PITCH

POTASSIUM INTAKE-RESPONSE
TRIAL TO CONTROL HYPERTENSION

PROTOCOL

PROTOCOL VERSION 1.5
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1. Study aim, background, and design

Cardiovascular disease (CVD) remains the leading cause of death in the US and globally.[1,2] Epidemiologic and clinical trial evidence have established the causal effects of several major, modifiable risk factors for CVD,[3] including hypertension, dyslipidemia, diabetes, and cigarette smoking.[4] Observational epidemiologic studies[5,6] and randomized controlled trials (RCTs)[7–13] have identified blood pressure (BP) lowering as a key component of CVD prevention and have informed the development of clinical guidelines for the prevention and treatment of hypertension.[14–17] Simulation analyses conducted by us have shown that achieving guideline-recommended targets for BP treatment could prevent a substantial number of CVD events and deaths.[18–20] Thus, BP is a key target for prevention of CVD and mortality,[5,6] including among individuals with hypertension.

The 2017 ACC/AHA hypertension clinical guideline recommends a BP treatment target of <130/80 mm Hg in all adults.[17] Pharmacological therapy is recommended for adults with stage 2 hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) and a minority with stage 1 hypertension (systolic BP 130-139 mm Hg or diastolic BP 80-89 mm Hg) at high 10-year risk for CVD, but nonpharmacological therapy is the primary approach for all adults, and the sole recommendation for adults with elevated BP (systolic BP 120-129 and diastolic BP <80) or stage 1 hypertension with low 10-year CVD risk.[3] Lifestyle modifications, including diet interventions, are effective in reducing intermediate risk factors for CVD, including BP[21–23] and a healthy diet is important for primary prevention of CVD.[24]

Although RCTs report that potassium supplementation lowers BP,[25] there is no RCT directly testing the intake-response relationship. Meta-regression analyses have indirectly evaluated the intake-response relationship between potassium supplementation and BP, but these explorations have been limited by the fact that all RCTs used a two-arm comparison of a single dosage of potassium supplementation (mostly 60 mmol per day) to placebo.[26–28] In 2019, the National Academies of Science, Engineering, and Medicine Committee to Review the Dietary Reference Intakes (DRIs) for Sodium and Potassium reflected this uncertainty, concluding, "There is moderate strength of evidence for a causal relationship between increased potassium intake (achieved by potassium supplementation) and decreased [BP] among adults with hypertension. However, a lack of an intake–response relationship, coupled with a lack of direct evidence of a causal relationship between potassium intake and [CVD], precluded the committee from establishing a Chronic Disease Risk Reduction Intake (CDRR) for potassium." "To strengthen the evidence on the relationship between potassium and chronic disease risk, future research would accomplish the following: Assess the effect of different doses… of potassium on [BP] so that an intake–response relationship can be established."[29]

The **P**otassium **I**ntake-response **T**rial to **C**ontrol **H**ypertension (**PITCH**) will test the intake-response relationship between potassium supplementation and BP, which may (1) inform clinical guidelines on the optimal level of potassium supplementation for BP lowering among adults with elevated BP and hypertension and dietary guidelines for population intake and (2) lay the foundation for further investigations, including mechanistic studies and outcome trials. A large meta-analysis of RCTs identified a dose-response relationship between BP lowering and risk of CVD, with a 5 mm Hg reduction in systolic BP reducing major CVD events by 10%.[8] Modeling studies suggest that as little as a one mm Hg reduction in the mean systolic BP in the US population would reduce >20,000 coronary heart disease, stroke, and heart failure events annually.[30,31]

Our long-term goal is to establish effective, scalable, and sustainable nonpharmacological

interventions, like potassium supplementation, for primary prevention of CVD. The specific goal of PITCH is to study the intake-response effect for 4 levels of potassium supplementation on 24-hour systolic BP among adults with untreated elevated BP or hypertension. We will test the following hypotheses:

Primary hypothesis: Compared with placebo (0 mmol/day potassium supplementation), there is a progressive, linear dose-response relationship between increasing doses of oral potassium supplementation (30, 60, and 90 mmol/day or 1173, 2346, 3519 mg/day) and decreasing levels of 24-hour systolic BP from baseline to 12-weeks of follow-up, and the largest BP lowering effect will be observed with a dose of 90 mmol/day (3519 mg/day).

Secondary hypotheses: Potassium supplementation improves levels of 24-hour diastolic BP, and office, daytime, and nighttime systolic and diastolic BP, and these improvements are greater with increasing potassium intake.

Exploratory hypotheses: We will examine the effects of potassium supplementation on other CVD risk factors, such as sodium excretion, and study the mediating effects of potassium-induced changes in CVD risk factors on BP. In addition, we will explore treatment effects by subgroups, including age, sex, race, baseline BP, central adiposity, and baseline sodium and potassium intake.

