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POTASSIUM SUPPLEMENTS VS HYDROCHLOROTHIAZIDE IN
HYPERTENSIVE AFRICAN AMERICANS: NONINFERIORITY TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

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List of Abbreviations

ABPM: Ambulatory blood pressure monitoring
PRA: Plasma Renin Activity
BP: Blood Pressure
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
MAP: Mean Arterial Pressure
BMI: Body Mass Index
RAAS: Renin Angiotensin Aldosterone System
KCl: Potassium Chloride
HCTZ: Hydrochlorothiazide
CCB: Calcium Channel Blocker
ACEI: Angiotensin Converting Enzyme Inhibitor
ARB: Angiotensin Receptor Blocker
ESRD: End Stage Renal Disease
LVH: Left Ventricular Hypertrophy
HF: Heart Failure
CVD: Cardiovascular Disease
MI: Myocardial Infarction
CHF: Congestive Heart Failure
DM: Diabetes Mellitus
GFR: Glomerular Filtration Rate
APOL1: Apolipoprotein L1 Gene
HbA1c: Hemoglobin A1c

Abstract

Hypertension disproportionately affects African Americans. First-line monotherapy for treating mild-to-moderate hypertension in African Americans is with thiazide-type diuretics, particularly hydrochlorothiazide. However, the efficacy of non-pharmaceutical control of blood pressure via potassium supplementation is comparable in this population and has a favorable side effect profile. We hypothesize that daily 80mEq potassium supplementation is non-inferior to 25.0mg hydrochlorothiazide in reducing systolic blood pressure in African American adults. To test this hypothesis, we will conduct a double-blind, randomized controlled trial and measure systolic blood pressure at 3 months and 6 months after initiating daily potassium supplementation versus low-dose hydrochlorothiazide and will evaluate this intervention's ability to remain within a non-inferiority margin. This study will elucidate the role of daily potassium supplementation in treating mild-to-moderate hypertension in African Americans as a safer alternative to hydrochlorothiazide monotherapy.

Chapter 1: Introduction

1.1 Background

1.1.1 Epidemiology

Hypertension is a leading cause of morbidity and mortality worldwide. It is common, poorly controlled, and a primary risk factor for a variety of chronic conditions and adverse health events. In the United States alone, 108 million people have hypertension and it contributes to over 400,000 deaths per year. The high cost of health services, antihypertensive medications, and lost productivity from related deaths cost the nation over \$48 billion annually.¹ In 2018, an age-adjusted 46.6% of adults over 20 were hypertensive. A variety of biological, environmental, and genetic factors precipitate a drastically uneven distribution of this disease throughout the population. In 2017-2018, the rate of hypertension among adults in the U.S. was 43.7% in whites, 45.1% in Hispanics and Latinos, and 47.2% in Asian Americans. These numbers pale in comparison to the 57.5% prevalence rate in African American adults.²

Blood pressure (BP) control is essential for hypertensives to reduce risk of adverse health effects. However, despite being preventable and treatable, only about half of Americans with hypertension reach blood pressure goals set by government health initiatives. Healthy People 2020 set a goal of 60.8% hypertension control, which was defined as <140mmHg systolic blood pressure (SBP), and <90mmHg diastolic blood pressure (DBP) for the years 2013-2016. The National Health and Nutrition Examination Survey (NHANES) determined that only 47.8% of adults had their hypertension under control during this period. Furthermore, rates of hypertension control are distributed

unevenly among racial/ethnic groups. Non-Hispanic white adults have a 55.7% control rate versus 48.5% in African Americans.³

Secondary to high prevalence and poor control, African Americans are much more likely to suffer from related morbidity and mortality. Sustained blood pressure above 130/80mmHg has deleterious effects on many organ systems. This encompasses a variety of cardiovascular pathologies like left ventricular hypertrophy (LVH), heart failure (HF), myocardial infarction (MI), stroke, and aneurysm. The prevalence of HF is 1.5x greater in African Americans, and the chance of developing HF at age <50 is 20-fold greater than in non-African Americans.⁴ Similarly, among adults over the age of 18, the prevalence of stroke in African Americans is 4.0% vs. 2.6% in white people.² Renal disease secondary to hypertension also disproportionately impacts this population. Hypertension is the second leading cause of end stage renal disease (ESRD), with an even greater risk in this population.⁵ African Americans account for a staggering 28% of hemodialysis patients, and nearly two thirds of ESRD patients with a principally hypertensive etiology.⁶ Of note, recent research suggests that the apolipoprotein L1 gene (APOL1) common in people of African Ancestry may play a large role in the marked excess of ESRD in this population.⁷ Additional sequelae include retinopathies, metabolic dysfunction, and cognitive decline. Largely due to the disparities in hypertension prevalence and control between ethnic/racial groups, there too are disparities in the end-organ manifestations of hypertension. Because these harmful sequelae are where the true costs lie, it is important to address the disproportionate rates at which African Americans are affected. Overall, hypertension may be responsible for up to 50% of the mortality disparity between African Americans and non-African Americans.⁸

1.1.2 Etiology

Hypertension has multiple etiologies which have been extensively investigated in African Americans. Its pathogenesis can be broken down into two categories: environmental and biological.

The first and most multifaceted group of etiologies pertains to environment, encompassing a wide variety of socioeconomic and psychosocial factors that contribute to an individual's lifetime risk of developing hypertension. One of the most effective methods of prevention and management of hypertension is adherence to a healthy diet. The DASH diet is a well-studied set of dietary guidelines proven to lower blood pressure, though a number of socioeconomic factors reduce the number of African Americans benefiting from it. The DASH diet is rich in fresh fruits, vegetables, and whole grains, and limits added sugars and saturated fats.⁹ Predominantly African American communities have significantly less access to healthy food and more access to fast-food than predominantly white neighborhoods.¹⁰ Discrepancies in food access also contribute to obesity. Its prevalence in African Americans is 48.6% and only 40.2% for white people.² Of all ethnic/racial groups, non-Hispanic African Americans are least likely to meet USDA fruit and vegetable consumption guidelines, largely due to limited access.¹¹ Poor availability of low sodium, high potassium food options elucidates this population's need for additional options for reducing blood pressure.

There are multiple biological factors which contribute to the undue burden of hypertension in African Americans. These fall into three main categories: vascular dysregulation, volume dysregulation, and renin-angiotensin-aldosterone system (RAAS) dysregulation.

There are a number of vasodilatory and vasoconstrictive mechanisms that regulate blood pressure. Overall, African Americans are more sensitive to sympathetic nervous system (SNS) mediated vasoconstriction, are less sensitive to endogenous vasodilators, and have decreased production of endothelium-dependent nitric oxide (NO).¹² Imbalances between vasodilatory and vasoconstricting forces predispose this population to essential hypertension. Additionally, central aortic pressures have been proven to outperform brachial pressures in predicting cardiovascular outcomes.¹³ This helps explain poorer outcomes in hypertensive African Americans compared to white people with comparable blood pressure control.

Blood pressure is also physiologically managed through volume regulation by the kidneys. The term salt-sensitivity encompasses the differences in individuals who develop high blood pressure with excess ingestion of sodium chloride, an estimated 50-60% of hypertensives.¹⁴ Enhanced salt-sensitivity has widely been reported to disproportionately affect African Americans. However, the correlation between race and salt-sensitivity is highly dependent on daily potassium intake. A 2021 review examined this relationship and found that when African Americans consume greater than 100mEq/day of potassium, their likelihood of being salt-sensitive was equal to that of non-African Americans.¹⁵ Therefore, utilizing potassium supplementation in this population may reduce disparities in hypertension by targeting renal mechanisms that respond to salt intake.

