NCT number: 02841280

Last updates 14 Dec 2019

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease (CLICK): A Randomized Control Trial

Final Protocol

Statistical Analysis Plan

Listing of Significant Amendments to Protocol

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INTRODUCTION

It is estimated that in the United States there are approximately 8 million individuals who have moderate to severe chronic kidney disease (CKD) [1]. Among them, hypertension is common and is often poorly controlled due to an expanded volume state; diuretics are frequently prescribed. Loop diuretics are potent and effective in lowering blood pressure (BP), however, their use is associated with acute kidney injury. Thiazide diuretics, on the other hand, are less potent and their use may be associated with less acute kidney injury. As of yet there is no firm data to support that thiazide diuretic therapy can improve BP in advanced CKD. In a review that we recently published, we found 13 studies on the use of thiazide diuretics in advanced CKD either alone or in combination with loop diuretics [2]. Of these, 9 studies were observational and only 4 were randomized clinical trials. Our review suggests that thiazides may be useful even among people with advanced CKD. Observational data show that thiazides lead to an improvement in seated clinic BP of about 10-15 mmHg systolic and 5-10 mmHg diastolic whereas randomized trials show about a 15-mmHg reduction in mean arterial pressure. Randomized trials had small sample sizes (7-23 subjects); accordingly, better studies are needed to evaluate the safety and efficacy of thiazide diuretics in moderate to advanced CKD. We choose chlorthalidone because it is three times more potent as a diuretic compared to hydrochlorothiazide, but it is about a tenth of the price of metolazone. Our preliminary studies that support its use in advanced CKD is further explained later in the protocol.

Our study focused on the potential mechanisms by which thiazides may reduce BP and offer target organ protection. These effects have not been evaluated so far. This randomized controlled trial, addresses a simple, inexpensive, yet an effective way to treating people with CKD who have poorly controlled hypertension. We use state-of-the-art methods such as body volume measurements (BodPod) and ambulatory BP monitoring for evaluations.

OBJECTIVES AND HYPOTHESIS

Objectives

Primary Objective

To test the hypothesis that CTD will improve BP, we will perform a double-blind, placebo-controlled, randomized trial among subjects with CKD and poorly controlled hypertension. After a two-week, single-blind placebo run-in, we will randomize 160 hypertensive patients confirmed by 24h ambulatory BP monitoring to either placebo or 12.5 mg CTD once daily. We will monitor BP at home twice daily for one week before each of their 4 weekly visits and titrate the dose of the drug based on the home BP. We will double the dose of the diuretic (up to a maximum CTD dose of 50 mg/d) or placebo every 4 weeks if home BP remains ≥135/85 mmHg (which is ~140/90 mmHg in the clinic). The primary endpoint will be assessed by change from baseline at 12 weeks in 24h ambulatory systolic BP.

Secondary Objective

To test the hypothesis that CTD will result in target organ protection, we will evaluate changes in albuminuria. Albuminuria will be assessed using overnight urine collections at baseline and every 4 weeks.

To test the hypothesis that CTD causes improvement in BP via a reduction in extracellular fluid volume, we will evaluate changes from baseline in the following extracellular fluid volume markers: N-terminal pro B-type natriuretic peptide (NT-proBNP), seated plasma renin, and plasma aldosterone. We will use the gold-standard for measuring body volume which is air displacement plethysmography. We predict that CTD use will be associated with loss of fluid weight and therefore a change in body volume. Our preliminary data show changes in each of these markers within 4 weeks.

Hypothesis

We hypothesize that among subjects with advanced CKD, chlorthalidone (CTD) will result in improved 24-hour ambulatory BP. Furthermore, CTD will improve albuminuria over 12 weeks providing evidence for target organ protection. CTD will produce these effects by shrinking the extracellular fluid volume (**Figure 1**).