Using a parallel arm trial design and a stratified, blocked randomization scheme, participants will be assigned to placebo or 1 of 3 active intervention arms. Assuming 85% follow-up, the trial will provide 90% power to detect an intake-response relationship based on a net 24-hour systolic BP reduction of 1.5 mm for each additional 30 mmol/day (1173 mg/day) of supplemental potassium intake during 12 weeks of treatment, with a significance level of 0.05. The net effects of BP reduction will be calculated as mean changes in BP from baseline in the potassium supplementation groups minus mean change in BP in the placebo group. To achieve these study aims, we will:

- Recruit 224 adults (n=56 in each group) with elevated BP or hypertension (defined as average untreated office systolic BP 120-159 mm Hg and diastolic BP <100 mm Hg).
- Randomize participants to placebo or 1 of 3 potassium supplementation arms in which 30, 60, or 90 mmol/day (1173, 2346, or 3519 mg/day) of additional oral potassium will be administered for 12 weeks.
- Measure BP, urinary excretion of sodium and potassium, and safety parameters in all participants at baseline, 6 weeks, and 12 weeks, using trained and certified study staff who are blinded to the participants' study assignment.
- Examine net differences in 24-hour systolic BP (primary outcome), 24-hour diastolic BP, and office, daytime, and nighttime systolic and diastolic BP, from baseline to 12 weeks of follow-up between the 4 groups per intention-to-treat analysis.
- Examine the effects of potassium supplementation on other CVD risk factors and explore mediating and modifying effects by CVD risk factors, including age, sex, race, baseline BP, central adiposity, baseline sodium and potassium intake, as well as changes in urine sodium.

Table 1. Study Timeline

	Year 1		Year 2		Year 3	
Finalize protocol, develop MOP, and study forms	X					
Training and certification, pilot testing, IRB approval	X					
Recruitment		X	X	X	X	
Intervention and data collection, quality control		X	X	X	X	
Data analysis					X	X

2. Subject Population

2A. Inclusion Criteria

- Men or women aged >18 years of any race/ethnicity
- Elevated BP or hypertension at screening (untreated office systolic BP 120-159 and diastolic BP <100 mm Hg)
- Willing and able to provide informed consent

2B. Exclusion Criteria

- Medical condition in which potassium supplementation is contraindicated:
    - History of heart failure, myocardial infarction, stroke, or cardiac arrythmia
    - History of chronic kidney disease or estimated glomerular filtration rate <60 ml/min/1.73m^2
    - History of diabetes or non-fasting glucose >200 mg/dL
    - History of major depressive disorder (PHQ-9 score ≥15) or psychosis
    - History of ulcer diseases, including esophageal-gastric ulcer
    - History of malignancy in the past 5 years
    - History of liver disease
    - History of organ transplant
    - History of Addison's disease (adrenal insufficiency)
- Use of medications which may alter serum potassium levels or in which potassium supplementation is contraindicated: antihypertensive agents, antihistamines, antiparkinson agents, antimuscarinic agents, antipsychotics, muscle relaxants, systemic corticosteroids, or chronic use of non-steroidal anti-inflammatory drugs
- Serum potassium ≥5.0 mEq/L
- Metabolic acidosis
- Consumption of >85th percentile of usual potassium intake among US adults (>3,750 mg/day)[29,32]
- For women, current pregnancy, breastfeeding, or plans to become pregnant during the study
- Consumption of ≥21 alcoholic beverages per week or consumption of ≥6 beverages per occasion
- Current or planned residence making it difficult to meet trial requirements or travel to the study site
- Current participation in another intervention or pharmaceutical trial
- Unable or unwilling to complete 24-hour BP or urinary sample collection
- Other concerns regarding ability to meet trial requirements, at the discretion of the investigators or staff

2C. Recruitment

Participant recruitment will be facilitated with support from the Tulane University Translational Science Institute's Clinical Research and Community Engagement Core. The investigative team has substantial experience with recruitment for both clinic trials and epidemiological studies. Based on this experience, we are keenly aware of the importance of recruitment and believe that we will have the appropriate population to fulfill our recruitment goals. In this study, we aim to recruit adults with elevated BP or hypertension from the greater New Orleans, LA metropolitan region, primarily from mass mailings targeting zip codes proximal to the study center. We also have several contingency plans.

Our recruitment strategies include:

Primary

Targeted mailing: The primary focus of recruitment will be from mass mailings in zip codes selected for proximity to the study center, with potential participants invited to have a brief pre-screening telephone interview and those potentially eligible being scheduled for a screening visit.

Secondary

Community: Pamphlets about the study will be placed in locations where adults with elevated BP or hypertension may be found, including physicians' offices or other study clinic waiting rooms and public venues such as community health fairs. We will seek approval from local businesses (e.g., United States Postal Service, Entergy, Shell) to distribute pamphlets to their staff and persons interacting with these local businesses.

In addition, we will conduct free blood pressure screenings in community settings to identify potentially eligible participants. After receiving approval from event organizers or business owners, staff will set up a pre-screening table and invite interested potential participants to complete the pre-screening questionnaire and free blood pressure measurement, after verbal consent is obtained. After determining basic eligibility, potential participants will be invited to schedule the first official screening visit at the study clinic.