Lastly, RAAS dysfunction plays a significant role in the high prevalence of uncontrolled hypertension in African Americans. RAAS activates when afferent arterioles of the kidney sense low blood volume and secrete renin which ultimately

increases circulating angiotensin II. Angiotensin II produces a number of physiologic effects including vasoconstriction, downregulation of renin synthesis, increased renal reabsorption of sodium, aldosterone release, and increased fibroblast and collagen deposition.⁶ Low renin-hypertension is common in African Americans and is likely caused by high local angiotensin II production, which has the additional effect of promoting inflammation, fibrosis, and renal salt retention.¹⁶ These effects mediate peripheral vascular dysfunction, LVH, diastolic dysfunction, and inappropriate fluid retention. Salt-sensitive, low-renin African Americans demonstrate high urine angiotensinogen and high SBP, suggesting overactivity of RAAS.¹⁷ Lastly, African Americans tend to have enhanced aldosterone sensitivity, further amplifying the hypertensive effects of RAAS dysfunction.¹⁸

1.1.3 Treatment

The International Society on Hypertension in Blacks derived a treatment algorithm with racial/ethnic differences in mind. They determined a blood pressure goal of <135/85mmHg with no target-organ injury or cardiovascular disease (CVD), and <130/80mmHg with target-organ injury or CVD. If an individual is <15/10mmHg above goal, recommended therapy is monotherapy with a diuretic or calcium channel blocker (CCB).¹⁹

Antihypertensive medications are crucial in hypertension control. Lowering SBP to a target of <120mmHg has significant implications regarding the risk of a major adverse cardiovascular event.²⁰ Thiazide diuretics are the most effective medication for reducing blood pressure and preventing multiple forms of major CVD, with an even greater effect in African Americans.^{21,22}

Thiazides exert their effect by inhibiting sodium-chloride channels in the proximal segment of the distal convoluted tubule (NCC) decreasing sodium and water reabsorption. Consequently, high concentrations of sodium in the nephron lumen are delivered to the distal segment of the distal convoluted tubule which increase the activity of aldosterone-mediated sodium-potassium antiporters (ENaC), leading to potassium wasting. This mechanism of action contributes to adverse effects like hypokalemia, hyponatremia, metabolic alkalosis, hypercalcemia, hyperglycemia, hyperuricemia, hyperlipidemia, and sulfonamide allergy reaction.²³

Potassium acts as a diuretic by increasing renal sodium excretion via NCC modulation, and also modifies neural mechanisms that regulate blood pressure.²⁴ Plasma potassium concentration plays a dominant role in regulating NCC, and extracellular potassium concentration indirectly affects NCC via modulation of intracellular chloride concentration.²⁵ This mechanism of action is akin to that of thiazide diuretics, exemplifying the similarly enhanced effect these treatments have on RAAS suppressed hypertensives. Additionally, the low sodium, high potassium diet associated with lower BP is also correlated with increased baroreceptor activity and therefore enhanced physiological antihypertensive response. Lastly, the potassium cation acts as a vasodilator by interacting directly with arteriolar smooth muscle.²⁴ Potassium supplementation as a means to lower SBP has been investigated in the African American population and has demonstrated significant decreases in SBP and DBP.²⁶

RAAS blockers and CCBs are also widely used, efficacious methods of blood pressure control in all populations. However, due to the unique etiologies of hypertension common among African Americans, thiazide diuretic monotherapy has the strongest BP-

reducing effects when compared to monotherapy with other antihypertensives.^{21,27}

Potassium supplementation demonstrates comparable efficacy with a favorable side effect profile.²⁸⁻³⁰

1.2 Statement of the Problem

African Americans are disproportionately affected by hypertension and associated morbidity and mortality due to high prevalence rates and low control rates. Monotherapy with thiazide diuretics is the most efficacious first-line pharmacological intervention for this population.²² Potassium supplementation also has a proven BP-reducing effect in this population and shares a similar mechanism of action.²⁶ A gap in the literature currently exists around the comparative efficacy of potassium supplementation versus thiazide-type diuretics in treating African Americans with hypertension. This, combined with the unfavorable side effect profile of thiazides compared with that of potassium supplementation, warrants investigation into the non-inferiority of the latter with regards to SBP control.²³ Furthermore, predominantly African American communities are more likely to be subject to high salt and low potassium diets, suggesting even greater efficacy with this treatment.¹⁰

1.3 Goals and Objectives

The goal of this study is to investigate the potential non-inferiority of daily potassium supplementation to hydrochlorothiazide (HCTZ). The primary outcome measure is change in SBP from baseline at 3 months and 6 months as measured by averaged 24hr ambulatory blood pressure monitoring (ABPM). If the SBP change in the intervention group is within the specified margin of non-inferiority, we can conclude that

daily potassium supplementation is a viable alternative to HCTZ in lowering SBP in our target population.

1.4 Hypothesis

In the management of hypertension in African American adults aged 20-65, daily potassium supplementation (80mEq/day) is non-inferior to low dose (25.0mg/day) HCTZ in reducing SBP as measured by averaged 24h ABPM at 3 months.

Table 1. American Heart Association Hypertension Staging

BP category	Systolic (mmHg)		Diastolic (mmHg)
Normal	Less than 120	And	Less than 80
Elevated	120-129	And	Less than 80
Hypertension Stage 1	130-139	Or	80-89
Hypertension Stage 2	140-180	Or	Higher than 90
Hypertensive Crisis	Higher than 180	And/Or	Higher than 120

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Chapter 2: Review of the literature

2.1 Literature Search

Beginning in December 2021, we repeatedly searched the online databases of PubMed, Ovid, and Cochrane Library to review the literature pertaining to potassium supplementation and HCTZ in the treatment of hypertension among African Americans. Searches were conducted with the following terms to produce papers with matching titles or abstracts. To encompass our target population, we used “African American,” “black,” and “African ancestry.” For our treatments, we used the terms “blood pressure,” “hypertension,” “hydrochlorothiazide,” “HCTZ,” “dietary potassium,” “oral potassium,” and “potassium supplement.” We included pertinent clinical trials, systematic reviews, and meta-analyses. Additionally, we included some papers which were referenced by those included by our original search terms. Time constraints were not enacted due to the long history of hypertension management.

Reviewing the literature further reinforces the differences in environment and biology which lead to high rates of hypertension in African Americans. It also highlights the benefit that potassium supplementation may have in this population and its potential role as an alternative therapy for mild-to-moderate hypertensives. Additionally, it outlines potassium’s favorable side effect profile. This review will highlight the benefits of potassium supplementation and reveal limitations in current research to reinforce the importance of our non-inferiority trial.

2.2 Review of Empirical Studies About Relationships Studied

2.2.1 Potassium and Blood Pressure in African Americans

Dietary potassium intake has demonstrated efficacy in reducing SBP in African Americans with hypertension.¹ Low-salt, high-potassium diets have long been regarded as beneficial in treating hypertension, thus forming the basis for the DASH diet.² A 2019 review summarizes that dietary potassium both modulates the RAAS which is often dysregulated in hypertensives, and acts as a regulator for multiple transporters in the renal tubules to reduce BP.³

Our literature search yielded four particularly relevant clinical trials pertaining to the blood pressure reducing effect of potassium supplementation on people of African ancestry. A randomized, single-blind, controlled trial conducted in 1986 investigated the BP-reducing efficacy of 65mmol/day potassium supplementation vs. placebo in hypertensive black females. Participants began the study with a washout period on placebo, followed by a 6-week trial period with BP measurements every 2 weeks. Researchers found that mean SBP at the end of the trial period was 7.0 mmHg lower in the potassium chloride group than the placebo group with $p < 0.01$. They also found that the SBP drop in the potassium group was associated with a significant rise in urine potassium during treatment from 51 ± 3 mmol/24h to 112 ± 8 mmol/24h ($p < 0.001$).⁴ Multiple limitations of this study warrant further investigation into the clinical applicability of potassium supplementation. First, because of the powdered form of the administered intervention, blinding participants was not possible due to changes in taste. Second, the study includes a small sample size of black female domestic servants in South Africa which limits external validity and generalizability of results to African

Americans. Third, the trial period lasted only 6 weeks and only 32 of 50 initial participants completed the trial, limiting the study's internal validity. Lastly, BP measurements were operationalized as the mean of three sphygmomanometer readings over five minutes which leaves results subject to white-coat hypertension or masked hypertension. This study provides valuable insight into the significant BP-reducing effect of potassium supplementation on people of African ancestry, but further investigation into its efficacy in broader study populations is warranted.

A 1989 RCT supported these findings by comparing the effect of 64 mmol/day of potassium supplementation with placebo on BP in Kenyans with newly diagnosed hypertension. Researchers selected 48 participants based off their age (20-60 years), DBP (90-109mmHg), SBP (>160mmHg), serum potassium (<4.5mmol/L), and serum creatinine (0.6-1.3mg/dL). Baseline characteristics were gathered 2 weeks after selection, and BP measurements were taken every 4 weeks for 16 weeks after randomization. Average SBP / DBP in the potassium group dropped from $175 \pm 10 / 100 \pm 3$ to $133 \pm 10 / 83 \pm 4$. In contrast, average SBP / DBP in the placebo group changed from $173 \pm 8 / 100 \pm 4$ to $172 \pm 7 / 100 \pm 4$.⁵ $P < 0.001$ for primary outcome measurements. These results demonstrate significant reduction of blood pressure after 16 weeks of daily potassium supplementation. This study's strengths include excellent adherence to protocol monitored by pill-count, 100% trial completion by participants, and adequacy in double-blinding. However, it also has multiple weaknesses. A small sample of newly diagnosed hypertensives in Nairobi limits generalizability to African Americans who experience vastly different socioeconomic circumstances. Additionally, BP readings were taken using an average of two sphygmomanometer readings at each clinic visit, subjecting

results to inaccuracies like white-coat hypertension or masked hypertension. Lastly, high sodium consumption acted as a potential confounder as it is associated with both the development of hypertension and an enhanced response to potassium supplementation. Authors address this association but did not implement measures to regulate sodium consumption over the 16-week trial period. Overall, this study sufficiently demonstrated antihypertensive effect of potassium supplementation in people of African ancestry.

