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Published in:
Journal of the American Society of Nephrology

DOI:
10.1681/ASN.2022020147

Effects of Short-Term Potassium Chloride Supplementation in Patients with CKD

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ABSTRACT

Background Observational studies suggest that adequate dietary potassium intake (90–120 mmol/day) may be renoprotective, but the effects of increasing dietary potassium and the risk of hyperkalemia are unknown.

Methods This is a prespecified analysis of the run-in phase of a clinical trial in which 191 patients (age 68±11 years, 74% males, 86% European ancestry, eGFR 31±9 ml/min per 1.73 m^2, 83% renin-angiotensin system inhibitors, 38% diabetes) were treated with 40 mmol potassium chloride (KCl) per day for 2 weeks.

Results KCl supplementation significantly increased urinary potassium excretion (72±24 to 107±29 mmol/day), plasma potassium (4.3±0.5 to 4.7±0.6 mmol/L), and plasma aldosterone (281 [198–431] to 351 [241–494] ng/L), but had no significant effect on urinary sodium excretion, plasma renin, BP, eGFR, or albuminuria. Furthermore, KCl supplementation increased plasma chloride (104±3 to 105±4 mmol/L) and reduced plasma bicarbonate (24.5±3.4 to 23.7±3.5 mmol/L) and urine pH (all P<0.001), but did not change urinary ammonium excretion. In total, 21 participants (11%) developed hyperkalemia (plasma potassium 5.9±0.4 mmol/L). They were older and had higher baseline plasma potassium.

Conclusions In patients with CKD stage G3b–4, increasing dietary potassium intake to recommended levels with potassium chloride supplementation raises plasma potassium by 0.4 mmol/L. This may result in hyperkalemia in older patients or those with higher baseline plasma potassium. Longer-term studies should address whether cardiorenal protection outweighs the risk of hyperkalemia.

Clinical trial number: NCT03253172

JASN 33: 1779–1789, 2022. doi: https://doi.org/10.1681/ASN.2022020147

CKD strongly increases the risk of hypertension, cardiovascular disease, and kidney failure.[1] Therefore, identifying novel approaches to reduce cardiovascular risk and CKD progression in patients with CKD is urgently needed. In addition to a healthy lifestyle, renin-angiotensin inhibitors, and emerging pharmacologic approaches,[2,3] dietary approaches represent a complementary, and perhaps underutilized, approach to reduce cardiovascular risk in patients with CKD.[4] With regard to dietary salt intake, high dietary sodium chloride intake is a recognized contributor to negative outcomes in patients with CKD.[5–8] Less studied are the negative effects of low dietary potassium intake, which may contribute to hypertension and kidney injury (kaliopenic nephropathy).[9,10] Previous studies that analyzed urinary potassium excretion in the general population[11,12] and in patients with CKD[13] showed that dietary potassium intake is approximately half of the dietary reference values of 90–120 mmol/day.[14,15] Furthermore, urinary potassium excretion is inversely associated with BP and cardiovascular risk.[11,16] Systematic reviews and meta-analyses of intervention studies with potassium supplementation illustrate its potential to reduce BP and the risk of stroke, especially in individuals with hypertension.[17,18] Similar findings were recently obtained with salt substitution,[19–21] the approach to partially replace the discretionary use of sodium chloride with potassium chloride (KCl).[22]

Several cohort studies showed that a higher urinary potassium excretion is also associated with better kidney outcomes or survival,[6,23–26] although this was not a universal finding,[27] and malnutrition and inflammation could be confounders. Because several of these studies included patients with CKD, this raises the possibility that patients with CKD might also benefit from increasing dietary potassium intake to recommended levels. However, it is unclear to what degree dietary potassium intake contributes to the plasma potassium concentration in patients with CKD.[28,29] In patients with CKD, high plasma potassium concentrations and overt hyperkalemia are also associated with an increased risk of cardiovascular morbidity and mortality.[30] Therefore, it is unknown how to weigh the risk of hyperkalemia in relation to the negative effects of low dietary potassium intake.[31] To address this, we initiated a randomized clinical trial in patients with CKD to study the long-term effects of potassium supplementation on kidney function.[13] This study includes an open-label run-in phase in which the participants receive 40 mmol KCl per day for 2 weeks alongside their regular diet. Here, we report the prespecified analysis of 191 patients who completed the run-in phase, with the aim to analyze the feasibility of potassium supplementation in CKD, its cardiorenal effects, and risk factors for hyperkalemia.

Significance Statement

Observational studies show health benefits from a higher potassium intake, but it is unknown if this is tolerated by patients with CKD. This 2-week study indicates that 40 mmol/day potassium chloride supplementation (the estimated gap between actual and adequate intake) increased plasma potassium by 0.4 mmol/L in 191 patients with CKD (eGFR 31 ml/min per 1.73 m^2, 83% on renin-angiotensin inhibitors). The majority of patients (89%) remained normokalemic. Higher baseline plasma potassium and older age were risk factors for developing hyperkalemia after supplementation. Potassium chloride supplementation did not lower office BP, but did cause a tendency toward hyperchloremic metabolic acidosis. Longer-term studies should determine whether the cardiorenal benefits of adequate dietary potassium intake outweigh the risk of hyperkalemia in patients with CKD.

METHODS

Participants

This is a prespecified analysis of the 2-week run-in phase of an ongoing placebo-controlled randomized clinical trial assessing the effects of potassium supplementation (KCl or potassium citrate) for 2 years on kidney function in patients with CKD.[13] The study was approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2017–226) and registered at ClinicalTrials.gov (NCT03253172). The ongoing trial is powered on the assumption that the intervention will cause a difference in eGFR of 3 ml/min per 1.73 m^2 in 2 years, which will require 399 randomizations.[13] Inclusion criteria are age ≥18 years, CKD due to any etiology stage G3b or G4 (eGFR 15–44 ml/min per 1.73 m^2 with or without albuminuria), with progressive eGFR decline (>2 ml/min per 1.73 m^2 per year in the previous 1–5 years), and hypertension. Patients with progressive eGFR decline were selected because the primary end point of the randomized clinical trial is a change in eGFR. Hypertension was defined as the use of antihypertensive medication and/or office BP>140/90 mm Hg. Main exclusion criteria are baseline plasma potassium >5.5 mmol/L, the use of mineralocorticoid receptor antagonists, potassium-sparing diuretics, double renin-angiotensin system blockade, calcineurin inhibitors, history of ventricular arrhythmia, and kidney transplantation. Eligible patients were recruited from the nephrology outpatient clinics of four university medical centers and affiliated regional hospitals. The study visits took place in the university medical centers.

Study Design

After baseline measurements, participants were treated for 2 weeks with KCl supplementation (two capsules, three times per day during meals) with a daily dose of 40 mmol (1.56 g) potassium and 40 mmol (1.42 g) chloride. The supplements were manufactured specifically for the trial (Laboratorium Medisan, Heerenveen, The Netherlands), and designed such that they were indistinguishable from the capsules containing placebo or potassium citrate that are used in the randomized phase of the trial. The supplements were taken with meals when insulin is usually present to facilitate a redistribution of potassium into cells.[32] The dose of 40 mmol/day was selected because this was assessed to be sufficient to increase dietary potassium intake to recommended levels, according to our previous analysis of urinary potassium excretion in patients with CKD stage G3b and G4 (n=3893).[13] Participants were instructed to maintain their regular diet. After 2 weeks, participants returned, and the measurements were repeated. Adherence was defined as usage of ≥75% of study supplements on the basis of pill counts. Patients who remained normokalemic, defined as a plasma potassium ≤5.5 mmol/L, were allowed to continue to the 2-year randomized phase of the study.[13]

Received February 7, 2022. Accepted March 2, 2022.

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See related editorial "Searching for the Risk-Benefitc Profile of Higher Potassium Intake in CKD: *Primum Non Nocere*," on pages 1633–1635, and perspective, "The Highs and Lows of Potassium Intake in CKD—Does One Size Fit All?," on pages 1638–1640.

Published online ahead of print. Publication date available at www.jasn.org.