Contingency plans: We have several contingency plans: 1) extending recruitment to medical centers in the New Orleans area (e.g., University Medical Center, Ochsner Health System, Tulane Medical Center); 2) targeted solicitation of referrals from primary care physicians; 3) TV/radio and social media advertisements. We have ample experience with each of these approaches. In use of social media platforms (e.g., Instagram, Twitter, Facebook) for recruitment, any communications from study staff will direct interested potential participants to follow a link to the study's secure webpage (https://pitchstudy.org/) for collection and confidential storage of contact information.

All participants will be age 18 years or older because elevated BP and hypertension are not common in children. There is no upper age limit and we expect the distribution of age of study participants to reflect the age distribution of adults with elevated BP or hypertension in the greater New Orleans, LA metropolitan region, which aligns with the overall goals of the study. The investigators have substantial prior experience carrying out clinical research among adults aged 18 and older. We plan to recruit approximately 50% women participants in the proposed trial. Although there is not strong evidence to suggest sex differences in blood pressure response to potassium supplementation, we will investigate the consistency of treatment effects

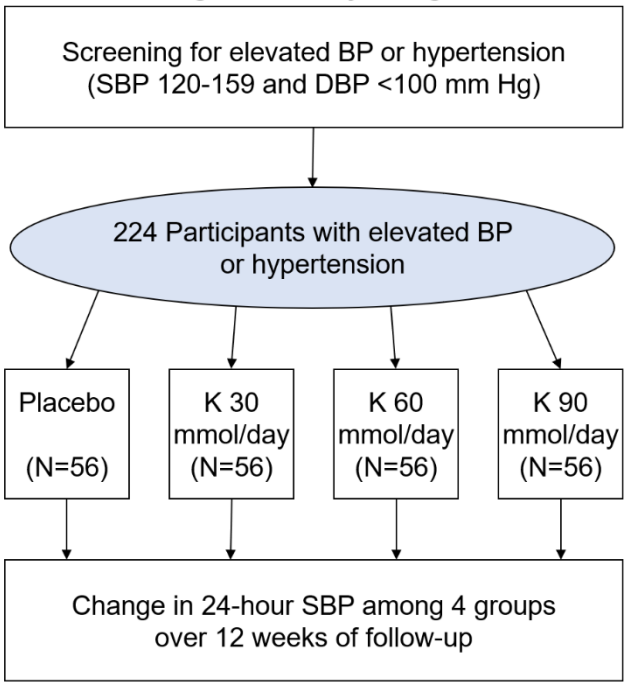
by sex in a pre-specified subgroup analysis. We plan to recruit approximately 40% ethnic minorities in the proposed trial. Previous trials suggest there may be racial differences in the effects of potassium supplementation on blood pressure. For example, black adults have shown a larger blood pressure response to supplementation in prior trials. Therefore, we will investigate the consistency of treatment effects by race in a pre-specified subgroup analysis.

3. Procedure

3A. Overview of Trial Design

We will conduct a randomized placebo-controlled double-blind trial testing the intake-response effect of oral potassium supplementation on BP in adults with elevated BP or hypertension (**Figure 1**).

Figure 1. Study Design



We will recruit 224 adults with elevated BP or hypertension (untreated office systolic BP 120-159 and diastolic BP <100 mm Hg) from the greater New Orleans metropolitan area and randomly assign them to placebo or 1 of 3 intervention arms in which in which 0, 30, 60, or 90 mmol/day (0, 1173, 2346, or 3519 mg/day) of additional potassium is given orally for 12 weeks. We will test the effects of various potassium doses on net 24-hour systolic BP changes from baseline to 12 weeks of follow-up (primary outcome). We will assess safety parameters and additional secondary and exploratory outcomes, including 24-hour diastolic BP, office and nighttime BP, other CVD risk factors, and consistency of effects by subgroups of age, sex, race, baseline BP, central adiposity, and baseline sodium and potassium intake. **Table 2** summarizes the trial components.

Table 2. Study Overview

Study Design	Randomized, double-blind, placebo-controlled, intake-response clinical trial
Study Participants	224 adults with elevated BP or hypertension (untreated office systolic/diastolic BP 120-159/<100 mm Hg)
Intervention Groups (n=56 per group)	Supplemental oral potassium in 3 arms: 30 mmol/day (1173 mg/day), 60 mmol/day (2346 mg/day), or 90 mmol/day (3519 mg/day) for 12 weeks
Control Group (n=56)	Placebo for 12 weeks
Primary Outcome	Difference in 24-hour systolic BP change from baseline to 12 weeks among the 4 groups
Secondary and other Outcomes	24-hour diastolic BP; office and nighttime BP; sodium excretion; effect mediation and modification by age, sex, race, baseline BP, central adiposity, baseline urine excretion of sodium and potassium, and change in urine sodium

3B. Randomization and Blinding

Eligible participants will be randomly assigned to placebo or 1 of 3 active intervention groups in a 1:1:1:1 ratio using a stratified (Black vs. non-Black) block (random sizes of 4 and 8) randomization scheme generated via computer program and concealed by an independent biostatistician within the Bioinformatics and Biostatistics Core. Randomization is expected to balance baseline characteristics (e.g., dietary intake) among groups. After eligibility is confirmed, clinical staff will ensure all baseline data is in place and checked for quality control purposes and will obtain the participant's randomization assignment via secure web-based database (REDCap). Once participants are randomized, every effort will be made to obtain complete follow-up information.