A 1996 randomized, double-blind, controlled trial investigated the BP-reducing effect of potassium supplementation on African Americans consuming a low-potassium diet. Researchers justified the need for this study with background evidence supporting inherent BP sensitivity to potassium, and the generally low-potassium consumption in this population. They investigated this association by providing all 87 participants a low-potassium diet over the 21-day intervention period while randomizing them to 80mmol/day potassium supplementation or placebo. At the conclusion of the trial period, mean SBP in the potassium group fell by 6.9mmHg (95% CI, -9.3 to -4.4mmHg; $p < 0.001$) and mean DBP fell by 2.5mmHg (95% CI, -4.3 to -0.8mmHg; $p = 0.01$). Additionally, after adjusting for baseline differences between groups in age, gender, BMI, 24h urinary potassium and sodium, alcohol use, and cigarette smoking, potassium supplementation was associated with an even greater magnitude of effect. SBP dropped by 7.1mmHg (95% CI, -9.7 to -4.5 mmHg) and DBP dropped by 2.7mmHg (95% CI, -4.5 to -1.0mmHg).⁶ At the final follow-up, the difference between groups reached 8.4mmHg (95% CI, -12.3 to -4.7mmHg) SBP and 4.4mmHg (95% CI, -7.4 to -1.4mmHg) DBP. This study further demonstrates the BP-reducing efficacy of potassium supplementation. Strengths of this study include adequate blinding, and excellent adherence to both the

low-potassium diet and pill taking. Limitations to this study include a short intervention period of 21-days which may not encompass the full degree of association between intervention and outcome. Additionally, BP measurements were taken via sphygmomanometer and operationalized as the mean of three readings taken at each visit. Lastly, 15% of participants did not complete the trial after randomization, possibly influencing outcome data. Overall, this study did an excellent job investigating the association between potassium supplementation and BP in African Americans consuming a low-potassium diet. This is particularly relevant due to evidence suggesting low-potassium consumption in this population, as well as biological mechanisms which predict enhanced sensitivity to potassium.⁷⁻⁹ It builds upon data previously collected on people of African ancestry living outside the United States, and is conducive to further investigation into the therapeutic role of potassium supplementation.

A fourth study conducted in 1987 was a randomized, double-blind, controlled trial investigating the blood pressure response of oral potassium vs. placebo in all populations. The study sample included 116 American adults with hypertension, 12 of whom were self-reported African Americans. Though African Americans were underrepresented in this trial, the BP-reducing efficacy of potassium supplementation in this population was staggering. Participants were randomized to 40mEq potassium chloride three times daily or placebo over an 8-week treatment period. The potassium group experienced an average change in SBP of -6.4 ± 13.7 mmHg ($p < 0.025$) vs. -0.11 ± 13 mmHg ($p = 0.96$) in the control group. DBP changed in the potassium group by -4.1 ± 8.3 mmHg ($p < 0.05$) and by -1.6 ± 6.5 mmHg ($p = 0.09$) in the control group. However, the five African Americans in the potassium group experienced a change in SBP / DBP of -19 ± 24 / $-13 \pm$

10 mmHg versus a change of $-1 \pm 7 / 0 \pm 6$ mmHg among the seven taking placebo.¹⁰

This study exemplifies the enhanced BP-reducing effect of potassium supplementation in African Americans. The dramatic BP response to potassium supplementation in this population may be explained by some of the socioeconomic^{11,12} and biological factors^{13,14} noted in the background section. The primary weakness of this study is the inadequate representation of African Americans in the study sample, limiting internal validity. Additionally, outcome data was collected as averaged office BP as measured by sphygmomanometer readings. Despite these weaknesses, this study provides valuable information on the BP-reducing ability of potassium supplementation among Americans, and demonstrates a significantly greater effect in African Americans.

2.2.2 Thiazides and Blood Pressure in African Americans

Thiazide-type diuretics are effective in treating hypertension, especially in the African American population. The 2017 American College of Cardiology guidelines for the treatment of hypertension recommend that initial therapy for stage 1 hypertension includes thiazide diuretics, CCBs, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the general non-black population. The recommendation for African Americans with stage 1 hypertension includes only thiazide diuretics and CCBs.¹⁵ These guidelines are the result of a number of trials examining the BP-reducing effect of antihypertensive pharmacotherapies in this population.^{16,17}

A 1996 study investigated the efficacy of HCTZ monotherapy on people of African ancestry as measured by ABPM. It included 19 participants with an average DBP of 95-115mmHg and excluded those with secondary hypertension, hypertensive emergency, SBP >200mmHg, CHF, recent MI or stroke, hepatic or renal disease, DM,

hyperuricemia, or thiazide intolerance. They initiated oral HCTZ 12.5mg daily, and titrated to 25mg daily if DBP did not decrease to <90mmHg at four weeks. At four weeks, SBP / DBP changed by -11 / -6 mmHg determined by 12h averaged ABPM, and -8 / -6 mmHg determined by 24h averaged ABPM. Surprisingly, increasing the HCTZ dose from 12.5mg to 25.0mg did not elicit a significant reduction in BP, but did produce a significant reduction in serum potassium (3.9 ± 0.4 mmol/L to 3.6 ± 0.4 mmol/L, $p>0.05$).¹⁸ These results demonstrate the BP reduction and associated electrolyte disturbances produced by HCTZ monotherapy in people of African ancestry. This study's strengths include its prospective design, pertinent study population, and variety of measurements. By measuring SBP and DBP with Dinamap devices as well as 12h and 24h ambulatory blood pressure monitoring, researchers evaluated changes in outcome data produced by different measurement techniques. A small sample size and a geographically limited population of only 19 participants from South Africa, hinders external validity. This trial provides additional evidence supporting the role of HCTZ in treating hypertension in people of African ancestry, as well as data to suggest that ABPM may provide more accurate BP measurements than traditional methods.

A 2017 randomized controlled trial compared the BP-reducing efficacy of HCTZ monotherapy with that of amlodipine in hypertensive people of African ancestry. Though the aim of the study was to compare efficacy and effects on electrolytes, it yields valuable information about HCTZ for the purposes of this paper. Fifty patients with newly diagnosed mild-to-moderate hypertension were randomized to 5mg amlodipine or 25mg HCTZ daily over a treatment period of 4 weeks. After the treatment period, the HCTZ group experienced a change in SBP of -8.55 ± 1.64 mmHg, change in DBP of $-5.22 \pm$

1.45 mmHg and change in MAP of -8.12 ± 2.15 mmHg ($p < 0.001$). Additionally, HCTZ significantly reduced serum sodium, potassium, and chloride from their baseline levels which is consistent with the study previously discussed.¹⁹ These results demonstrate the BP reduction and electrolyte disturbances elicited by daily HCTZ. However, this study had multiple limitations. First, the narrow study population consisted of only 50 participants from Enugu, Nigeria. Data from this population has limited generalizability to African Americans due to different socioeconomic and cultural circumstances. Additionally, BP readings were recorded as the average of two sphygmomanometer readings taken at five-minute intervals instead of using ABPM to control for white-coat and masked hypertension.

A 2016 study evaluating rates of BP control among various initial drug selection strategies provides insight into the role of thiazide diuretics in treating African Americans. This study retrospectively analyzed data previously collected in the PEAR-1 study, whose sample consisted of 294 African American subjects and 439 non-African American subjects with hypertension. Participants were randomized to 50mg atenolol or 12.5mg HCTZ daily, titrated to 100mg or 25mg respectively. After the 9-week trial period, African American participants taking HCTZ experienced an average change in SBP of -15.6 ± 14.4 mmHg and average change in DBP of -9.3 ± 8.7 mmHg.²⁰ Though the primary outcome of this study was percentage BP control based on treatment initiation strategy, it provides valuable information on the BP-reducing efficacy of 12.5 – 25mg HCTZ in African Americans with hypertension.