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When patients developed hyperkalemia after the run-in phase, management was on the basis of the degree of hyperkalemia. If plasma potassium was ≤6.0 mmol/L, potassium supplements were discontinued and plasma potassium was checked a few days later. If plasma potassium was >6.0 mmol/L, hyperkalemia was treated according to national guidelines with temporary discontinuation of renin-angiotensin inhibitors and the use of potassium exchange resins and/or sodium bicarbonate.

Measurements

Demographic data were collected including self-reported ethnicity. Plasma potassium, pH, and bicarbonate were measured in whole-blood on a blood gas analyzer (ABL90 Series Radiometer), because it is the most direct method and prevents pseudohyperkalemia.[33] Other measures to prevent pseudohyperkalemia were the instruction to avoid fist clenching and routine monitoring of the hemolysis index. Plasma and urine creatinine, sodium, and chloride were measured on an automated Cobas 8000 chemistry platform (Roche Diagnostics). eGFR was calculated by the CKD Epidemiology Collaboration equation, with use of the race coefficient.[34] Hemoglobin and hematocrit were determined in whole blood from EDTA tubes and were analyzed on a Sysmex XN900 (Sysmex). Plasma renin (Cisbio, Codolet, France) and aldosterone (Demeditec, Kiel, Germany) were measured by radioimmunometric assays. Next, 24-hour urine was collected on the day before the study visits. Accurate collection was verified by urine creatinine excretion in relation to age, sex, and body mass index.[35] Urine ammonium and citrate were measured using the Berthelot method[36] and an enzymatic method (Instruchemie, Delfzijl, The Netherlands), respectively. Urine pH was measured using a high-resolution pH meter (HI15221, Hanna Instruments, Nieuwegein, The Netherlands). Office BP was measured three times with an automated device at the nondominant arm in seated position after a 10-minute rest. The first measurement was discarded, and the mean of the second and third measurement was used.[37] At baseline, ambulatory (24-hour) BP was also measured at the nondominant arm using the 90217 A Ultralite device (Spacelabs Healthcare). This device measures BP every 15 minutes during the day and every 30 minutes during the night. When ≥70% of measurements were successful, the data were included for analysis.[37]

Statistics

This prespecified analysis was performed after 191 patients had completed the run-in phase, because, on the basis of previous literature, this number of patients should provide sufficient power to detect a difference in urinary potassium excretion, plasma potassium, and BP.[17,18,38] Data are reported as mean±SD for normally distributed data and as median (interquartile range) for non-normally distributed data. Data with a non-normal distribution were log-transformed, after which normal distribution was confirmed before analysis. Data from baseline and 2-week visits were compared using a paired *t* test. Multivariable linear regression analysis was used to identify baseline characteristics associated with the change in plasma potassium after KCl supplementation. The characteristics of patients who did or did not develop hyperkalemia after KCl supplementation were compared using an independent *t* test or chi-squared test. Logistic regression was used to analyze which characteristics were independently associated with the development of hyperkalemia. Variables with a biologically plausible relationship with a rise in plasma potassium or hyperkalemia were included in the multivariable analyses. In the multivariable logistic regression only six variables were included in the model because of the limited number of events. Data on plasma potassium and eGFR were complete for all participants. Data with 0.5%–7% of missing measurements were imputed using the multiple imputation tool in SPSS. Ambulatory BP (15% missing data because the measurement was refused by the participant or did not fulfill quality criteria), venous pH (51% missing data), and urine citrate (34% measurements below detection limit) were not imputed. All data were analyzed using SPSS (IBM, version 25). $P \leq 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

The run-in phase was started by 240 patients and completed by 205 patients (86%, Supplemental Figure 1). During the run-in phase, 35 patients discontinued (15%) because of gastrointestinal symptoms (22 patients), pill or trial burden (eight patients), and other reasons (two screen failures, two worsening comorbidities, one other symptoms). None of the patients reported symptoms of hyperkalemia, such as muscle weakness. In total, 14 patients were excluded because of nonadherence (6%). Data of 191 participants were used for analysis. Participants were aged 68±11 years, 141 (74%) were male, and eGFR was 31±9 ml/min per 1.73 m^2 (Table 1). In the majority of participants, hypertension, diabetes mellitus, and/or renovascular disease were considered the primary cause of CKD. A subset of participants had a specific cause of CKD, including polycystic kidney disease (n=24), glomerular disease (n=14), or a urological cause (n=6); nine patients had a previous history of nephrectomy. Baseline ambulatory systolic and diastolic BP were 127±15 and 74±9 mm Hg, respectively. The participants used 2.3±1.1 antihypertensive drugs, including 158 (83%) participants who used renin-angiotensin inhibitors. Four patients used a sodium-glucose cotransporter 2 inhibitor.

Effects of KCl Supplementation on Electrolyte and Volume Homeostasis

Urine potassium excretion increased from 72±24 to 107±29 mmol/day after 2 weeks of KCl supplementation (P<0.001,

Table 1. Baseline characteristics

Characteristic	*n*=191
Age, yr	68±11
Male sex, *n* (%)	141 (74)
Body mass index, kg/m^2	28.8±4.4
Self-reported ethnicity	
Asian	15 (8)
Black	11 (6)
White	165 (86)
Baseline eGFR, ml/min per 1.73 m^2	31±9
eGFR decline, ml/min per 1.73 m^2 per year	3.4 (2.7–4.8)
Diabetes, *n* (%)	72 (38)
Hypercholesterolemia, *n* (%)[a]	126 (66)
Cardiovascular and/ or cerebrovascular disease, *n* (%)[b]	80 (42)
24-hour systolic BP, mm Hg	127±15
24-hour diastolic BP, mm Hg	74±8
24-hour heart rate, beats/min	69±10
Number of antihypertensive medications, *n* (%)	2.3±1.1
Renin-angiotensin inhibitor	158 (83)
Calcium channel blocker	100 (52)
Loop and/or thiazide diuretic	82 (43)
Beta-blocker	77 (40)
Alpha-blocker	14 (7)
Sodium-glucose cotransporter 2 inhibitor	4 (2)

[a]Defined as the use of statins.
[b]Defined as a history of previous cardiovascular or cerebrovascular events.

Figure 1A). Urine sodium excretion remained stable (154±62 to 152±62 mmol/day, P=0.57, Figure 1B). Plasma potassium increased from 4.3±0.5 to 4.7±0.6 mmol/L (range −0.6 to 2.1 mmol/L, P<0.001, Figure 1C). KCl supplementation increased plasma aldosterone from 281 (198–431) to 351 (241–494) ng/L (P<0.001, Figure 1D), but had no effect on measures of extracellular fluid volume including plasma renin (34 [20–73] ng/L to 37 [18–94] ng/L, P=0.46) or hematocrit (stable at 0.40±0.05 L/L, Figure 1, E and F, P=0.69). In 28 participants (15%), plasma potassium did not increase. The increase in urine potassium excretion of these patients, however, was similar compared with the participants in whom plasma potassium did increase (change in urine potassium 39±24 versus 34±19 mmol/day, P=0.23, Supplemental Figure 2), suggesting adequate adherence. Baseline characteristics that were independently associated with a larger increase in plasma potassium after KCl supplementation were the use of renin-angiotensin inhibitors and older age (Figure 2, Supplemental Table 1, Supplemental Figures 3 and 4). A lower body weight or body mass index was not associated with a larger increase in plasma potassium after KCl supplementation (data not shown). Conversely, factors that were independently associated with a smaller increase in plasma potassium were diuretic use and baseline levels of plasma potassium and plasma bicarbonate (Figure 2, Supplemental Table 1, Supplemental Figures 3 and 4). Addition of ethnicity to the model did not materially change the results (Supplemental Figure 5).

Effects of KCl Supplementation on Acid-Base Balance

KCl supplementation was associated with a decrease in plasma bicarbonate (24.5±3.4 to 23.7±3.5 mmol/L) and increase in plasma chloride (104±3 to 105±4 mmol/L, both P<0.001, Figure 3, A and B). Urine chloride increased from 151±61 mmol/day at baseline to 186±64 mmol/day at follow-up (Figure 3C, P<0.001). In the subset of patients in whom venous pH was measured (n=94), this decreased from 7.36±0.03 to 7.34±0.04 (P<0.001, Figure 3D). Urine ammonium excretion did not change significantly (18 [12–26] to 16 [11–24] mmol/day, P=0.22, Figure 3E), whereas urine citrate increased (1.19 [0.77–1.75] to 1.20 [0.86–1.81] mmol/day, P=0.06, Figure 3F) and urine pH decreased (5.90 [5.52–6.50] to 5.74 [5.36–6.33], P=0.01, Figure 3G).