The proposed trial will employ placebo control and blinding of participants and study staff recording participant information, which are effective measures to account for the possibility of intervention placebo effects. The Bioinformatics and Biostatistics Core will control the randomization and intervention allocation, preserving the blinding of the investigators and Clinical Research and Community Engagement Core study staff in charge of day-to-day operations. Study participants will receive potassium tablets or placebo and will be unaware of their placebo or dosing assignment, and therefore unlikely to differentially change their diet over the course of the trial (i.e., cross-over). 24-hour BP monitoring is resistant to placebo effects and is unlikely to be affected by the possibility of observe unblinding.[33]

3C. Intervention and Control

All participants will be asked to avoid changing their diet over the course of the trial. Potassium supplements (Klor-Con M15 tablets to achieve 30 mmol, 60 mmol, or 90 mmol potassium) and placebos (0 mmol potassium) will be purchased through Tulane Medical Center Research Pharmacy (New Orleans, LA) and Zeebo (South Burlington, VT), respectively. Participants randomized to the placebo arm will receive 1, 2, or 3 inert placebo tablets twice daily (i.e., 2, 4, or 6 tablets per day) for 12 weeks. Participants randomized to the 30 mmol per day group will receive 1 potassium chloride tablet (15 mmol strength) twice daily (i.e., 2 tablets per day) for 12 weeks. Participants randomized to the 60 mmol per day group will receive 2 potassium chloride tablets (15 mmol strength) twice daily (i.e., 4 tablets per day) for 12 weeks. Participants randomized to the 90 mmol per day group will receive 3 potassium chloride tablets (15 mmol

strength) twice daily (i.e., 6 tablets per day) for 12 weeks. Participants will be instructed to take tablets with food and/or an 8oz glass of water.

We will assess participant adherence after the trial primarily via the measurement of 24-hour urinary potassium excretion at baseline, 6, and 12 weeks, and comparison of mean levels across the intervention groups. The Tulane Medical Center Research Pharmacy will be responsible for receipt and proper storage of study medication, maintaining site product delivery records, dispensing of product to each participant, and return of product to designee at the end of the study.

Safety of potassium chloride intervention: Potassium supplementation of 17-140 mmol/day is considered safe, in various patient populations.[29,34–40] Hyperkalemia-related adverse events are associated with acute ingestion of extremely high doses (>200 mmol/day beyond usual intake), impaired renal function, and antihypertensive medications use,[29] but are rare in the general population,[41,42] including in long-term population-based RCTs[43] and short-term loading studies up to 400 mmol/day.[44–46] We will include untreated adults consuming <85% of usual potassium intake among US adults, and having normal renal function.[29,42] The maximum dose will be 90 mmol/day and participants will be monitored for side effects by an experienced study physician (Dr. Jing Chen). A Data Safety and Monitoring Board (DSMB) will review cumulative study and safety data and can recommend premature termination.

3D. Study Visit Schedule and Description

Table 3. Study Visit Schedule and Data Collection

	Pre-screen	SV/ BV1	SV/ BV2	RZ	1-wk Call	6-wk visit	12-wk visit 1	12-wk visit 2
Verbal consent and eligibility	X							
Written informed consent		X						
Eligibility confirmation				X				
Demographics		X						
Social and behavioral factors			X					
Medical history, medications		X				X	X	
Height (SV1), weight, waist circ.		X				X	X	
24-hour dietary recall*		X				X	X	
3 office BP measurements		X	X			X	X	X
24-hour urinalysis		X	X	Confirm		X	X	X
Non-fasting blood samples		X				X	X	
Ambulatory BP monitoring			X	Confirm		X	X	Confirm
Symptoms assessment			X		X	X	X	
Dispense medication				X		X		

SV/BV=screening and baseline visits and RZ = randomization visit; *Two 24-hour dietary recalls, the first in-person and the second by telephone. 24-hour urine and ambulatory BP measures will be evaluated for completion and confirmed prior to randomization into the trial.

Pre-screening: For in-person and telephone pre-screening visits, verbal consent will be obtained from potential participants who will then be assessed for basic eligibility. When conducting pre-screening in community settings, blood pressure measurements will be obtained to assess eligibility. After determining basic eligibility, potential participants will be scheduled for the first screening visit.

Screening/baseline visits: At screening visit 1, we will obtain written informed consent for the trial and measure height, weight, BP, obtain a medical history and medications list, and collect a blood sample for a basic metabolic panel. Two 24-hour dietary recalls will be conducted to assess eligibility based on dietary potassium intake, with 1 in-person and 1 via telephone. Individuals will be instructed on collecting a 24-hour urine specimen and asked to bring it to the clinic for screening visit 2. At screening visit 2 (between 3 and 14 days from first screening) we will measure BP, assess baseline symptoms, and confirm eligibility. Each participant will be fitted with an ambulatory BP monitor (ABPM) and receive instruction on its use. Individuals will be instructed to collect a second 24-hour urine specimen and return it and the ABPM 24 hours after screening visit 2.