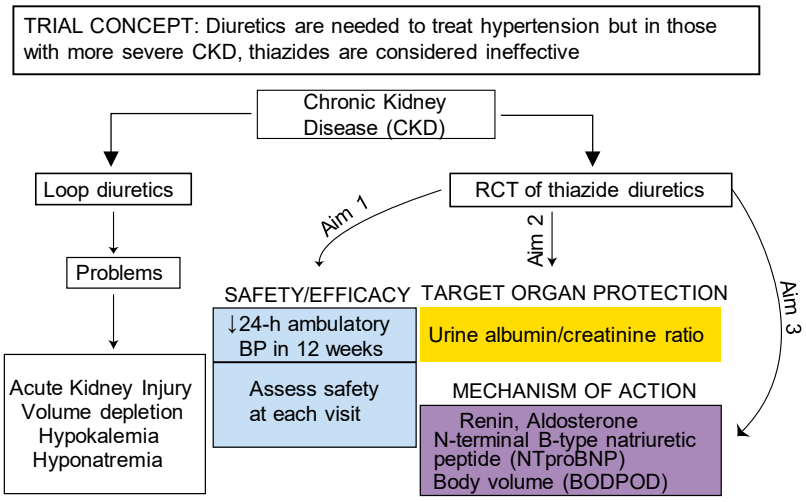


Figure 1

BACKGROUND

The burden of CKD is high; hypertension is common in CKD

It is estimated that in the United States approximately 7.7% of the population has moderate (Stage 3) and 0.35% severe (Stage 4) chronic kidney disease (CKD) [3]. The prevalence of hypertension in CKD is high. For example, a survey of >10,000 individuals at high risk for kidney disease screened in every state in the United States, revealed that 86% of the subjects had hypertension and 70% were treated. The control of hypertension to recommended levels was dismal; adequate control was present in only 13% [4]. In the US adult population the prevalence of hypertension is 31%; 70% are treated and 46% are controlled [5]. Although BP was controlled to <130/80 mmHg in 48% of those with hypertension but without CKD, among those with CKD and hypertension, the control rate was only 31% [6]. Thus, compared to those without CKD, among people with CKD, hypertension is more prevalent and more often treated but less often controlled.

Dietary excess of sodium (Na) is an important cause of hypertension

Increased dietary Na intake in modern societies is an important and treatable cause of hypertension. A meta-analysis combining results of 50 studies shows that 78 mmol/d (1.8 g) reduction of dietary Na is associated with a reduction in BP among hypertensive people of 5.0/2.7 mmHg [7]; among non-hypertensives, BP is reduced by 2.0/1.0 mmHg [7]. The Dietary Approaches to Stop Hypertension (DASH) randomized controlled trial [8] showed that compared to the highest Na intake (150 mEq/d), BP was reduced 2.1 mmHg systolic with moderate Na restriction (100 mEq/d). Compared to the highest Na intake, BP was reduced 6.7 mmHg systolic with greater (65 mEq/d) Na restriction. The greatest reductions in BP were seen among blacks, women, and those with hypertension.

To lower the incidence of hypertension, the Institute of Medicine has recommended that dietary Na should be restricted to <1500 mg/d (65 mmol/d) [9]. However, recent estimates (2005-2006) suggest that the average man in the US consumed 4 g Na; the average woman 2.8 g/d [10]. Dietary Na restriction is also recommended as an initial step to treat pre-hypertension and stage I hypertension. Data is now emerging that even people with later stage hypertension including those being treated with multiple antihypertensive agents such as those with resistant hypertension can benefit with this strategy [11]. Although dietary Na restriction is important in controlling hypertension, in our salt-rich society, long-term adherence to this life-style change is challenging.

Na overload and extracellular volume expansion is common in CKD and leads to hypertension

Progressive loss of renal function leads to both a reduction in glomerular filtration rate (GFR) and tubular mass. Reduced GFR results in reduced filtered Na load and volume expansion. Volume expansion provokes reduced renal tubular Na absorption, but failure to fully suppress Na reabsorption increases extracellular fluid (ECF) volume. In some CKD states, such as the nephrotic syndrome, an increase in tubular Na reabsorption may be the primary

abnormality causing ECF excess. Indeed, epidemiological studies suggest greater association of hypertension with proteinuria than reduced GFR [12-14].

Among patients with end-stage renal disease, both dietary and dialysate Na restriction are the cornerstones for treating resistant hypertension [15]. More important, volume reduction through ultrafiltration in patients consuming recommended intake of Na is an effective way to lower BP. Since these patients are treated with multiple drugs, this is an effective strategy of controlling poorly controlled hypertension. The volume control strategy has been tested in one randomized controlled trial [16]. In the Dry-weight Reduction In hypertensive hemodialysis Patients (DRIP) trial we randomized 150 patients in 2:1 ratio to either aggressive volume reduction or a control group [16]. Within 4 weeks, BP reduction assessed by interdialytic ambulatory BP monitoring of about 7/3 mmHg was achieved; this effect persisted through the 8-week duration of the trial. Despite the intake of an average of 2.5 antihypertensive drugs, this reduction in BP suggests that in this difficult to treat group, volume control was effective in providing additional antihypertensive effect.

Recommendations of the Guidelines on the use of diuretics in CKD

For the treatment of hypertension in CKD, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends that those with advanced renal disease (estimated GFR <30 ml/min 1.73 m^2), should increase doses of loop diuretics and be used in combination with other drug classes [17] . The JNC 8 has no statement in this group of patients.

According to the National Kidney Foundation (NKF), Kidney Disease Outcomes Quality Initiative (KDOQI) diuretics should be used to treat hypertension in most patients with CKD [18]. For those with estimated GFR ≥30 mL/min/1.73 m^2 thiazide diuretics given once daily are recommended. However, loop diuretics are recommended for those with estimated GFR <30 mL/min/1.73 m^2. Loop diuretics given once or twice daily, in combination with thiazide diuretics can be used for patients with ECF volume expansion and edema. All these recommendations have an evidence level of A.