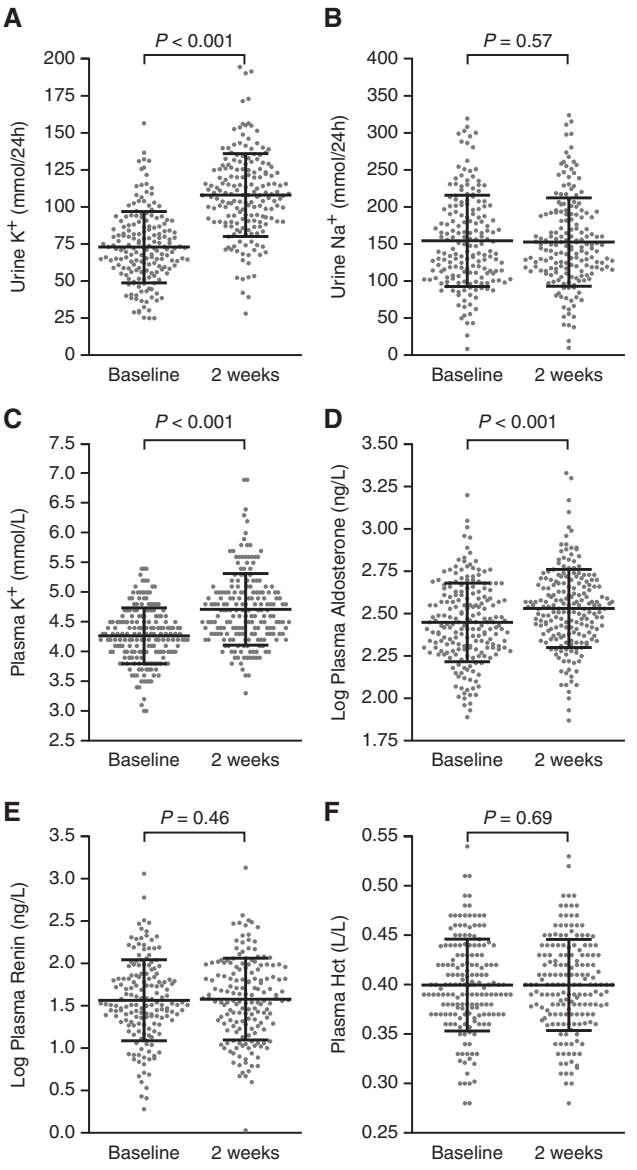

Figure 1. Effects of 40 mmol KCl supplementation for 2 weeks. The effects are shown on (A) urine potassium (K^+) excretion, (B) urine sodium (Na^+) excretion, (C) plasma potassium (K^+), (D) plasma aldosterone, (E) plasma renin, and (F) hematocrit (Hct). Data before and after KCl supplementation are shown in 191 patients. Data were analyzed by paired *t* test.

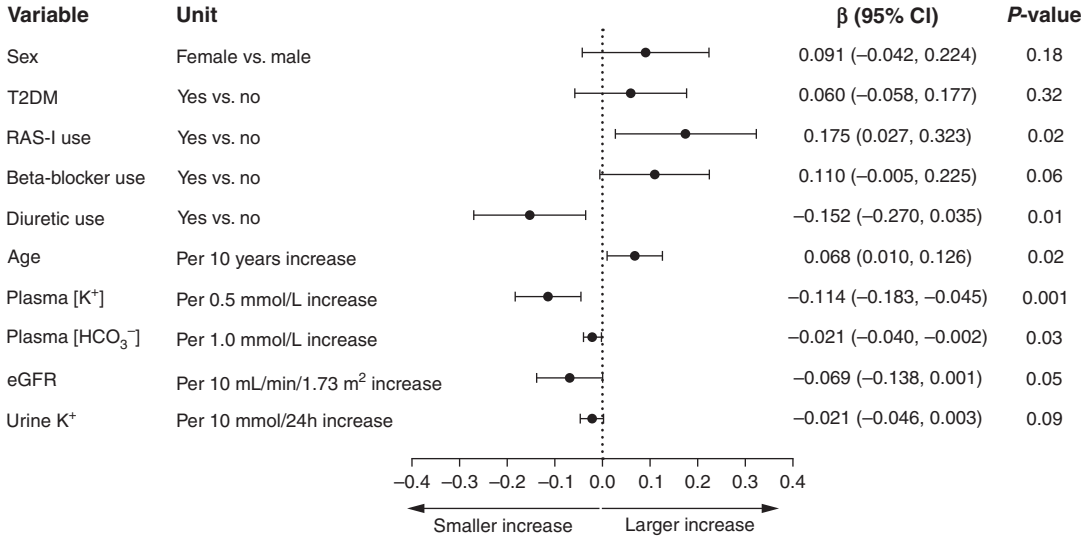

Figure 2. Baseline characteristics that were associated with a smaller or larger increase in plasma potassium after KCl supplementation for 2 weeks. Data were analyzed by multivariable linear regression. See Supplemental Table 1 for univariable analysis. T2DM, type 2 diabetes mellitus; RAS-I, renin-angiotensin inhibitor; HCO_3^-, bicarbonate; K^+, potassium.

Risk of Hyperkalemia after KCl Supplementation

In total, 21 participants developed hyperkalemia (11%). In these patients, average plasma potassium increased from 4.9±0.4 to 5.9±0.4 mmol/L (range 5.6–6.9 mmol/L). Patients who developed hyperkalemia after KCl supplementation were older, had higher baseline plasma potassium, lower baseline plasma bicarbonate, lower eGFR, and used diuretics less often (Table 2). On univariable analysis, higher age and baseline plasma potassium increased the risk of hyperkalemia, whereas higher plasma bicarbonate, eGFR, and diuretic use decreased this risk (Figure 4A). On multivariable analysis, only older age and a higher baseline plasma potassium were independently associated with the risk of hyperkalemia after KCl supplementation (Figure 4B). Patients who developed hyperkalemia had a smaller increase in urine potassium excretion compared with those who remained normokalemic (24±24 versus 36±20 mmol/day, $P=0.02$, Supplemental Figure 6). In participants with mild hyperkalemia (plasma potassium 5.6–6.0 mmol/L, $n=16$) the only intervention was discontinuation of KCl supplementation. In participants with a plasma potassium between 6.1 and 6.9 mmol/L ($n=5$), electrocardiograms were performed, which showed no signs of hyperkalemia. In these participants, hyperkalemia was treated by discontinuation of KCl supplementation, sodium polystyrene sulfonate, sodium bicarbonate, and/or temporary discontinuation of renin-angiotensin inhibitors (Supplemental Table 2). Plasma potassium normalized on follow-up in all patients, after which renin-angiotensin inhibitors were resumed.

Effects of KCl Supplementation on Kidney Function and BP

KCl supplementation had no significant effect on eGFR (stable at 31±9 ml/min per 1.73 m^2, Figure 5A) or albuminuria (0.17 [0.04–0.83] to 0.21 [0.04–0.80] g/day, Figure 5B, $P=0.63$). Similarly, KCl supplementation had no significant effect on office systolic or diastolic BP (from 133±16 to 133±17 mm Hg and 78±11 to 78±11 mm Hg, Figure 5, C and D) or heart rate (70±11 to 71±13 bpm, $P=0.08$, Figure 5E). A higher baseline office systolic BP correlated with a greater reduction in office systolic BP in response to KCl supplementation (Supplemental Figure 7A). However, this probably reflects regression to the mean, because baseline 24-hour systolic BP did not show this correlation (Supplemental Figure 7B).[39] Baseline values for urine sodium and potassium excretion and eGFR did not correlate with the BP response to KCl supplementation (Supplemental Figure 7, C–E).