Furthermore, thiazide diuretics consistently show the greatest BP-reduction in African Americans when compared with other antihypertensive monotherapies. A

subgroup analysis of the landmark ALLHAT¹⁶ trial revealed differences in outcomes among African American vs. non-African American participants taking chlorthalidone, amlodipine, or lisinopril. African Americans taking daily chlorthalidone experienced a change in SBP from baseline of -7.7 ± 19.2 , -8.6 ± 20.1 , and -10.5 ± 20.4 mmHg at 1 year, 2 years, and 4 years respectively. BP-reduction was inferior in the amlodipine and lisinopril groups for this population, but was comparable in non-African American participants.¹⁷ This subgroup analysis of the ALLHAT trial elucidates the superior antihypertensive effect of thiazide-type diuretics this population, and justifies their role as the first-line antihypertensive.

2.2.3 Thiazide Diuretics vs. Potassium Supplementation

A 1991 randomized controlled trial investigated the efficacy of bendrofluazide versus potassium supplementation in hypertensives living in Nairobi, Kenya. The study sample consisted of 84 newly diagnosed hypertensives of African ancestry with DBP 105-110mmHg who were randomized to 64mEq/day of potassium or 10mg/day of bendrofluazide. Baseline characteristics were collected 2 weeks after recruitment, followed by a 4-week placebo period to eliminate placebo responders. SBP and DBP were measured at baseline and at 4-week increments during the trial period. SBP / DBP in the potassium group dropped from $165 \pm 16 / 108 \pm 5$ mmHg to $150 \pm 12 / 95 \pm 5$ mmHg. The BP reduction in the bendrofluazide group was from $165 \pm 14 / 108 \pm 5$ mmHg to $146 \pm 5 / 92 \pm 4$ mmHg ($p < 0.01$ for potassium group, $p < 0.001$ for bendrofluazide group).²¹ Authors also note that mean 24h urine sodium increased from 139 to 156 mmol in the potassium group versus 142 to 149 mmol in the bendrofluazide group, $p < 0.01$ and $p < 0.05$ respectively, demonstrating potassium's superior natriuretic

effect. Weaknesses of this study include its narrow sample limited to residents of Nairobi with severe hypertension. This hinders generalizability to African Americans with mild-to-moderate hypertension. Additionally, authors only include BP results through 8 weeks in the bendrofluazide group, despite the trial period lasting 28 weeks. This limits comparison between the intervention groups, as the progressive BP decrease with potassium supplementation was not directly compared with that of bendrofluazide. Lastly, BP measurements were taken with a random zero sphygmomanometer, and the authors do not specify time of day or number of readings averaged at each measurement. Overall, this study provides valuable data regarding BP-reducing efficacy of bendrofluazide and potassium supplementation, as well as insight into differences in side effects between the two treatments. However, multiple limitations warrant further investigation into the potential of potassium supplementation as an alternative to thiazide diuretics for African Americans with hypertension.

2.3 Review of Studies about Adverse Effects

2.3.1 Adverse Effects of Thiazide Diuretics

Thiazide diuretics are generally well tolerated but can cause adverse effects. Skin photosensitivity and increased risk of squamous cell carcinoma of lips and basal cell carcinoma of skin occur with cumulative use. Reversible electrolyte disturbances like hypokalemia, hypomagnesemia, hypercalcemia, and hyponatremia may occur and increase the risk of cardiac arrhythmias. Hyperuricemia may occur and precipitate gout or gouty arthritis. Lastly, hypersensitivity reactions are a risk, especially in individuals with known intolerance to thiazide diuretics.²²

The previously mentioned study comparing bendrofluazide with potassium supplementation outlines multiple differences in side effects between the treatments. Authors note that 15 of the 42 participants in the bendrofluazide group developed hyperuricemia without gout, hyperglycemia, and hypokalemia, whereas none of the patients in the potassium group developed biochemical abnormalities.²¹ Additionally, Skoularigis et al.'s 1995 study measuring HCTZ efficacy in African Americans revealed that a daily HCTZ dose of 25.0mg was associated with a significant decrease in serum potassium: 3.9 ± 0.4 mmol/L to 3.6 ± 0.4 mmol/L, $p < 0.05$.¹⁸ Thiazide diuretics frequently produce a number of electrolyte abnormalities that are largely absent in those treated with potassium supplements.

2.3.2 Adverse Effects of Potassium Supplementation

Oral potassium supplementation is generally well tolerated but also may elicit adverse effects. The most serious is hyperkalemia leading to potentially fatal arrhythmias, though this is much more likely during intravenous administration than oral intake. More common side effects include gastrointestinal symptoms like diarrhea, flatulence, nausea, vomiting, and abdominal pain. Gastrointestinal ulcers are rare.²³

Previously mentioned studies investigating potassium supplementation's efficacy in reducing BP provide evidence to support its mild side effect profile. The 1987 study by Svetkey et al. noted that side effects of potassium were primarily abdominal pain and gas, and zero participants experienced altered renal function, gastrointestinal bleeding, or hyperkalemia.¹⁰ Obel et al.'s 1989 study revealed that serum electrolytes after 16 weeks of potassium supplementation remained stable; average serum sodium changed from 139 ± 3 to 140 ± 4 mmol, and serum potassium remained unchanged at 4.0 ± 0.3 mmol/L pre-

and post-treatment.⁵ Lastly, Matlou et al.'s 1986 study revealed no significant biochemical abnormalities after 6 weeks of daily potassium chloride.⁴ Studies examining potassium supplementation as a means to control BP reveal a relatively benign side effect profile and support its superiority to thiazide diuretics in this regard.

2.4 Review of Relevant Methodology

2.4.1 Possible Confounding Variables

In Brancati et al.'s 1996 study comparing daily potassium supplementation with placebo in regards to blood pressure reduction in African Americans, regression analyses identified variables which contributed to the magnitude of the primary outcome. They found that cigarette smoking was an independent predictor of blood pressure response to the intervention. After simultaneous adjustment for age, gender, BMI, baseline BP, alcohol use, urinary sodium and potassium excretion, nonsmokers experienced a decrease in SBP of 5.0 mmHg (95% CI, -10.2 to 0.2) when compared to smoking counterparts.⁶ Urinary potassium excretion was also identified as a variable associated with potassium intake and blood pressure by multiple studies, but is part of the causal pathway and therefore not a confounder.^{4-6,10,21}

Plasma renin activity (PRA) is associated with both potassium supplementation and HCTZ. Obel et al.'s 1991 study comparing the efficacy of bendrofluazide with potassium supplementation showed a statistically significant PRA increase in response to both treatments. PRA increased from 0.42 ± 0.60 to 2.64 ± 1.92 ng/mL/hr $p < 0.001$ in the potassium group, and from 0.44 ± 0.83 to 2.37 ± 1.72 ng/mL/hr $p < 0.01$ in the bendrofluazide group over the 28-week trial period.²¹ Furthermore, Garaibeh et al's 2016 study comparing drug selection strategies for initial antihypertensive therapy made two

relevant findings. First, PRA suppression (<0.6 nl/ml/hr) was more common in black subjects (64%) vs white subjects (22%). Second, African Americans with suppressed PRA had improved BP control rates with HCTZ: 57.9% control as measured by 24h ABPM.²⁰ PRA levels are associated with the magnitude of BP response in patients taking potassium supplements or HCTZ.

2.4.2 Noninferiority Design

Noninferiority trials serve to determine if new treatments are not unacceptably less efficacious than treatments already part of standard practice. This study will investigate the noninferiority of daily potassium supplementation to HCTZ monotherapy. Because this comparison has not been conducted with this study design, we will extrapolate an appropriate margin of noninferiority from similar trials. The OPTiMISE trial examined whether antihypertensive deprescription in the elderly is possible without significant changes to blood pressure control. Researchers determined a noninferiority margin of 10% change in SBP at the primary endpoint. Because of this study's primary endpoint and similar design, the noninferiority margin of 10% gives insight into the margin required for our study.²⁴ Another study comparing the effects of Azilsartan-Medoxomil and Olmesartan on systolic blood pressure calculated a noninferiority margin of 1.5mmHg, approximately equal to 10%. This trial's randomized, parallel group, double-blind, placebo-controlled design combined with its examination of SBP-reducing efficacy as measured by ABPM suggest that this noninferiority margin matches the needs of our study.²⁵ Lastly, a randomized controlled trial comparing the SBP reduction produced by Zofenopril-HCTZ with Irbesartan-HCTZ utilized a noninferiority margin of 10%. This study's design, methodology, and primary endpoints parallel that of our study

and provides support for our use of a similar noninferiority margin.²⁶ Our proposed study will not incorporate a third control arm because the efficacy of our interventions versus placebo are already established.^{6,18}