Randomization visit: Approximately 24 hours after screening visit 2, participants will return the 24-hour urine specimen and ABPM machine. The ABPM record will be checked for completion (>70% valid measurements and at least 20 daytime and 7 nighttime measurements; see below under Study Measurements), and then the participant will be randomized with medication dispensation by an unblinded, unaffiliated staff member.

Safety telephone visit: 1 week after randomization, we will administer a questionnaire via telephone assessing key safety indicators (i.e., symptom frequency and duration, and potential adverse events).

Midterm (6 week) follow-up visit: Participants will be scheduled for a 6-week follow-up visit to collect interim measurements and specimens as described in the study visit schedule table above. Urine potassium measurements from this visit will be used to determine adherence to the intervention. Key safety indicators (i.e., symptoms and serum potassium) will be assessed.

End of study (12 week) follow-up visits: Participants will be scheduled for 2 termination visits during week 12 to collect final measurements and specimens. 2 separate visits will be conducted to increase precision in office BP and 24-hour urine measurements over 2 days. At the final study visit after all data collection, participants will meet with a registered Research Dietitian for 15-30 minutes to discuss their dietary habits and suggestions for improvement.

3E. Study Measurements

Study measurements and methods will be based on standard methods used in previous studies conducted by the Tulane University Office of Health Research. Staff within the Clinical Research and Community Engagement Core will be trained and certified in administering all measurements, and rigorous quality control measures will be implemented. Study visits will require approximately 2 hours to complete questionnaires (30-60 minutes), BP and anthropometric measurements (15-30 minutes), and blood collection (15-30 minutes). All study visits will occur at the Office of Health Research (1440 Canal St, Suite 1100, New Orleans, LA 70112) during normal clinic hours (8am to 4pm).

Questionnaires: A medical history and medications questionnaire will be administered at the first screening visit and updated at weeks 6 and 12 to ascertain conditions requiring changes in therapy. Social and behavioral risk factors will be assessed. Safety questionnaires will be administered at screening and subsequently over the trial to assess safety, potential adverse events, and symptoms classified by frequency and severity. 24-hour dietary recalls will be administered by a trained study dietitian or technician (1 in-person, 1 via telephone).

BP and anthropometric measures: Office BP will be measured 3 times at each study visit, with averages of the 6 measurements at the 2 baseline and 2 12-week visits used to minimize random error. BP measurements will be performed by staff trained and certified in a standardized BP measurement protocol using the same model of validated oscillometric device (Omron HEM-907xl) for each participant at each study visit. Participants will be asked to rest quietly while seated in a chair with an upright back with their feet flat on the ground for five minutes prior to BP measurements. Participants will be instructed to avoid alcohol, coffee, smoking, and exercise 30 minutes prior to BP measurements. An appropriate size cuff will be used over a bare arm for a mid-brachial reading at heart level. The participant's arm will be rested comfortably, and no talking will be permitted before or during the measurement. Calibrated instruments will be used to measure height at the initial screening visit, and weight and waist circumference at each visit.

Ambulatory Blood Pressure Monitoring: ABPM will be conducted at baseline and termination using validated monitors (Spacelabs 90227 Ontrak) and a protocol based on European Society of Hypertension guidelines.[47] At the second screening, week 6, and first week 12 visit, participants will be fitted with a monitor and undergo measurements for 24 hours. Participants will be given written instructions. Readings will be obtained every 20 minutes during the hours of 6:00AM to 10:00PM and every 30 minutes during the hours of 10:00PM to 6:00AM over the 24-hour period. 24-hour BP will be averaged from all readings, weighted by the time interval between successive readings. Nighttime BP will be calculated as the mean of readings during the hours of midnight to 6:00AM, and daytime BP as the mean of readings during the hours of 10:00AM to 8:00PM. These shorter fixed clock-time intervals are chosen to eliminate transitional periods resulting in readings closer to awake and asleep levels.[48] Recordings are considered complete if 70% of the expected number of readings is obtained in 24 hours and at least 20 valid daytime and 7 nighttime BP readings are collected.[47] If a complete recording is not obtained, participants will be asked to repeat the monitoring.

24-hour urine collection: 24-hour urine collections will be obtained a total of 5 times. Participants will be instructed to collect two 24-hour specimens using a standard protocol, concurrent with their screening and week 12 study visits. Participants will collect one 24-hour urine specimen at week 6. Urine collections will be within a 2-day window of study visits. Samples will be reviewed by the study coordinator for completeness. Participants providing <500 mL will be asked to repeat the collection. The purpose of the two collections at screening/baseline and week 12 is to capture variability and reduce random error. Additional samples will be stored for future analyses.

Blood tests: Venipuncture for a basic metabolic panel, including serum sodium, potassium, creatinine, bicarbonate, and glucose will occur on 3 occasions, at the first screening visit, week 6, and week 12 by trained, certified staff members. 40 mL (about 3 tablespoons) will be collected per visit. Serum creatinine values will be used to calculate estimated glomerular filtration rate according to the 2021 CKD-EPI equation. Additional samples will be frozen and stored for future analyses.