DISCUSSION

This study presents the changes observed in a cohort of patients with CKD exposed to short-term KCl supplementation. With a supplementation of 40 mmol KCl per day (the amount of potassium in approximately four bananas) the average urine potassium excretion increased from 72 to 107 mmol/day. This translates to a dietary intake of approximately 120 mmol/day when considering approximately 10% fecal potassium loss[40] and is therefore at the higher end of the current dietary reference values (90–120 mmol/day).[14,15] Potassium supplementation was associated with a rise in the plasma potassium concentration of on average 0.4 mmol/L. The majority of patients remained normokalemic, despite the prevalent use of renin-angiotensin inhibitors. Older age and higher baseline plasma potassium were independent risk factors for developing hyperkalemia after KCl supplementation. KCl supplementation did not reduce office BP, although it

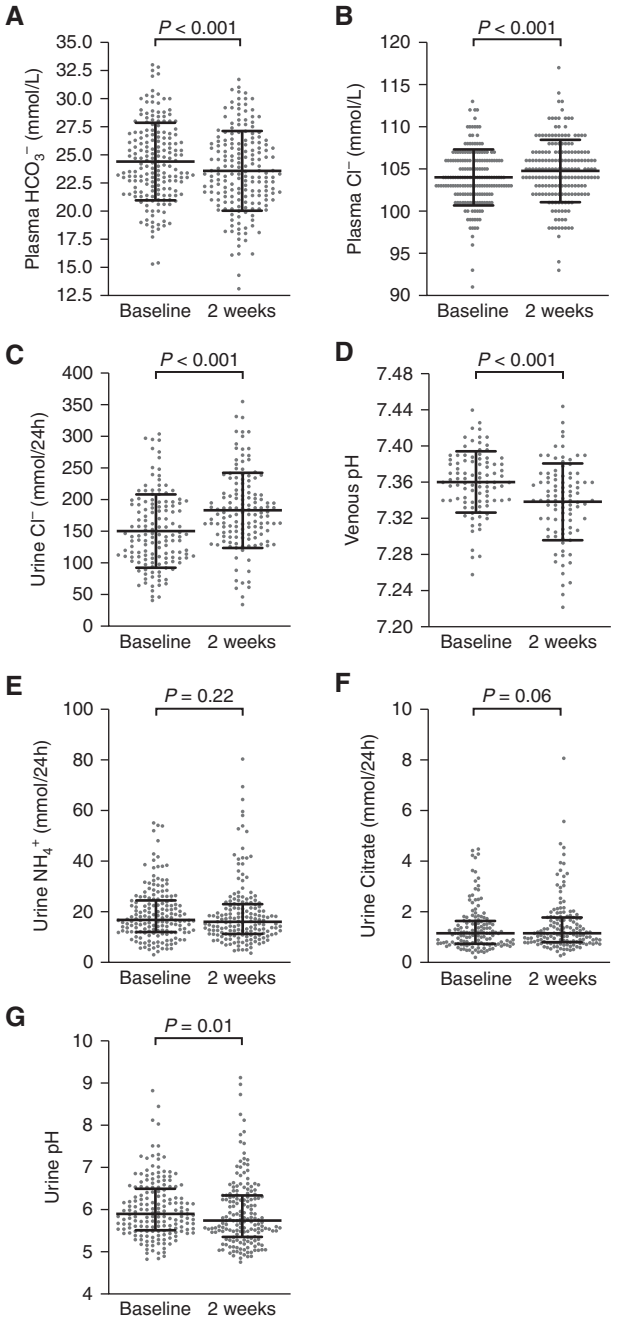

Figure 3. Effects of 40 mmol KCl supplementation for 2 weeks. The effects are shown on (A) plasma bicarbonate (HCO_3^-), (B) plasma chloride (Cl^-), (C) venous pH, (D) urine ammonium (NH_4^+) and (E) citrate excretion, and (G) urine pH. Data before and after KCl supplementation are shown in 191 patients (A), (B), (D), (G), 94 patients (C), and 126 patients (E). Data were analyzed by paired *t* test.

did cause a tendency toward hyperchloremic metabolic acidosis. The 2-year randomized phase of our study, which also includes potassium citrate and placebo, should inform whether the proposed cardiorenal benefits of increasing potassium intake outweigh the risks of hyperkalemia.[13]

A systematic review and meta-analysis of randomized controlled trials in people with normal kidney function using potassium supplementation (average increase in urinary potassium excretion 46 mmol/day) showed a small but significant increase in plasma potassium of 0.14 mmol/L.[38] On the basis of these previous data, it appears that potassium supplementation causes a greater rise in plasma potassium in patients with CKD than in subjects with normal kidney function. A previous study in which the response to 50 mmol KCl for 5 days was compared in six healthy subjects to ten patients with CKD reached a similar conclusion.[41] We identified several baseline characteristics that independently contributed to the rise in plasma potassium after KCl supplementation, including age, use of renin-angiotensin inhibitors, diuretics, and beta-blockers, and baseline levels of plasma potassium, bicarbonate, and eGFR. Of note, a higher baseline potassium was associated with a smaller increase in plasma potassium after KCl supplementation, which we explain by regression to the mean. Most of these factors also contributed to the development of hyperkalemia, although only age and baseline plasma potassium were identified as independent associations. Recently, higher baseline plasma potassium and lower eGFR were also identified as risk factors for hyperkalemia with the use of finerenone, whereas diuretic use was protective.[42] Our results suggest changes in plasma potassium with KCl supplementation are mostly driven by factors regulating tubular potassium secretion and acid-base balance.[43] The identification of these factors may help to individualize potassium supplementation in patients with CKD. Of note, potassium supplementation likely has a larger effect on plasma potassium than potassium in food because the bioavailability of potassium from natural foods is lower, and because potassium-rich foods cause a tendency toward metabolic alkalosis.[28,44,45] However, the effects of KCl supplementation are still relevant because salt substitution is emerging as public health intervention.[46]

We observed no effect of KCl supplementation on office BP. This observation is different from previous studies showing that potassium supplementation usually reduced BP in patients with hypertension.[18] However, our observation is in agreement with a recent randomized feeding trial (40 versus 100 mmol potassium/day) in patients with CKD stage G3, which did not observe significant differences in 24-hour BP.[47] There may be several explanations for why potassium supplementation did not reduce BP in our patients with CKD. First, ambulatory BP was well controlled in our cohort, leaving little room for further BP reduction. Second, the relationship between urinary potassium excretion and BP follows a U-shaped relationship, suggesting a "therapeutic window." Indeed, BP reduction is attenuated when potassium supplementation increases urinary potassium excretion ≥30 mmol/day, whereas BP even increases with higher supplementation.[18,48] Third, the fact that we did not observe a rise in plasma renin suggests that KCl supplementation failed to

Table 2. Comparison between patients who remained normokalemic and who developed hyperkalemia after KCl supplementation

Characteristic	Normokalemia (*n*=170)	Hyperkalemia (*n*=21)	*P* Value
Female sex, *n* (%)	44 (26)	6 (29)	0.79
Diabetes mellitus, *n* (%)	61 (36)	11 (52)	0.14
Renin-angiotensin inhibitor use, *n* (%)	139 (82)	19 (90)	0.32
Beta-blocker use, *n* (%)	66 (39)	11 (52)	0.23
Diuretic use, *n* (%)	78 (46)	4 (19)	0.02
Age, yr	67±11	74±8	0.005
Baseline plasma potassium, mmol/L	4.2±0.4	4.9±0.4	<0.001
Baseline plasma bicarbonate, mmol/L	24.7±3.4	22.5±3.5	0.007
Baseline eGFR, ml/min per 1.73 m^2	32±8	24±8	<0.001
Baseline urine potassium excretion, mmol/day	73±25	65±16	0.11

induce potassium-induced natriuresis. In healthy males, 90 mmol KCl did increase plasma renin and angiotensin II, likely reflecting urinary sodium chloride loss with secondary activation of the renin-angiotensin system.[49] Potassium-induced natriuresis is one of the proposed mechanisms by which potassium reduces BP, an effect that is mediated by potassium's inhibition of the thiazide-sensitive sodium-chloride cotransporter.[31,50–52] Finally, the BP-lowering effect of potassium may have been offset by the increase in plasma aldosterone or the development of hyperchloremic metabolic acidosis. Patients with CKD may be more prone to the hypertensive effects of aldosterone in response to a rise in plasma potassium than healthy subjects.[53,54] Similarly, both hyperchloremia and metabolic acidosis can increase BP in CKD.[55–57]