2.4.3 Ambulatory Blood Pressure Monitoring

ABPM provides many advantages over conventional BP measuring modalities. It provides greater reproducibility of results in clinical trials, accounts for circadian variation in blood pressure, and eliminates biases caused by white-coat hypertension or masked hypertension. Additionally, ABPM reduces the size of placebo effect on blood pressure. Lastly, it eliminates the need for multiple postural readings at a clinic, reducing burden to the patient while simultaneously producing more accurate results.²⁷

2.4.4 Primary Outcome Variable

Systolic blood pressure is a common outcome variable to measure BP-reducing efficacy of antihypertensive regimens. The SPRINT trial prospectively investigated the association between the degree of SBP control with cardiovascular events. This study randomized 9361 50+ year old hypertensives with SBP 130-180 to intensive SBP control (target <120mmHg) or standard SBP control (target <140mmHg). Cardiovascular events occurred in 1.65% per year of participants in the intensive treatment group, and in 2.19% per year of those in the standard treatment group. The hazard ratio with intensive treatment was 0.75; CI 95%, 0.64 to 0.89 p<0.001.²⁸ This landmark study demonstrates the significance of SBP control and justifies it as a primary outcome variable for our antihypertensive study.

2.4.5 Secondary Outcomes

There are a range of secondary outcome variables associated with HCTZ and potassium supplementation. A 1985 study administered potassium supplementation to patients with uncomplicated hypertension who were hypokalemic after diuretic therapy, monitoring BP along with a variety of secondary outcomes. In addition to changes in BP, patients experienced changes in PRA, urine potassium, urine sodium, and serum potassium. PRA was 3.62 ± 0.88 ng/ml/hr in the control group and 3.29 ± 0.22 ng/ml/hr in the potassium supplementation group ($p=0.047$) after the trial period, indicating that potassium intake may be associated with a change in PRA. Additionally, the control group's average serum potassium was 2.94 ± 0.1 mmol/L while that of the potassium group was 3.56 ± 0.1 mmol/L ($p<0.001$). 24-hour urine potassium was 45.6 ± 5.7 mEq/L in the control group and 81.9 ± 7.0 mEq/L in the potassium group ($p<0.001$).²⁹ This study provides prospective data on the associations between potassium supplementation and PRA, 24hr urine potassium, and serum potassium and indicates their utility as secondary outcomes.

Incidence of diabetes is also associated with long-term use of thiazide diuretics. The ALLHAT trial revealed that the prevalence of new diabetes was significantly higher in patients taking chlorthalidone than in those taking lisinopril or amlodipine.¹⁶ The mechanism underlying this relationship likely pertains to the hypokalemic effect of thiazide diuretics, as potassium is a cofactor for insulin.^{30,31} Including Hemoglobin A1c (HbA1c) as a secondary variable may provide insight into the differential risk of developing metabolic dysfunction with thiazide diuretics vs potassium supplements as it represents long-term blood glucose control.³²

HCTZ is also associated with changes in urine and serum electrolytes. A prospective trial comparing HCTZ and amlodipine found that HCTZ was associated with significant decreases in serum potassium and significant increases in urine potassium, chloride, and sodium.¹⁹ Another study investigating the association between race, PRA, and response to antihypertensive therapy revealed that African Americans with low PRA had an enhanced BP response to HCTZ.²⁰ Additionally, the 1991 trial comparing bendrofluazide with potassium supplementation noted differences in serum glucose between groups at the end of trial. 15 of 45 patients in the bendrofluazide group developed hyperglycemia vs 0 patients in the potassium group.²¹ Lastly, HCTZ is associated with increased serum uric acid and is known to precipitate gout flares.^{22,33} A study comparing the effects of atenolol vs. HCTZ monotherapy on a range of outcome variables provides significant prospective data on this relationship. After 9 weeks of HCTZ monotherapy, participants' serum uric acid increased by an average of 1.0 ± 0.9 p<0.0001.³⁴ Contrarily, correlations between potassium supplementation and hyperuricemia have not been observed in existing prospective trials.²¹

2.4.6 Inclusion and Exclusion Criteria

Inclusion criteria for our study include the following: self-reported African American ancestry, age 20-65 years old, and newly diagnosed or unmanaged hypertension <10mmHg SBP above goal. There are multiple modalities by which participants can be identified as African American, including self-reporting, investigator observed, database, EMR, survey instrument, etc.³⁵ We believe that self-reporting is the most respectful, accurate, and culturally sensitive modality. The age range of 20-65 is common among trials of antihypertensives among the adult population.⁶ This range

encapsulates a large percentage of African Americans with hypertension and excludes the extremes of age at which severe, refractory, or secondary hypertension are more common.³⁶ Also, HCTZ is a Beers Criteria medication and should be avoided in the elderly when possible.^{22,33} Lastly, newly diagnosed or unmanaged hypertension <10mmHg SBP above goal is appropriate for inclusion because this is the patient population in which monotherapy with a diuretic is indicated.³⁷

Exclusion criteria will include 1) Use of medications that affect blood pressure or urinary excretion of sodium or potassium (ie. antibiotics, antidepressants, laxatives, diuretics, stimulants, decongestants, lithium); 2) Alcohol consumption exceeding 14 drinks per week; 3) Use of recreational drugs; 4) CVD requiring medication other than aspirin (ie. CHF, MI, stroke); 5) Peptic ulcer disease requiring treatment in the last 2 years; 6) Diabetes mellitus or random blood glucose >200mg/dL; 7) Malignancy requiring treatment in the last year; 8) Serum potassium >4.5mmol/L; 9) Estimated GFR <45mL/min; 9) History of intolerance to thiazides; 10) Hepatic or renal disorders; 11) Secondary hypertension. These exclusion criteria are commonly implemented in hypertension research pertaining to potassium supplementation and HCTZ. They reduce bias and confounding when identifying relationships between our interventions and SBP.^{4-6,10,18,21}

2.4.7 Incentives

Potential clinical trial participants prefer an incentive and this preference increases with increasing value of said incentive. A 2020 discrete choice experiment revealed that individuals were 1.9 times more likely to participate with a \$40 incentive, and 5.9 times more likely to participate with a \$80 incentive. They also preferred cash to

vouchers.³⁸ Given this information, we expect that patients will appreciate a substantial incentive to participate over a 6-month period. Also, we predict that this incentive will increase the likelihood of reaching our target sample size.

2.5 Conclusion

Hypertension disproportionately affects African Americans. HCTZ is a thiazide-type diuretic that is often used as first-line monotherapy for African Americans with mild-to-moderate hypertension. However, it is associated with a number of adverse effects and biochemical abnormalities that are rarer or non-existent in studies of potassium supplementation as an antihypertensive. Potassium supplementation has comparable BP-reducing efficacy in this population and a favorable side effect profile. The proposed noninferiority study will address the role of potassium supplementation as an alternative to HCTZ in the treatment of mild-to-moderate hypertension in African Americans.

Chapter 2 References

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Chapter 3: Study Methods

3.1 Study Design

The proposed study is a randomized, double blind, parallel clinical trial designed to assess noninferiority of potassium supplementation versus HCTZ in regards to SBP reduction. This study will include self-identified African American adults aged 20-65 with blood pressure elevated such that diuretic monotherapy is indicated. Research team members will manage participants at various primary care clinics throughout the duration of the study. Baseline characteristics will be gathered after recruitment and before randomization. Participants will be randomized to either daily potassium supplementation or daily HCTZ, with both participants and researchers blinded to intervention groups. Team members will continue to assess adherence and outcome measurements at follow-up visits.

3.2 Study Population and Sampling

We will recruit patients with newly diagnosed or unmanaged hypertension in New Haven, Fairfield, and Hartford counties. Our methods for recruiting will include referrals from healthcare providers or friends, and flyers strategically placed in clinics and community spaces. We will provide potential participants with information on blood pressure control and health benefits as incentive for participation. Our recruitment period will last 12 months, or until we enroll our goal of 1238 participants.

3.3 Inclusion Criteria

Self-identified African American adults aged 20-65 with newly diagnosed or unmanaged mild-moderate hypertension defined as <10mmHg SBP above goal.