3F. Quality Assurance and Quality Control

Throughout the entire investigation, strict quality assurance (QA) and quality control (QC) measures will be used. This section describes some of the approaches.

Manual of Procedures: We will develop a study protocol and detailed manual of procedures (MOP) that identifies and details standard procedures for all elements of data collection in the trial. The MOP will be adapted from MOPs used successfully in previous RCTs conducted within the Office of Health Research

Training and Certification: Office of Health Research personnel will be trained based on established and effective methods. Training will focus on core trial elements, such as recruitment, retention, intervention, blinding, and data completeness and quality. Periodic re-training/certification sessions will be conducted to ensure all trial-related procedures are being applied in a standard manner across all participants. Throughout the trial, the investigators will monitor every aspect of study performance throughout the trial to make sure that the objectives are met, that study visits are timely and comprehensive, and that data are complete and of high quality. The accuracy of all laboratory measures, particularly crucial exposure, outcome, and intervention monitoring variables, will be carefully scrutinized.

3G. Statistical Design and Power

The trial is designed to detect a 1.5 mm Hg reduction in 24-hour systolic BP for each additional 30 mmol/day supplemental potassium compared with placebo, assuming 60 mmol/day achieves a 3 mm Hg reduction based on meta-analyses.[25–29,34,35,49] We calculated our sample size assuming: 90% statistical power; a 2-sided significance level of 0.05; and a standard deviation of 7 mm Hg in 24-hour systolic BP change based on prior BP RCT experience in this population.[50,51] The sample size calculation assumes analysis using a 4-group dose-response contrast test and the estimated sample size for each group based on these assumptions is 47. To allow for an 85% follow-up rate, we will recruit 56 trial participants in each group for a total of 224.

3H. Data Management

All study data will be double-entered. The study coordinator will conduct quality control checks on all study forms, study measures, and laboratory data. Data will be cleaned and logically checked and entered into a secure REDCap database.

3I. Statistical Analysis Plan

Intention-to-treat analyses will be conducted such that the primary and secondary study outcomes will be evaluated among participants according to their randomization assignment at study entry.

Preliminary Data Analysis: Baseline participant characteristics will be summarized as the mean ± standard deviation or median (interquartile range) for continuous variables and number (%) for categorical variables. Intervention groups will be compared on baseline characteristics to identify possible baseline imbalances.

Analyses of Main Effects: In the analysis of the primary and secondary outcomes, we will test the hypothesis that increasing doses of supplemental potassium result in monotonically greater reductions in levels of outcomes from baseline to 12 weeks follow-up in an intake-response

fashion. To test this hypothesis, we will use linear regression and the F-test of the hypothesis that there is a linear trend in mean net response in outcomes across the 4 randomized groups over 12 weeks. Rejection of the null hypothesis ($\mu_0 = \mu_{30} = \mu_{60} = \mu_{90}$) indicates that there is a significant intake-response relationship (i.e., $\mu_0 \leq \mu_{30} \leq \mu_{60} \leq \mu_{90}$ and $\mu_0 < \mu_{90}$) where the net effects will be calculated as mean changes in outcomes from baseline to 12 weeks follow-up in the potassium supplementation groups minus mean change in outcomes in the placebo group). The linear contrast will be tested using contrast coefficients of -3, -1, 1, 3. This approach is standard for dose-response RCTs.[52–54] The optimal dose will be defined as that which shows the greatest net decrease in systolic BP over 12 weeks compared with placebo.

Based on a prior meta-analysis, the intake-response shape of potassium supplementation on systolic BP is uncertain.[28] The proposed trial is designed to evaluate a linear intake-response effect but will have sufficient power to characterize other possible relationships, including threshold effects, using contrast structures like modified linear, quadratic, exponential, and sigmoid.[52–54]

In additional analyses, we will use linear mixed effects regression models incorporating follow-up outcome measures at both weeks 6 and 12, and will conduct pairwise comparisons between randomized groups in an exploratory analysis.

Missing Data and Covariable Adjustment: In the primary analyses, we will use Markov-chain Monte Carlo methods to impute missing values assuming an arbitrary missing pattern and a multivariate normal distribution for the data.[55,56] We will compare point estimates and confidence intervals from this analysis with a secondary analysis using available data without imputation. In this proposed RCT, we expect baseline characteristics to be balanced between intervention groups. Therefore, in the primary analysis, we will include the stratified randomization variable (i.e., race) as a covariable, but other covariable adjustments will not be used. However, if imbalances are detected, we will adjust for these covariables in secondary multivariable-adjusted regression models.

Analyses of Effect Modification and Mediation: We will evaluate the consistency of intervention effects by age, sex, race, baseline BP, central adiposity, and baseline sodium and potassium intake in stratified analyses. Effect modification will be tested using intervention arm * subgroup interaction terms in regression models. Mediation analysis will be used to evaluate potential mechanisms of potassium supplementation on outcomes. We will compare changes in covariables that could be impacted by the intervention, such as urinary excretion of sodium and potassium, and use structural equation modelling (SEM). SEM allows for simultaneously modelling both indirect and direct effects; i.e., effects of the intervention on the mediator, effects of the mediator on the outcome, as well as the direct effects of the intervention on the outcome (e.g., systolic BP).[57]

The proposed trial is designed to test one primary hypothesis and the other analyses will be considered hypothesis generating. Therefore, a significance level of 0.05 without adjustment for multiple comparisons will be used in analyses of secondary outcomes, subgroups, and effect mediation and modification.