KCl supplementation caused a clear tendency toward hyperchloremic metabolic acidosis. In previous studies in people with normal kidney function, KCl supplementation (in the range of 40–100 mmol/day) did not reduce plasma bicarbonate.[58–60] This suggests patients with CKD are more susceptible to the acidifying effect of dietary chloride, although the effects we observed were still modest. KCl-induced acidosis has been observed previously in experimental settings and has been attributed to a form of renal tubular acidosis.[61] Recent data indicate hyperkalemic (type IV) renal tubular acidosis is caused by a direct inhibitory effect of plasma potassium on kidney ammoniagenesis.[62] We also observed that urinary ammonium excretion failed to increase in response to the development of acidosis, whereas

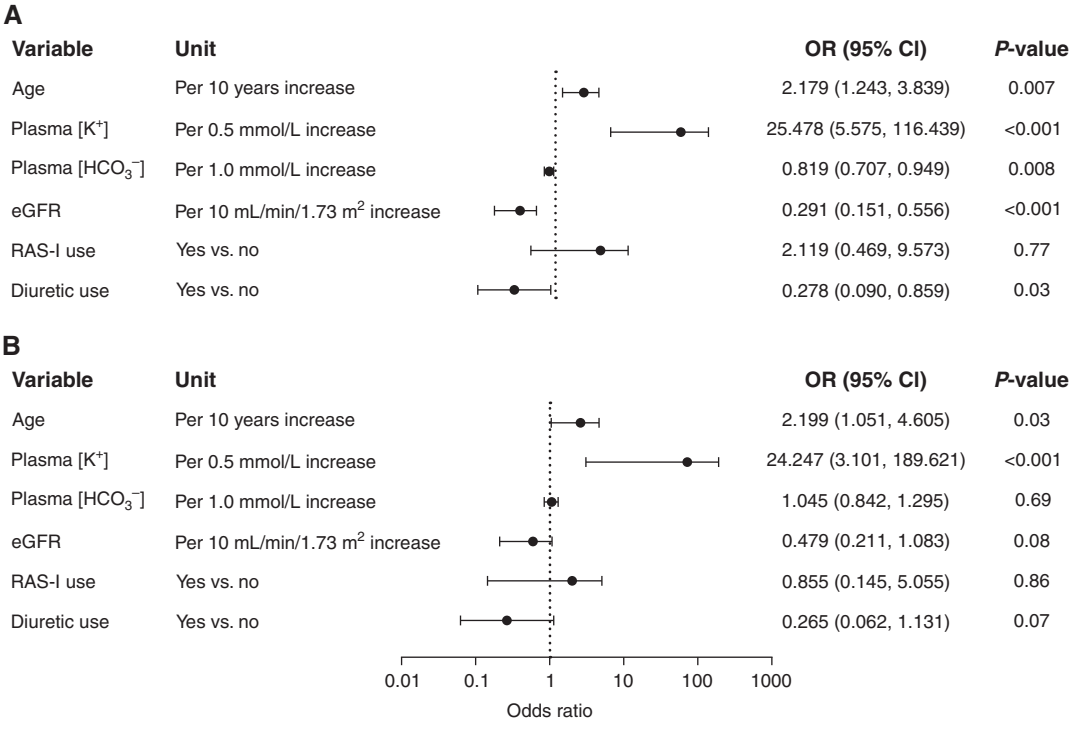

Figure 4. Baseline characteristics associated with the development of hyperkalemia after KCl supplementation for 2 weeks. Data were analyzed by (A) univariable and (B) multivariable logistic regression.

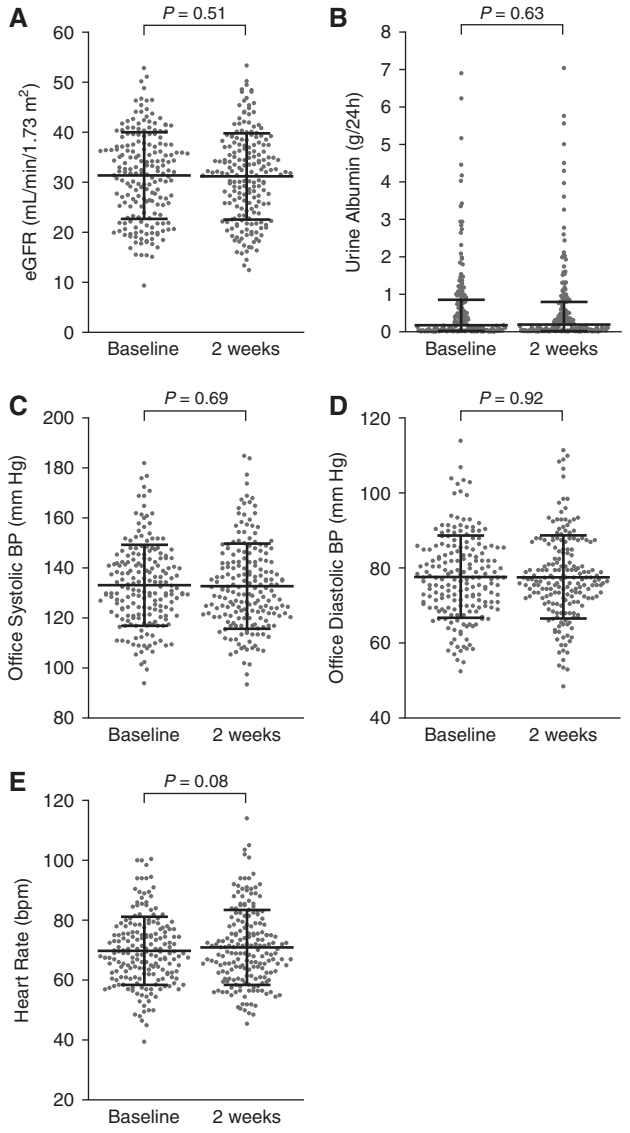

Figure 5. Effects of 40 mmol KCl supplementation for 2 weeks. The effects are shown on (A) eGFR, (B) urine albumin excretion, (C) office systolic BP, (D) office diastolic BP, and (E) heart rate. Data before and after KCl supplementation are shown in 191 patients. Data were analyzed by paired *t* test.

urine pH decreased appropriately. Because metabolic acidosis is clearly recognized as a risk factor for CKD progression and outcomes,[63,64] our data suggest potassium supplementation with other anions such as citrate or bicarbonate may be preferable in patients with CKD. Of interest, a trend toward an increase in urine citrate excretion was observed, which is a recognized effect of KCl supplementation.[65]

Our study has a number of limitations. First, this was an uncontrolled, single-arm, open-label intervention study. This study design has inherent limitation, although some of these limitations may have been overcome by the large sample size. Second, ambulatory BP and body weight were not measured at the second study visit, which precludes a more detailed analysis of effects on BP and volume status. Finally, urinary potassium excretion was higher in our patients than in a previous cohort of patients with CKD stage G3b and G4 (72 versus 50 mmol/day),[13] which may have limited effect size and generalizability. Other factors that may have limited generalizability were subject refusal, premature drop-outs (largely because of gastrointestinal symptoms, likely related to the fact that the supplements were not slow release), and the inclusion of primarily male participants.

In summary, in patients with CKD stage G3b–4 who were mostly on renin-angiotensin inhibitors, increasing dietary potassium intake to recommended levels with KCl supplementation raises plasma potassium by 0.4 mmol/L. Although the majority of patients remained normokalemic, hyperkalemia may develop especially in older patients or those with higher baseline plasma potassium. In addition, the anticipated BP lowering effect of KCl supplementation was not observed, whereas it did cause a tendency toward hyperchloremic metabolic acidosis. Longer-term studies should address if the proposed cardiorenal protection of adequate potassium intake outweighs the risk of hyperkalemia in patients with CKD.