3.4 Exclusion Criteria

1) Use of medications that affect blood pressure or urinary excretion of sodium or potassium (ie. antibiotics, antidepressants, laxatives, diuretics, stimulants, decongestants, lithium); 2) Alcohol consumption exceeding 14 drinks per week; 3) Use of recreational drugs; 4) Cardiovascular disease requiring medication other than aspirin (ie. CHF, MI, stroke); 5) Peptic ulcer disease requiring treatment in the last 2 years; 6) Diabetes mellitus or random blood glucose >200mg/dL; 7) Malignancy requiring treatment in the last year; 8) Serum potassium >4.5mM; 9) Estimated GFR <45mL/min; 9) History of intolerance to thiazides; 10) Hepatic or renal disorders; 11) Secondary hypertension. Individuals who fall into any of these categories will be excluded from the study sample.

Table 2. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Self-identified African American • Adult aged 20-65 • Hypertension <10mmHg SBP above goal, newly diagnosed or unmanaged 	<ul style="list-style-type: none"> • Use of medications that affect blood pressure or urinary excretion of sodium or potassium (ie. antibiotics, antidepressants, laxatives, diuretics, stimulants, decongestants, lithium, ACEI/ARBs) • Alcohol consumption exceeding 14 drinks per week • Use of recreational drugs • Cardiovascular disease requiring medication other than aspirin (ie. CHF, MI, stroke) • Peptic ulcer disease requiring treatment in the last 2 years • Diabetes mellitus or random blood glucose >200mg/dL • Malignancy requiring treatment in the last year • Serum potassium >4.5mM • Estimated GFR <45mL/min • History of intolerance to thiazides • Hepatic or renal disorders • Secondary hypertension

3.5 Subject Protection and Confidentiality

Study protocol will be submitted to the Yale University Human Investigation Committee (HIC) for Institutional Review Board (IRB) approval. This process will grant us permission to involve human subjects in our research. All team members will complete Health Insurance Portability and Accountability Act (HIPPA) training and provide appropriate documentation.

Team members will brief each participant with expectations, associated benefits, and safety concerns. They will answer questions regarding study protocol. Participants will sign the most recent HIC-approved Informed Consent Form prior to enrollment. This form must be signed by either the patient or by his/her Power of Attorney. Protected patient information will be kept on a secure workstation connected to the Yale network, protected by passwords and security software.

3.6 Recruitment

We will contact primary care clinics in New Haven, Fairfield, and Hartford counties to ask about their interest in proposing our clinical trial to their eligible patients. With their permission, we will place informational flyers in waiting rooms. In addition, we will place these flyers in public community spaces like libraries, event centers, etc. We will take special consideration to ensure that selected primary care clinics serve a significant number of African American patients by using publicly available demographic information.¹ By defining a clear minority recruitment target and utilizing evidence-based recruitment strategies like community-based recruitment by healthcare providers, we expect to reach our recruitment goal in the allotted timeframe.²

3.7 Randomization

Enrolled participants will be randomized 1:1 to potassium supplementation or HCTZ using randomization software which will minimize differences in baseline characteristics between groups. Participants will each be provided an identification number to de-identify baseline characteristics and outcome data.

3.8 Blinding of Intervention

Both participants and team members will be blinded to assigned interventions. The pharmacy distributing the pills will be the only group with knowledge of whether pills are potassium or HCTZ. MEMS® TrackCap pill containers containing the 6-month supply will be marked with ID numbers which correspond with ID numbers assigned to participants. Neither the participants nor the research associates will know which ID numbers belong to which group. The pills will be identical in size, color, and shape.

3.9 Blinding of Outcome

The data analysis team will be blinded to the randomization of participants. They will be aware of identification numbers assigned to each participant, but not of the intervention group they are assigned to. The research team will remain blind to the treatment groups throughout the duration of the study and subsequent statistical analyses.

3.10 Adherence to Treatment

MEMS® TrackCap pill containers are pill dispensers with computer chips in their spring-loaded caps. The MEMS® TrackCap pill container wirelessly documents each time a pill is dispensed and has a battery life far exceeding the study duration. This

allows us to retrieve accurate adherence data for analysis, and eliminates the need for more frequent office visits to assess adherence via manual pill counting.

3.11 Study Variables and Measures

We will collect baseline characteristic data after recruitment and before randomization via clinical evaluation by a physician assistant, nurse practitioner, or physician. Baseline characteristics include: Age (years), sex (male/female), education (years), alcoholic drinks (number/wk), 24h urine potassium, sodium, calcium, magnesium, aldosterone (mEq/L), weight (kg), BMI, systolic and diastolic blood pressure (mmHg), serum potassium (mmol/L), plasma renin activity (ng/ml/hr), serum creatinine (mg/dL), cigarette smoking (yes/no). Using randomization software, we will minimize significant differences in baseline characteristics between treatment groups.

The independent variable will be the intervention: potassium supplements (80mEq) or HCTZ (25.0mg). These agents will be taken by mouth daily. The dependent variable will be SBP after 3 months as measured by averaged 24h ABPM. We will follow this up with a second reading at 6 months to determine the sustainability of these results. Secondary outcomes measures include diastolic blood pressure, 24h urine electrolytes, serum potassium, serum glucose, serum uric acid, HbA1c, and PRA which will be recorded during follow-up clinic visits.

Table 3. Baseline Characteristics

Characteristic	Potassium Supplementation	Hydrochlorothiazide	p-value
Age (years)			
Sex (female, %)			
Education (years)			
Weight (kg)			

BMI (percentage) <18.5 18.5 – 24.9 25.0 – 30.0 >30.0			
Blood Pressure (mmHg): Systolic Diastolic			
24h Urine Aldosterone (µg):			
24h Urine Electrolytes (mEq/L): Potassium Sodium Magnesium Calcium			
Serum Potassium (mmol/L)			
Serum Uric Acid (mg/dL)			
Serum Glucose (mmol/L)			
Plasma Renin Activity (ng/ml/hr)			
Serum Creatinine (mg/dL)			
Hemoglobin A1c (%)			
Cigarette Smoking (y/n)			
Alcoholic Drinks/week (#)			

3.12 Monitoring Adverse Events

Participants will have access to hotlines to report adverse events. Team members will be trained to properly document and timestamp adverse events as they occur, and will direct the caller to the proper source of care if necessary. Risks of adverse events will be thoroughly discussed with participants before obtaining informed consent.

3.13 Data Collection

Primary and secondary outcome data will be collected during office visits at 3 months and 6 months after initiation of treatment. Patients will be given ambulatory blood pressure monitoring devices prior to these dates and wear the device for 24 consecutive hours before returning to their doctor's office. Patients will be instructed not to change their activities of daily life or sleep habits during this period. Blood pressure readings will be averaged over 24-hour periods. Secondary outcome results will be obtained through urine testing and blood draws at the aforementioned time intervals.

3.14 Sample Size Calculation

The blood pressure reducing effect of daily potassium supplementation versus daily HCTZ has never been compared in a non-inferiority trial. Consequently, we used noninferiority studies referenced in chapter 2 to guide us in developing a noninferiority margin of 10%. Referring to outcome data in existing literature, mean SBP reduction with potassium supplementation in African Americans is 17.98 mmHg, mean SBP reduction with HCTZ in this population is 15.17 mmHg, and the standard deviation (SD) is 12.5. This study will be powered at 80% with a standard type I error of 5%. Due to the long trial duration and daily participation requirement, we will assume a 10% dropout rate. Using these values and the PowerAndSampleSize.com noninferiority trial sample size calculator, we determined that the required sample is 1125. With the expected dropout rate, this number increases to 1238; 619 participants in each arm.

3.15 Analysis

Mean values for our primary outcome variable will be measured at baseline and at each follow-up visit. An intention-to-treat analysis will use a student t-test to compare

mean decrease in SBP between groups. This variable will be operationalized as normally distributed mean \pm SD. Per-protocol analysis will also be utilized for participants who were adherent through the first follow up period but not the second. A two-tailed 95% confidence interval will be calculated to determine whether the upper margin falls within our predetermined margin of non-inferiority.

Secondary outcomes will utilize the student t-test to compare means between groups after the trial period. All secondary outcome measures will be operationalized as normally distributed means \pm SDs.

If significant differences in baseline characteristics are present prior to randomization, regression models will be used based on the type of variable to control for potential confounders. Multiple linear regressions will be utilized for normally distributed continuous baseline measures, and multiple logistic regressions will be utilized for dichotomous baseline measures. Continuous baseline variables will be operationalized as mean \pm SD and evaluated with the student t-test. These include age, education, weight, SBP, DBP, 24h urine aldosterone, potassium, sodium, magnesium, and calcium, serum potassium, PRA, serum creatinine, serum glucose, serum uric acid, HbA1c, and alcoholic drinks per week. Sex, cigarette smoking, and BMI are operationalized as categorical variables expressed as percentages and will be evaluated using the chi-square test.

