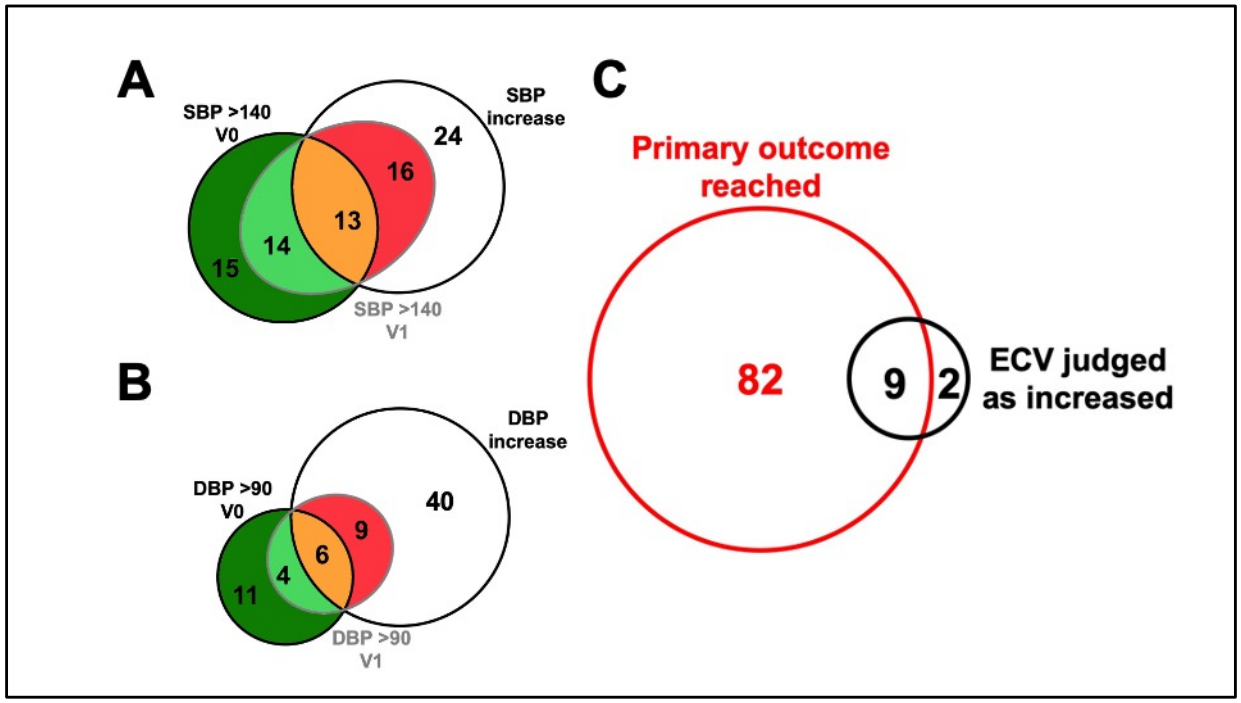

Figure S3. Meaningful components of the primary outcome. A. At inclusion (V0), 42 (33%) patients had a systolic blood pressure higher than 140 mmHg (SBP>140, bottom left black circle). Out of them, 15 (36%) did not increase their SBP (deep green area), while 14 (33%) remained steady (light green area), and 13 (31%) increased again (orange area). Among the 53 (42%) patients who increased their SBP (SBP increase, top right black circle), 24 (45%) did not reach the 140 mmHg cutoff value (white area), while 16 (30%) did (red area). Note that the sizes of the circles are proportional to the number of patients. **B.** At V0, 21 (17%) patients had a diastolic blood pressure higher than 90 mmHg (DBP>90, bottom left black circle). Out of them, 11 (52%) did not increase their DBP (deep green area), while 4 (19%) remained steady (light green area), and 6 (29%) increased again (orange area). Among the 55 (43%) patients who increased their DBP (DBP increase, top right black circle), 40 (75%) did not reach the 90 mmHg cutoff value (white area), while 9 (16%) did (red area). **C.** The ECV increase was assessed by a composite outcome: Primary outcome was composed by an increase of body weight (BW), of systolic blood pressure (SBP), of diastolic blood pressure (DBP) or a new-onset edema. The clinical appreciation by physicians (ECV increase) was in accordance in only 9 (10%) cases.