DISCLOSURES

E. Hoorn reports receiving research funding from Aurinia; reports receiving honoraria from UpToDate; and reports having an advisory or leadership role on the editorial boards of the *American Journal of Physiology and Renal Physiology*, *Journal of the American Society of Nephrology*, and the *Journal of Nephrology*; and reports being a Board Member of the ERA Working Group on Inherited Kidney Diseases, and a Board Member of the Dutch Federation of Nephrology. F. Geurts reports receiving research funding from Novo Nordisk Foundation (NNF18OC0031686). J. Rotmans reports having an advisory or leadership role on the Advisory Board Neokidney; and reports having other interests or relationships as the Chair Thematic Working Group Vascular Tissue Engineering at TERMIS, president-elect Vascular Access Society, and Member guideline committee Dutch Society of Nephrology. L. Vogt reports having consultancy agreements with AstraZeneca, The Netherlands, ISIS Pharmaceuticals, Inc. Carlsbad, CA, and Vifor Pharma, The Netherlands; and reports having an advisory or leadership role as Associate Editor of BMC Nephrology. M. De Borst reports having consultancy agreements with Astellas, AstraZeneca, Kyowa Kirin, Pharmacosmos, Sanofi Genzyme, and Vifor Pharma; reports receiving research funding from Sanofi Genzyme, and Vifor Pharma; and reports having an advisory or leadership role as Associate Editor of Nephrology Dialysis Transplantation. All remaining authors have nothing to disclose.

FUNDING

This study was supported by the Dutch Kidney Foundation (grants CP16.01 and 21OK+013).

ACKNOWLEDGMENTS

The authors thank all of the patients who participated in this study and all of the nephrologists who helped with the inclusion of patients. The authors also thank the research nurses M. Cadogan, E. Kreukniet, M. Boer-Verschragen, B. Nome, and J. Sierra.

AUTHOR CONTRIBUTIONS

M. de Borst, E. Hoorn, J. Rotmans, and L. Vogt conceptualized the study; F. Geurts, M. Gritter, E. Hoorn, M. Wieers, R. Wouda, and S. Yeung were responsible for the data curation; M. de Ridder, F. Geurts, M. Gritter, E. Hoorn, and R. Wouda were responsible for the formal analysis; M. de Borst, E. Hoorn, J. Rotmans, and L. Vogt were responsible for the funding acquisition; F. Geurts, M. Gritter, E. Hoorn, C. Ramakers, M. Wieers, R. Wouda, and S. Yeung were responsible for the investigation; M. de Ridder, F. Geurts, M. Gritter, E. Hoorn, C. Ramakers, and S. Yeung were responsible for the methodology; M. de Borst, E. Hoorn, J. Rotmans, and L. Vogt were responsible for the project administration; M. de Borst, M. de Ridder, E. Hoorn, J. Rotmans, and L. Vogt provided supervision; M. de Borst, E. Hoorn, C. Ramakers, J. Rotmans, and L. Vogt were responsible for the resources; M. de Ridder, M. Gritter, R. Wouda, and S. Yeung were responsible for the validation; M. Gritter and E. Hoorn were responsible for the visualization; M. Gritter and E. Hoorn wrote the original draft; and M. de Borst, M. de Ridder, F. Geurts, E. Hoorn, C. Ramakers, J. Rotmans, L. Vogt, M. Wieers, R. Wouda, and S. Yeung reviewed and edited the manuscript.

DATA SHARING STATEMENT

All data used in this study are available in this article.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2022020147/-/DCSupplemental.

Supplemental Table 1. Baseline characteristics associated with a smaller or larger increase in plasma potassium after KCl supplementation.

Supplemental Table 2. Treatment of participants with plasma potassium >6.0 mmol/L after KCl supplementation.

Supplemental Figure 1. Flowchart of screened and included patients.

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Supplemental Figure 4. Correlations between the change in plasma potassium (K^+) after KCl supplementation with age and selected baseline laboratory measurements.

Supplemental Figure 5. Exploratory analysis of baseline characteristics that were associated with a smaller or lager increase in plasma potassium after KCl supplementation for 2 weeks with the addition of ethnicity.

Supplemental Figure 6. Change in urine potassium (K^+) excretion in patients with or without hyperkalemia after KCl supplementation.

Supplemental Figure 7. Correlations between the change in office systolic BP with baseline BP, urinary sodium (Na^+), and potassium (K^+) excretion, and eGFR.

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Supplementary material – Gritter *et al.*

Table S1: Baseline characteristics associated with a smaller or lager increase in plasma potassium after KCl supplementation.

Table S2: Treatment of participants with plasma potassium > 6.0 mmol/L after KCl supplementation.

Figure S1: Flowchart of screened and included patients.

Figure S2: Change in urine potassium (K^+) excretion in participants with or without an increase in plasma K^+ after KCl supplementation.

Figure S3: Change in plasma potassium (K^+) after KCl supplementation classified by sex, presence of diabetes mellitus, and the use of renin-angiotensin inhibitors, beta blockers, or diuretics.

Figure S4: Correlations between the change in plasma potassium (K^+) after KCl supplementation with age and selected baseline laboratory measurements.

Figure S5: Exploratory analysis of baseline characteristics that were associated with a smaller or lager increase in plasma potassium after KCl supplementation for two weeks with the addition of ethnicity.

Figure S6: Change in urine potassium (K^+) excretion in patients with or without hyperkalemia after KCl supplementation.

Figure S7: Correlations between the change in office systolic blood pressure (BP) with baseline blood pressure, urinary sodium (Na^+) and potassium (K^+) excretion, and estimated glomerular filtration rate (eGFR).

Table S1: Baseline characteristics associated with a smaller or lager increase in plasma potassium after KCl supplementation.

Variable	**Univariable regression**		**Multivariable regression**	
	β (95% CI)	***P***	**β (95% CI)**	***P***
Female sex	0.112 (-0.022, 0.246)	0.100	0.091 (-0.042, 0.224)	0.182
Type 2 diabetes mellitus	0.118 (-0.003, 0.239)	0.056	0.060 (-0.058, 0.177)	0.320
Renin-angiotensin system inhibitor use	0.079 (-0.077, 0.235)	0.322	0.175 (0.027, 0.323)	0.021
Beta blocker use	0.147 (0.028, 0.266)	0.015	0.110 (-0.005, 0.225)	0.062
Diuretic use	-0.110 (-0.229, 0.008)	0.068	-0.152 (-0.270, -0.035)	0.011
Age, per 10 years increase	0.069 (0.015, 0.123)	0.013	0.068 (0.010, 0.126)	0.021
Baseline plasma potassium, per 0.5 mmol/L increase	-0.036 (-0.098, 0.027)	0.264	-0.114 (-0.183, -0.045)	0.001
Baseline plasma bicarbonate, mmol/L	-0.022 (-0.039, -0.005)	0.011	-0.021 (-0.040, -0.002)	0.033
Baseline eGFR, per 10 mL/min/1.73 m^2 increase	-0.090 (-0.157, -0.023)	0.008	-0.069 (-0.138, 0.001)	0.053
Baseline urine potassium, per 10 mmol/day increase	-0.041 (-0.064, -0.017)	0.001	-0.021 (-0.046, 0.003)	0.089

Table S2: Treatment of participants with plasma potassium > 6.0 mmol/L after KCl supplementation.

Participant	**Plasma potassium after 2 weeks KCl supplementation**	**Treatment**	**Plasma potassium at follow-up**
5035	6.2 mmol/L	Sodium bicarbonate 3 x 1 g/day for 2 days	4.9 mmol/L
7038	6.4 mmol/L	Sodium polystyrene sulfonate 2 x 30 g/day for 3 days; temporary discontinuation of losartan	3.9 mmol/L
7041	6.9 mmol/L	Sodium polystyrene sulfonate 2 x 30 g/day for 3 days; temporary discontinuation of irbesartan	4.3 mmol/L
8069	6.3 mmol/L	Sodium polystyrene sulfonate 1 x 15 g/day for 3 days; temporary discontinuation of lisinopril	4.9 mmol/L
8103	6.9 mmol/L	Sodium polystyrene sulfonate 2 x 30 g/day; temporary discontinuation of lisinopril	3.9 mmol/L

Figure S1: Flowchart of screened and included patients.