3.16 Timeline and Resources

After approval by the Institutional Review Board, recruitment will begin and continue for a total of 12 months. This period allows for our team members to contact primary care clinics and distribute flyers throughout New Haven, Fairfield, and Hartford

counties, and screen potential participants for eligibility. Because of our relatively extensive inclusion and exclusion criteria, we will allow ample time to recruit our target of 1238 participants.

After the 12-month recruitment period, baseline characteristics will be measured via an initial clinic visit. Participating primary care clinics must have the ability to perform routine bloodwork and urine studies either in house or through a third-party lab. Eligible participants will be randomized to their treatment group and provided a 3-month supply of pills. At the time of initial follow-up, participants will return to their clinic for repeat measurement of primary and secondary outcomes. They will also be provided with their second 3-month regimen of pills at this time. At 6-months, participants will return to the clinic for final outcome measurement and return their MEMS® TrackCap pill containers.

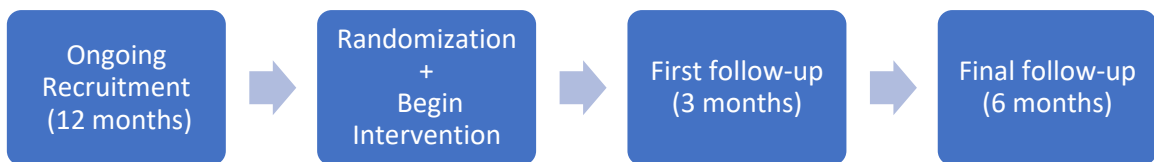
Our study will be overseen by a coordinator in charge of communication with the primary care clinics through which we will operate. Additionally, we require a physician assistant, nurse practitioner, or physician to determine eligibility of potential participants. A third team member will be responsible for communication with participants after the study has commenced, recording adherence, adverse effects, dropouts, and other comments or concerns. We also require a pharmaceutical scientist to develop 6-month supplies of HCTZ 25mg and oral potassium chloride 80mEq that are identical in appearance. Lastly, a statistician will be responsible for data entry and statistical analysis.

Participants will be incentivized for their involvement in the trial. Each subject will receive \$40 for participating through the 3-month follow up, and an additional \$40 for reaching the 6-month follow-up. They will also receive an additional \$10 for

returning a functional MEMS® TrackCap pill container. Patients will be compensated for any costs they incur during the study related to their participation, including bus passes, parking fees, tolls, and gas. Our budget for participant compensation is approximately \$65,000.

The average cost of a generic HCTZ 25mg tablet is 13.3 cents. The total cost of a 6-month supply equals \$24. The estimated average daily cost of correctly dosed generic oral potassium supplementation is 31 cents. The total cost of a 6-month supply equals \$54.90. The total treatment cost among both groups over the 6-month trial period is approximately \$95,000. Lastly, the cost of each MEMS® TrackCap device is \$110, totaling an additional \$136,180 for all 1238 participants.

Figure 1. Timeline of Study



Chapter 3 References

1. ZIP Code Demographics by City. 2010.
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Chapter 4: Conclusion

4.1 Strengths

Our study has many advantages which allude to its unique role in supplementing current research around hypertension management in African Americans. The randomized, parallel, double-blind, non-inferiority design will provide prospective data with minimal bias which clinicians and policymakers can use to direct pharmacological antihypertensive treatment. The noninferiority design commonly used for new or alternative treatments will be invaluable in assessing potassium supplementation's role in therapy.¹ Also, by including a large sample size, this study will provide stronger data than previous research on potassium supplementation in this population. The variety of baseline measurements and inclusion/exclusion criteria allows for great control of potential confounders by facilitating effective randomization and allowing for regression analyses. Assessing success of randomization and utilizing regression analyses will yield high quality results and provide excellent internal validity. Furthermore, by measuring a variety of secondary outcomes, this study will provide high quality prospective data that may be useful in post-hoc analyses or facilitate the development of future studies with similar research questions. Lastly, this study design does not include strict dietary restrictions during the trial period, improving its generalizability to a broad study population while also allowing for analysis of the impact of dietary habits through measurement of secondary variables i.e., urine electrolytes.

4.2 Limitations

Contrarily, this study has multiple limitations. First, the study sample is geographically limited to primary care centers in New Haven, Fairfield, and Hartford

counties. This limits the generalizability of our results as African Americans with hypertension in other regions of the United States may be subject to vastly different socioeconomic and environmental conditions.² Extensive inclusion and exclusion criteria further limits generalizability. Additionally, to maintain feasibility we include only one dosage option for each treatment, though a variety of dosages would provide more complete data on the comparative efficacy and safety of potassium supplementation versus HCTZ. Furthermore, due to the relatively large standard deviation and narrow margin between the effect size of HCTZ and potassium, a large sample size is required to adequately power this trial. Consequently, the implicated costs are very high, threatening feasibility. This study also fails to measure long-term differences in blood pressure control and adverse events. Because the aim of BP control is to reduce risk of adverse outcomes, it is important to consider long-term cardiovascular events, kidney disease, etc. associated with these treatments. This is not possible in this trial due to feasibility constraints, but long-term outcomes require investigation in future research. Lastly, further research into combination antihypertensive therapy with potassium supplementation is warranted as current research suggests that potassium may have an amplified benefit when used in conjunction with thiazide diuretics due to its ability to counteract diuretic-induced hypokalemia.³

4.3 Significance

4.3.1 Clinical Significance

Establishing potassium supplementation as a safe alternative to HCTZ for BP control would greatly benefit African Americans with mild-to-moderate hypertension. It is a relatively benign intervention which produces few adverse effects compared to

HCTZ, potentially improving adherence and safety outcomes.^{4,5} Secondly, results of this study will provide further prospective data on the significant BP-reducing effect of potassium. Its implications may span beyond supplementation and provide valuable evidence reinforcing data which correlates potassium intake with BP reduction. Additionally, this study may prompt research investigating potassium supplementation as an option for African Americans with resistant hypertension or an intolerance to thiazide diuretics. Lastly, potassium supplementation is associated with a range of positive outcomes beyond BP reduction which traditional antihypertensives do not provide, such as counteracting high salt diets with enhanced natriuresis.⁶

4.3.2 Public Health Implications

This study may also have a variety of public health implications. First, it will directly address the drastically higher rates of uncontrolled hypertension in African Americans.⁷ Providing additional antihypertensive resources to this population will lessen degree of inequality between African Americans and non-African Americans in regards to BP and related morbidity and mortality. Additionally, past and present conduct of the American healthcare system has bred mistrust and facilitated inequity for African Americans.⁸ By offering an equally efficacious, safer alternative to traditional pharmacologic therapy, we hope to restore trust between patients and providers to ultimately improve BP control. Furthermore, by targeting hypertensives who are only <10mmHg SBP above their goal, we aim to produce more evidence in support of early intervention to further minimize the prevalence of sustained, uncontrolled hypertension. Lastly, the findings of this study have the potential to reduce healthcare costs by decreasing adverse events related to hypertension in an overburdened population.⁹

Chapter 4 References

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Appendices

Appendix A: Consent Form

Adapted from Consent for Participation in a Research Project 200 FR. 1 (2016-2)

Yale University School of Medicine

Study Title: Potassium Supplements vs Hydrochlorothiazide in Hypertensive African Americans: Noninferiority Trial

Principal Investigator: David Geller, MD/PhD

Invitation to Participate and Description of Project:

You are invited to participate in a research study designed to compare hydrochlorothiazide with potassium supplementation to reduce blood pressure. You have been asked to participate because you are an adult who self-identifies as African American and your systolic blood pressure is <10mmHg above your goal. Approximately 1250 participants will be involved whom are recruited from primary care centers throughout New Haven, Fairfield, and Hartford counties.

To decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the medications that will be given, any risks of the medications, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures:

Guidelines:

- If you agree to participate in this study, you will be asked various questions about your background and past medical history. You will also undergo blood and urine testing to obtain baseline characteristics.
- A computer system will randomly assign you to either receive daily hydrochlorothiazide or potassium supplements which have both been shown to effectively reduce blood pressure. Additionally, you will receive a MEMS® TrackCap pill container which will wirelessly log each time you dispense a pill.
- The trial period lasts for a total of 6 months. During this time, are expected to take one pill every morning and return to your primary care clinic at 3-months and 6-months.
- During these visits, blood and urine labs will be repeated to obtain outcome data. Additionally, you will be given an Ambulatory Blood Pressure Monitoring device to wear for 24 consecutive hours before returning to the office to accurately

measure your blood pressure. In total you will visit the office twice at 3 months, and twice at 6 months.