4. Risks

4A. Description of Potential Risks

Risks associated with potassium supplementation, venipuncture, and collection of confidential medical information are the main risks associated with this study.

Potassium supplementation may lead to adverse effects, including nausea, gastrointestinal discomfort, and hyperkalemia in participants taking certain antihypertensive medications or having comorbidities associated with impaired potassium excretion (e.g. heart failure, decreased renal function). However, meta-analyses suggest potassium supplementation of 17-140 mmol/day is safe with few side effects, primarily gastrointestinal discomfort.[29,34–36] Short-term supplementation up to 120 mmol/day (total urinary potassium excretion 167-225 mmol/day) has been used in RCTs without significant side effects in various patient populations.[37–40] Hyperkalemia-related adverse events are associated with acute ingestion of extremely high doses of potassium (>200 mmol/day beyond usual intake), impaired renal function, and antihypertensive medications use,[29] but are rare in the general population.[41,42] Hyperkalemia was not observed in short-term potassium loading studies conducted in healthy volunteers that employed doses up to 400 mmol/day.[44–46] We expect our interventions to be safe and well tolerated because we will include only unmedicated adults consuming <85% of usual potassium intake among US adults, and having normal renal function.[29,42]

Minimization of Risk: We will include only unmedicated adults consuming <85% of usual potassium intake among US adults, and having normal renal function and serum potassium levels (<5.0 mEq/L). The maximum dose will be 90 mmol/day and participants will be monitored for side effects. We will closely monitor potential adverse events according to the protocols below. An experienced study physician (Dr. Jing Chen) will evaluate safety concerns throughout the trial. During follow-up, study staff will collect data on side effects via a safety questionnaire form at each visit and 1 week post-randomization. At the first screening visit, 1-, 6-, and 12-week visits, we will administer symptoms questionnaires, which will consist of a checklist to identify participant complaints. Participants will be encouraged to contact the study team if they experience any new symptoms. Additionally, at the 6- and 12-week visits, we will conduct blood tests to evaluate serum sodium and potassium levels. Severe adverse events will be promptly reported to the Data and Safety Monitoring Board (DSMB). Management of adverse effects will be based on the protection and safety of the participant. If severe adverse effects are reported by a participant, potassium supplementation will be examined and altered in order to mitigate the adverse effect. In any extreme cases, participants will be instructed to stop the intervention.

There is a small risk of bruising and a rare chance of local infection associated with standard venipuncture to collect blood samples.

Minimization of Risk: Our proposed study will employ trained and certified study staff and phlebotomists to minimize adverse events associated with venipuncture.

There is a potential risk of unauthorized disclosure of medical information.

Minimization of Risk: This risk will be prevented by using a strict protocol for data processing and by the appropriate training of all study personnel. Confidentiality of all data collected during the study will be maintained through the use of unique, encrypted study identification (ID

numbers, rather than patient names, in the study database). These encrypted ID numbers will not be mathematical derivation of the subject's medical record number or any other patient identifier. No information will be disclosed in an individually identifiable form in any type of presentation or publication. There will be password-required access to the computerized file linking the study numbers to patient identifiers at the study clinics. Password-access will be restricted to pertinent research staff only. All study data will be kept in locked file cabinets in locked rooms, accessible only by study staff with permission. All data transmissions will use HIPPA-compliant password protected system and will be secured through a virtual private network.

4B. Safety Monitoring and Reporting

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any clinically significant abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

A serious AE (SAE) is an adverse event that meet any of the following criteria:

- fatal or life-threatening,
- result in significant or persistent disability,
- require or prolong hospitalization,
- result in a congenital anomaly/birth defect, or
- are important medical events that investigators judge to represent significant hazards or harm to research participants and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (e.g., hospitalization, death, persistent disability).

Any adverse event that meets any of these criteria will be documented and reported as a serious adverse event. Participants will be queried for side effects and AEs at the 1-week telephone visit and each clinic visit (week 6, week 12). In addition, information on serious adverse events may also be reported to study staff spontaneously by participants between study visits. In addition to local reporting requirements, all serious adverse events will be recorded by clinic staff and forwarded to the study physician within 72 hours of knowledge of the event. SAEs will be collected and reported from screening to the end of the study follow-up period for an individual participant. SAEs will be followed until resolution, stabilization, or until it is determined that study participation is not the cause. The Principal Investigator will be responsible for timely reporting to the NIH and the DSMB. The Principal Investigator will provide reports of serious adverse events for review by the DSMB at their meetings.

In addition, standard clinical safety alerts will be employed. When a measurement attains a defined alert level as described in the bullet points below, study staff will immediately notify the study physician for further evaluation.