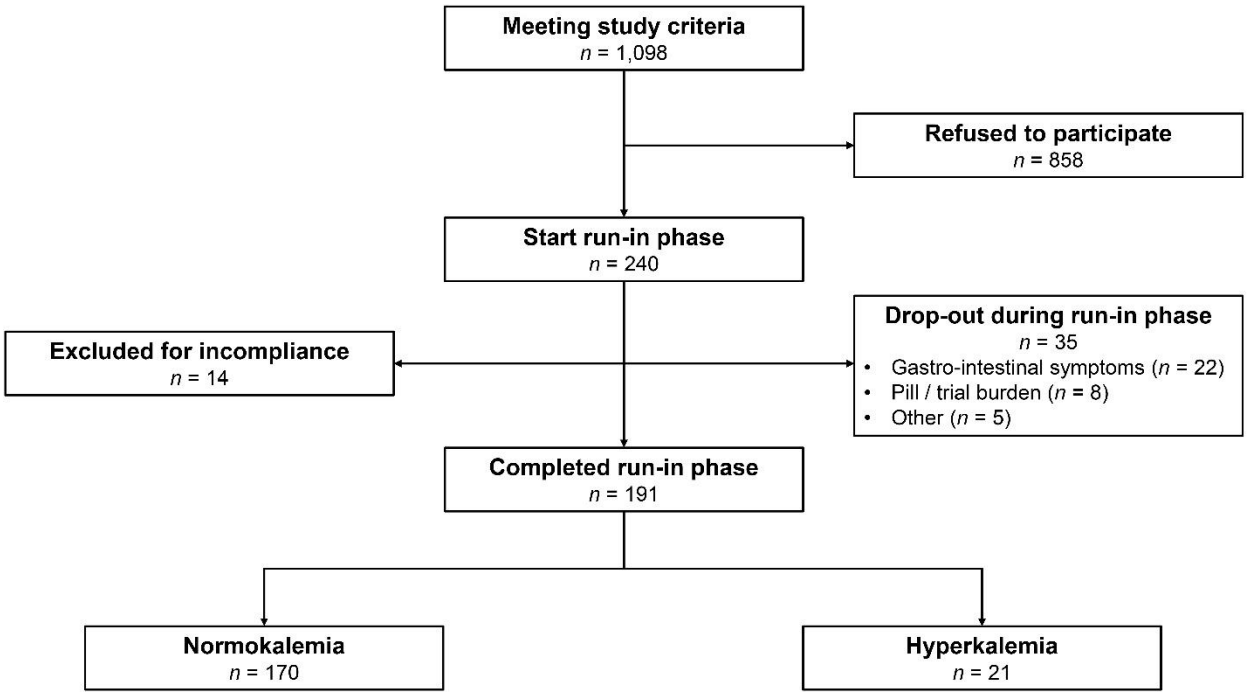


Figure S2: Change in urine potassium (K^+) excretion in participants with or without an increase in plasma K^+ concentration after KCl supplementation.

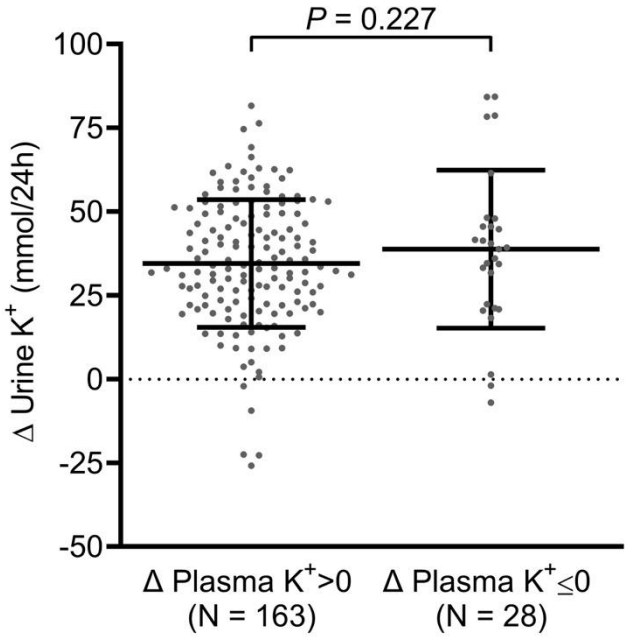
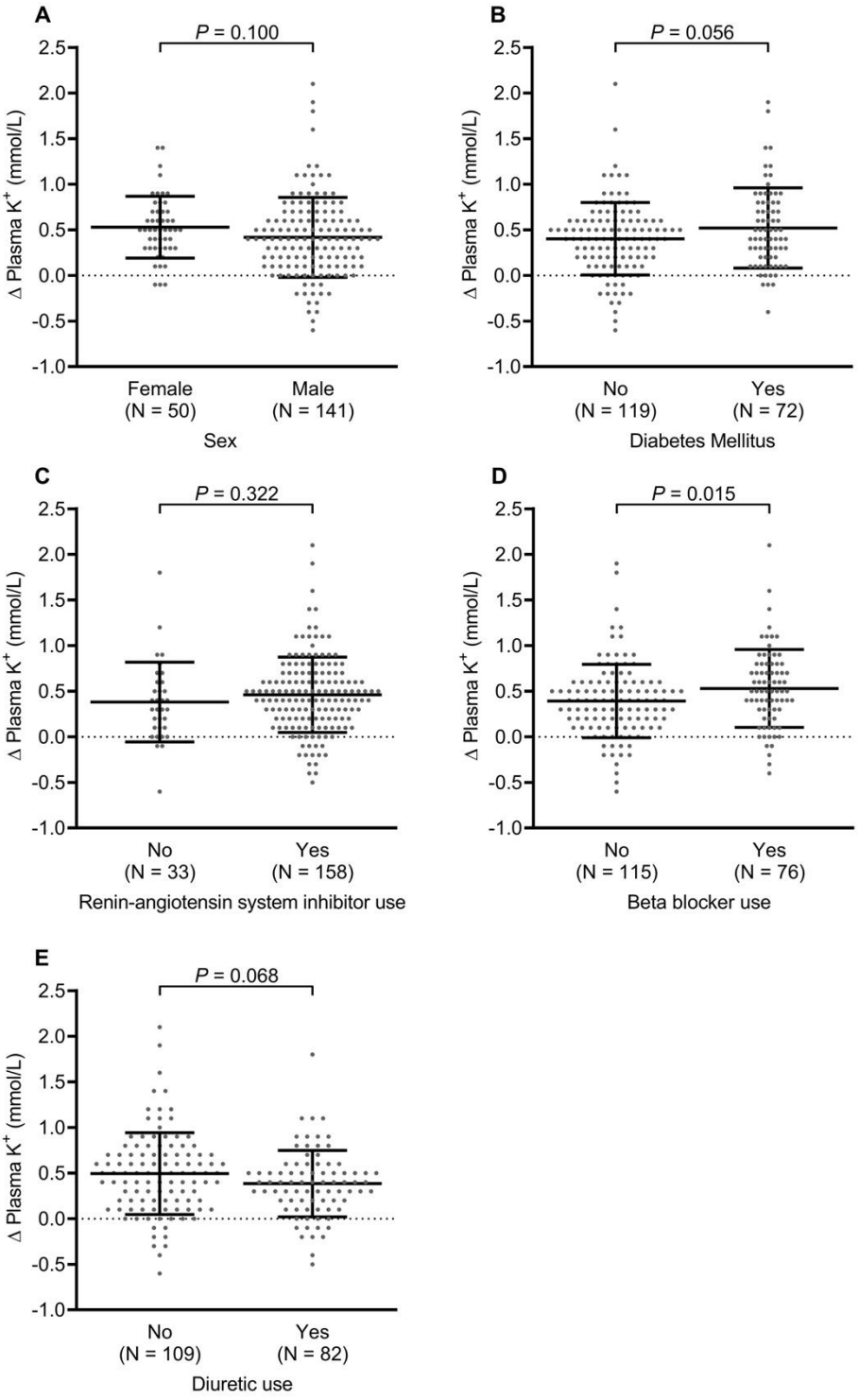


Figure S3: Change in plasma potassium (K^+) after KCl supplementation classified by sex, presence of diabetes mellitus, and the use of renin-angiotensin inhibitors, beta blockers, or diuretics.