- Throughout the trial period, there will be a hotline available for you to report adverse effects.
- The study will conclude at your final office visit at 6-months. At this time, you will return your MEMS® TrackCap pill container.
- Compensation will be provided at the 3-month and 6-month follow-ups. An additional reward will be provided for returning an undamaged MEMS® TrackCap pill container.

A description of this study will be publicly available on <http://ClinicalTrials.gov>, as required by US law. This will include a summary of results and exclude any identifying information about you or other participants.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences:

Guidelines:

- Participation in this trial may put you at risk for developing any of the known side effects of oral potassium supplements or hydrochlorothiazide. These medications are generally well tolerated and serious adverse events are exceedingly rare, but the possible adverse effects are as follows:
 - Hydrochlorothiazide:
 - Photosensitivity
 - Reversible electrolyte abnormalities
 - Arrhythmias
 - Hyperuricemia leading to precipitation of gout
 - Potassium Supplements:
 - Arrhythmias (much more common with IV administration)
 - Gastrointestinal symptoms:
 - Diarrhea, flatulence, nausea, vomiting
 - Abdominal pain
 - Gastrointestinal ulcers
- A risk associated with both interventions is hypotension. You may experience dizziness or lightheadedness, fainting, blurry vision, nausea, fatigue, or lack of concentration.
- In the event that any of these events occur, please contact the provided hotline to notify our team.

Benefits:

- Findings of this study may aid in reducing the risk of uncontrolled hypertension and related diseases in yourself as well as the African American community as a whole.
- You will likely benefit from blood pressure reduction regardless of the intervention that you are assigned to. If you are assigned to potassium supplementation you may experience this benefit with a decreased risk of side effects.

Economic Considerations:

- You will receive \$40 at the 3-month follow-up visit and an additional \$40 at the 6-month follow-up visit. You will also receive \$10 for returning an undamaged MEMS® TrackCap pill container.
- Medications throughout the trial period will be covered.
- Transportation to and from clinic visits will be reimbursed. Please keep record of all study-related transportation costs (ie. bus passes, gas receipts, toll receipts)
- If you experience treatment-related adverse event requiring medical attention, all costs will be reimbursed.

Treatment Alternatives:

If you decide against participating in this study, you will be provided the option to receive the standard-of-care pharmacotherapy to treat your elevated blood pressure. You will also be encouraged to implement non-pharmacologic treatments like diet and exercise.

Confidentiality:

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Identifying information collected during this study will be kept confidential by being stored on a password protected computer located in a locked room, connected to only the Yale network. Additionally, data will be deidentified prior to randomization as part of the blinding process. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

In Case of Injury:

If you are injured during the study, seek treatment and contact the research team as soon as you are able.

If you become ill or are physically injured due to the potassium supplements or hydrochlorothiazide, or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study medications or properly performed non-standard of care investigational procedure required by the study will be covered by the Sponsor as long as you have followed the directions of the research team.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the research team.

The only other payment you will receive is the compensation mentioned in a previous section. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study. You do not give up any of your legal rights by signing this consent form.

Voluntary Participation and Withdrawal:

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the study: If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to participate. This will cancel any future appointments, but you will still be responsible for returning the MEMS® TrackCap pill container to avoid a \$110 fee.

The researchers may withdraw you from participating in the research if necessary. The conditions whereby this may happen include: progression of disease/poor response to treatment, development of serious side effects, or subject non-compliance.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the primary care clinic through which you were recruited. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and

Do you have Hypertension?

Seeking participants for a clinical trial that could benefit you!

If you are 20-65 years old, identify as African American, and have newly diagnosed or uncontrolled hypertension, you may be eligible!

This study is designed to compare hydrochlorothiazide with potassium supplementation to reduce blood pressure

If you choose to participate, you will be assigned to one of these regimens for 6-months

All study-related costs covered. You will be compensated for your participation!

Eligibility:

- Age 20-65
- Identify as African-American
- Systolic blood pressure <10mmHg above goal

Potential Benefits:

- Control your blood pressure
- Compensation for participation
- Contribute to reducing hypertension-related disease in African Americans

If you're interested, please contact us at:

marshall.walters@yale.edu



Yale University
School of Medicine

Appendix C: Baseline Characteristics Survey

Name: _____

Date: _____

Research Assistant: _____

Clinic Name: _____

General Information:

Age: _____

Gender: _____

Education (years): _____

Current cigarette smoking (y/n): _____

Alcoholic drinks per week: _____

Measured Values:

Height (cm): _____

Weight (kg): _____

Calculated BMI: _____

Systolic Blood Pressure (mmHg): _____

Diastolic Blood Pressure (mmHg): _____

Appendix D: Baseline Characteristics Lab Values

Baseline Characteristic	Lab Value
24h Urine Aldosterone (μg)	
24h Urine Potassium (mEq/L)	
24h Urine Sodium (mEq/L)	
24h Urine Magnesium (mEq/L)	
24h Urine Calcium (mEq/L)	
Serum Potassium (mmol/L)	
Serum Uric Acid (mg/dL)	
Serum Glucose (mmol/L)	
Plasma Renin Activity (ng/mL/hr)	
Serum Creatinine (mg/dL)	
Hemoglobin A1c (%)	

Appendix E: Participant Follow-up

Participant Identification Number: _____

Name of Research Assistant: _____

3-Month or 6-Month visit (circle one)

Today's date: _____

Name of Clinic: _____

Adherence to Protocol:

Morisky Scale Score: _____

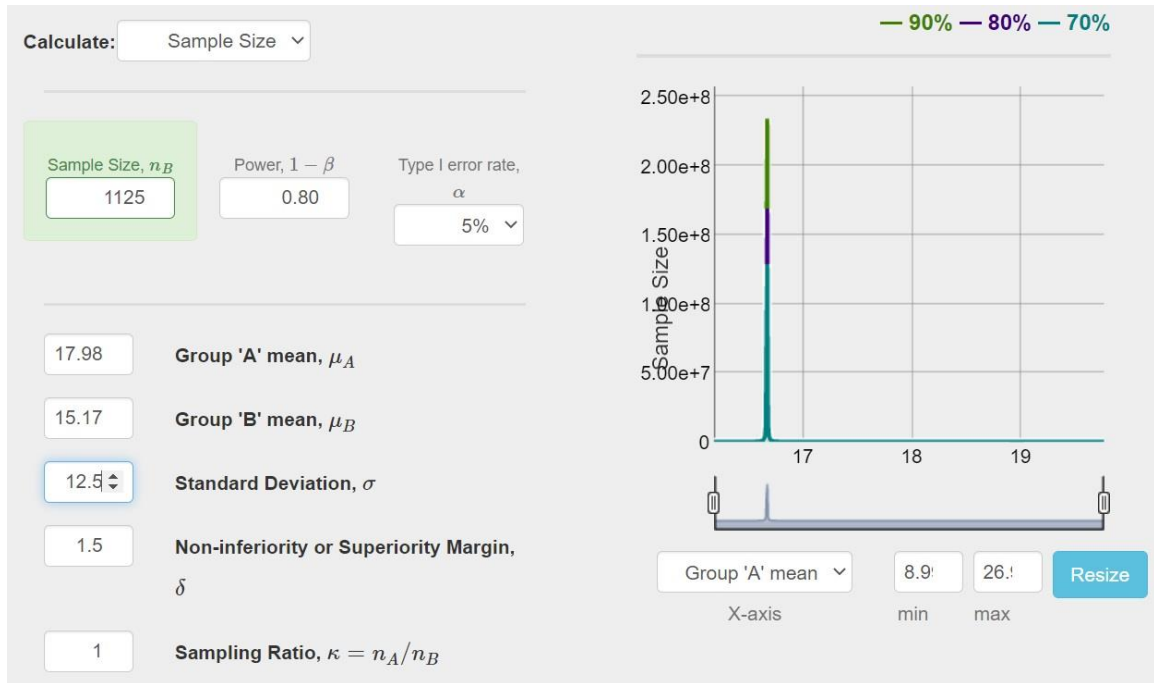
Notable Lab Values:

Lab	Value

Other comments, concerns, reports of adverse events by participant:

Primary and secondary outcome data will be recorded separately.

Appendix F: Power and Sample Size Calculation



We used the 2-Sample Non-Inferiority calculator on PowerandSampleSize.com to determine a sample size of 1,125 to adequately power our study at 80% with a two-sided type I error of 0.05. Our noninferiority margin was determined to be 10% as discussed in chapter 2. We will account for a 10% dropout rate, leaving us with a final sample size requirement of 1,238 participants, 619 per arm.

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