- Systolic BP >180 or diastolic >110
- Heart rate <40 bpm
- Serum potassium ≥6.0 mEq/L or ≤3.0 mEq/L
- Serum sodium <130 mEq/L or >155 mEq/L
- Serum total bicarbonate <15 mEq/L or >40 mEq/L
- Serum calcium <8 or >11 mg/dL

- Plasma glucose <50 mg/dL or >350 mg/dL
- Serum creatinine doubling from last value
- CBC hemoglobin <7.0 gm/dL
- “Acute Distress” (includes chest pain or other signs or symptoms constituting an emergency)

5. Benefits

Potential Benefits: Participants may not receive any direct benefit from participating in the study. However, participants may have improved blood pressure, glucose, lipid levels, and may have improvement in other risk factors for cardiovascular disease. Participants will receive multiple blood pressure and weight measurements, blood analyses, and urine analyses. If vital signs or lab values are clinically abnormal, participants will be referred to their primary care physician, or if they do not have a primary care physician, one will be assigned through the Tulane University Community Health Center, which is a part of the core clinical facilities. At the end of the study, we will provide the participants’ primary care physician with a copy of all the blood pressure, weight, and laboratory results. Participants will also receive free parking for each intervention and study visit, and a small financial compensation for their time. Finally, participants will receive a free consultation with a registered Research Dietitian at the completion of their time in the study.

Importance of the Knowledge to be Gained: Information from this study may contribute to the establishment of dietary guidelines for potassium supplementation and may inform scientific knowledge on the intake-response relationship between potassium supplementation and blood pressure. Furthermore, information from this study may contribute to reducing the burden of cardiovascular disease in Louisiana and the general US population. The study has potential for large clinical and public health impacts.

6. Remuneration

Participants will receive payments in the form of gift cards to a common vendor (e.g., Amazon or Walmart): $40 for the second baseline visit, $20 and a small study-branded gift worth approximately $10 for return of the ABPM and randomization, $60 for the 6-week visit, $40 for the first 12-week visit, and $60 for the second 12-week visit for a total of $230. Additionally, participants will receive a free consultation with a registered Research Dietitian at the completion of their time in the study. Throughout the recruitment and screening process, no potential participant will be coerced or pressured in any way to participate - participation is completely voluntary.

7. Academic or Extra Credit

NA

8. Costs

Participants will pay for travel as necessary to attend study visits.

9. Alternatives

Potential participants will be assured they do not have to participate in the research.

10. Consent process and documentation

The proposed study will be conducted following strict guidelines for the protection of the rights of human volunteers. Verbal informed consent will be obtained before any pre-screening activities, including blood pressure screening in community settings. The trial informed consent document will be signed by all participants at the first screening/baseline visit. The informed consent form will be developed in the first year of the study and approved by the IRB. The consent form will clearly state the purpose, eligibility criteria, and protocol of the study, the potential benefits and risks of participation, and the subject's right to refuse to participate or withdraw. Prior to signing the informed consent, research staff will review the details of the consent form orally with the participant, and answer any questions that the participant has concerning participation in the study. In the case of potential participants with low or no literacy, the informed consent form will be read to the participant in its entirety and any questions will be answered prior to the participant signing or marking the form. Specifically, the following must be accomplished during the informed consent process:

- The participant must be informed that participation in the study is **voluntary** and that refusal to participate will involve no penalty or loss of benefits.
- The participant must be informed of the **purpose** of the study and that it involves **research**.
- The participant must be informed of any **alternative procedures**, if applicable.
- The participant must be informed of any reasonably foreseeable **risks**.
- The participant must be informed of any **benefits** from the research.
- An outline of safeguards to protect participant **confidentiality** will be included, as well as an indication of the participant's right to withdraw without penalty. This should be balanced with a discussion of the effect that withdrawals will have on the study, and the responsibility a participant has, within limits, to continue in the study if he or she decides to enroll.
- The participant must be informed of his or her right to have **questions answered** at any time and **whom to contact** for answers or in the event of research-related injury.
- The participant must be informed as to whether or not **compensation** is offered for participation in the study and/or in the event of a medical injury.
- The participant must be informed that he/she will be notified of any significant **changes** in the protocol that might affect their willingness to continue in the study.

Written authorization for the disclosure of protected health information will be obtained during the consent process on a separate form (HIPPA authorization).

11. Qualifications of the investigators

Dr. Joshua Bundy, the Principal Investigator (PI) of the trial, is a chronic disease epidemiologist with substantial training in epidemiology and biostatistics, and special expertise in clinical epidemiology of CVD and renal disease. Dr. Bundy has published high-impact papers in the fields of hypertension,[12,18,58–60] risk prediction,[61,62] and risk factors for CVD and kidney disease progression.[20,59,63–66]

Dr. Jiang He is a nationally and internationally renowned expert in clinical and translational research in cardiometabolic disease, including nutrition interventions and hypertension.[50,67–69]

Dr. Paul Whelton is an internationally renowned clinical trialist with extensive experience in BP-lowering trials, including with potassium supplementation.[9,28,34,67,70–72]

Dr. Jing Chen is a board-certified internist, nephrologist, and hypertension specialist with decades of clinical research experience in hypertension, including in RCTs.[50,68,69,73]

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