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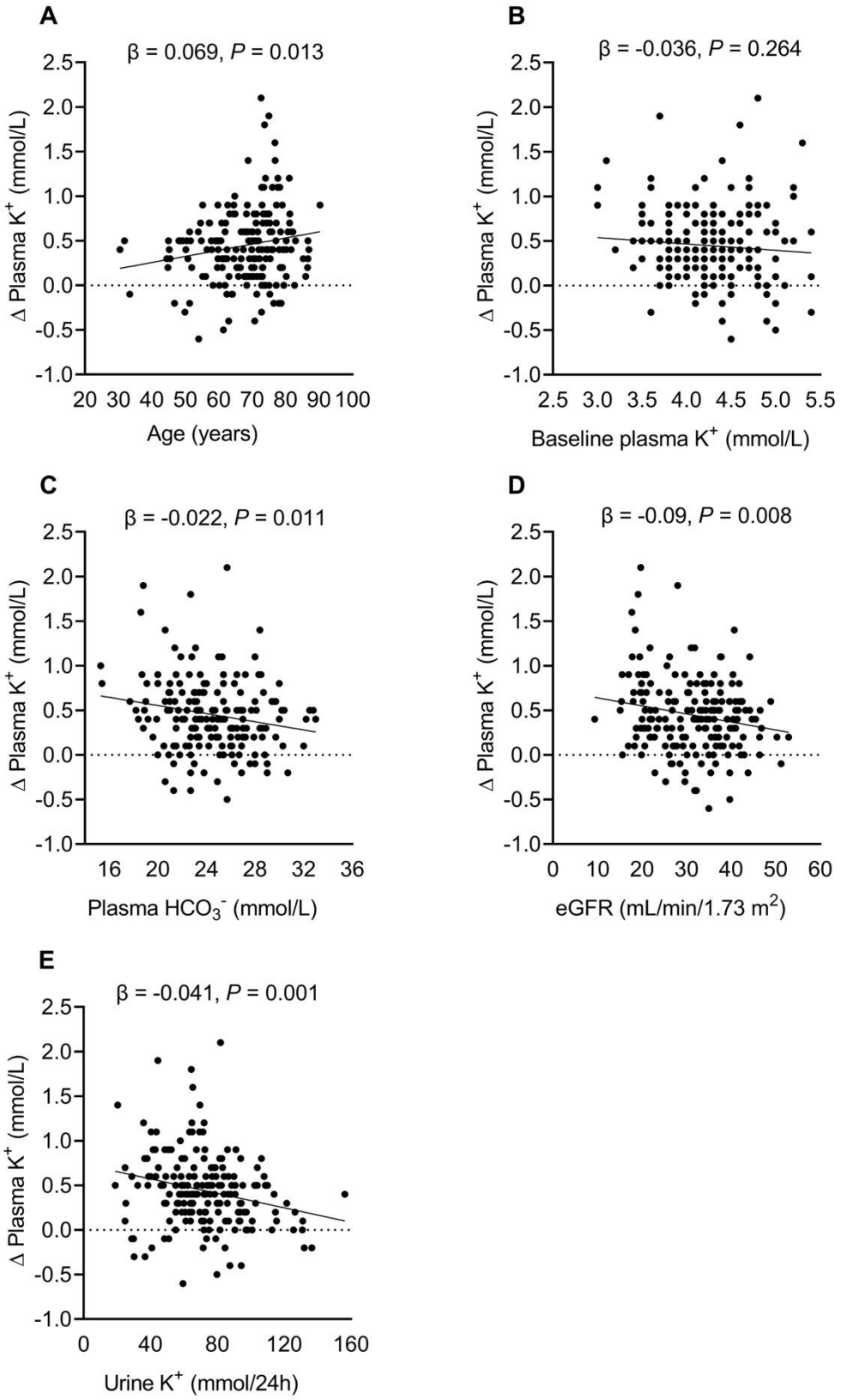
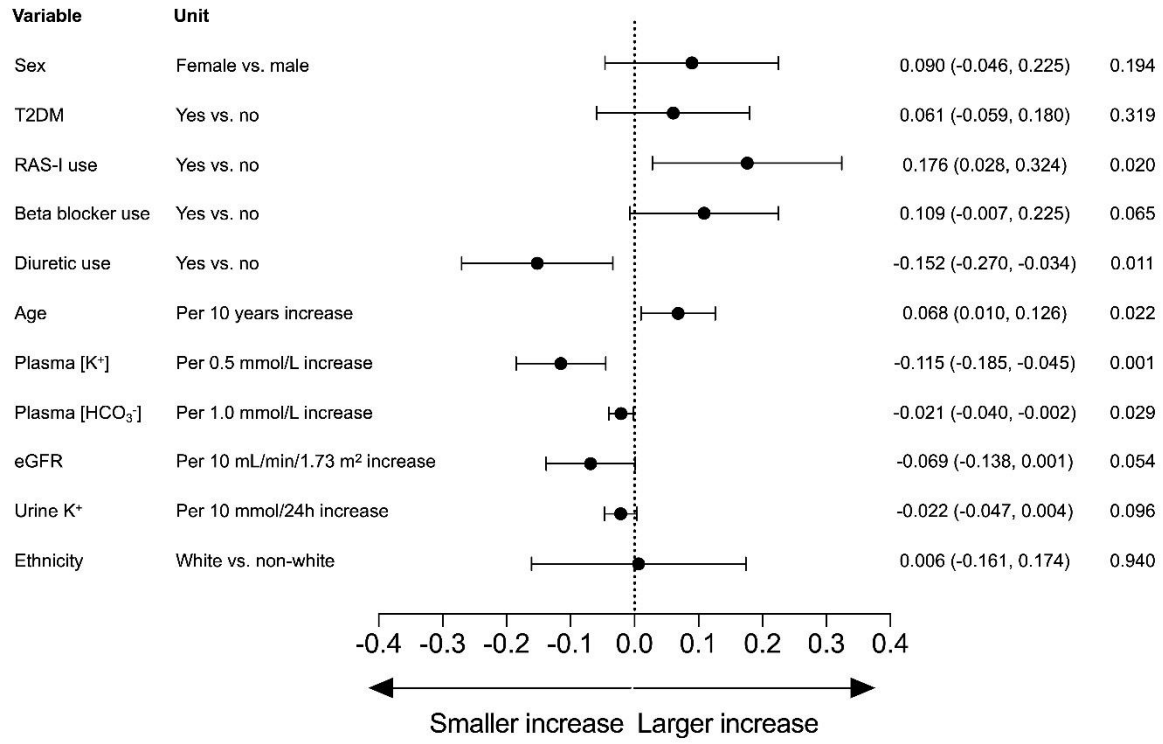


Figure S5: Exploratory analysis of baseline characteristics that were associated with a smaller or lager increase in plasma potassium after KCl supplementation for two weeks with the addition of ethnicity.



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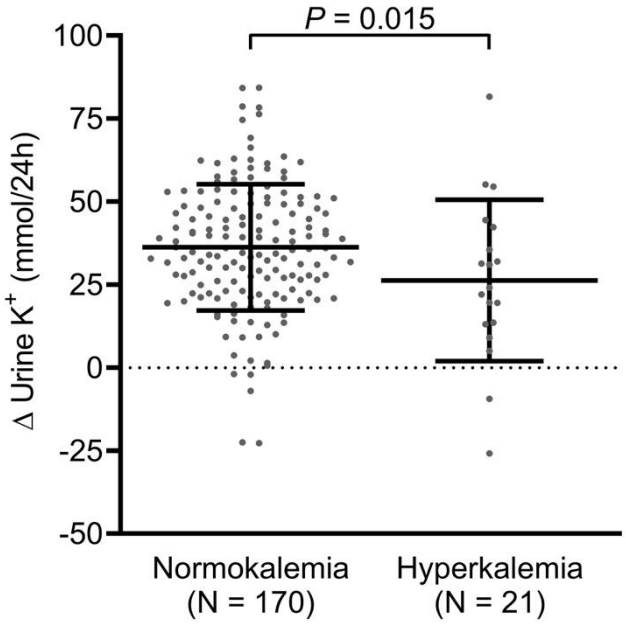

Figure S7: Correlations between the change in office systolic blood pressure (BP) after potassium chloride supplementation with baseline office and 24-hour systolic blood pressure, urinary sodium (Na^+) and potassium (K^+) excretion, and estimated glomerular filtration rate (eGFR).