The Caring for Australasians with Renal Impairment (CARI) guidelines [19] and the UK National Institute of Health and Clinical Excellence (NICE) guidelines[20] are silent on the role of thiazides in CKD. The Canadian Hypertension Education Program states that for patients with non-diabetic CKD, thiazide diuretics are recommended as additive antihypertensive therapy (Grade D) [21]. For patients with CKD and volume overload, loop diuretics are an alternative (Grade D). The Veterans Administration Department of Defense guidelines state that among those with CKD a diuretic should be used when a second BP medication is needed, or if hyperkalemia occurs [22]. Thiazide diuretics may be used if estimated GFR > 30 ml/min/1.73m^2, but loop diuretics are usually needed for patients with lower estimated GFR.

Taken together, the guidelines do not strongly support the use of thiazide diuretics in advanced CKD. This is because the evidence base to support this recommendation is weak.

Small studies in CKD suggest that thiazide diuretics can cause natriuresis and BP lowering

We found 13 studies on the use of thiazide diuretics in advanced CKD either alone or in combination with loop diuretics.[23] Of these 9 studies were observational and 4 were clinical trials. Of the 4 clinical trials, 2 were single-blind, cross-over studies, and 2 were double-blind cross-over trials. Each of the observational studies was small and included between 8-20 participants.

1. The first study reported in 1972 was conducted in 14 participants with advanced CKD (creatinine clearance (Ccr) 1.2 to 12 mL/min); metolazone was administered in doses ranging from 20-150 mg per day (equivalent to about 200 mg to 1500 mg HCTZ). [24] Urine Na excretion increased >2 times.
2. Bennett et al reported a study in 20 participants with CKD (Ccr 4-48 mL/min) [25]. Over 3 months of the study the dose of metolazone was titrated from 5 mg to 25 mg depending on response. Weight fell by 1.4 kg and diastolic BP fell by 12.5± 11.7 mmHg among the 12 hypertensive participants Hypokalemia, AKI, and an increase in fasting blood glucose were the major complications noted.
3. Craswell et al reported 12 participants with CKD, and all but one had Ccr of <60 mL/min [26]. Oral metolazone was given in variable doses for durations lasting from 2-20 weeks. Weight was reduced 1.4 kg, edema improved, and BP fell by 14.2/3.2 mmHg from a baseline of 147/92 mmHg. Most participants (67%) required potassium supplementation, AKI was noted, and uric acid increased despite no patient experiencing an attack of gout.
4. Dargie et al reported 11 participants with nephrotic syndrome and 6 with CKD (GFR was between 1-7 mL/min) treated with metolazone in doses of 5-200 mg for 7-180 days [27]. Nephrotic participants weighed on average 71.2 kg and lost 5.2 kg weight. Those with CKD weighed on average 63.0 kg and lost 3.8 kg weight. Changes in BP were not reported.
5. Paton et al reported a study in 10 participants with CKD and 10 participants with nephrotic syndrome [28]. Among 10 participants with CKD, BP improved from 173/96 mmHg at baseline to 158/88 mmHg with metolazone (mean dose 11.0 mg over 56.6 weeks). Among 10 participants with nephrotic syndrome, BP improved from 147/97 mmHg to 137/88 mmHg with metolazone (mean dose 14.9 mg, 114.4 weeks).
6. Wollam et al studied 8 participants with mean serum creatinine 3.31 mg/dL and performed an interventional before-and-after study [29]. Increasing the dose of furosemide to between 320 and 480 mg/day had only a modest additional diuretic effect; plasma volume and arterial pressure were not significantly changed. Adding HCTZ, 25 to 50 mg twice a day, produced a marked diuresis, and a significant reduction in weight, plasma volume and mean arterial pressure. Three of the 8 participants were treated with combined HCTZ-furosemide therapy. These participants had an inadequate response to either diuretic alone but had 34/13 mmHg reduction in supine BP with the combination. These data suggest that the

combination of a loop diuretic with a thiazide may reduce plasma volume and BP even in advanced CKD.

7. Additionally, thiazides (HCTZ 50 mg daily or metolazone 5 mg daily or placebo in 4 week periods in a cross-over study lasting 6 months) have been used among dialysis participants making <100 mL urine per day. There was no effect on pre and post-dialysis BP, body weight, plasma volume, and plasma renin[30].
8. Cirillo et al compared effect of fixed dose CTD 25 mg QD among people with estimated GFR < 60 mL/min/1.73 m2 and poorly controlled hypertension to those with eGFR >60 (n=60) [31]. At 8 weeks, office systolic BP and body weight were both significantly reduced from baseline by 19 mmHg and 0.88 kg respectively. Importantly, both the subgroups of 28 subjects with eGFR 30-44 and 9 subjects with eGFR 15-29 had similar reductions in systolic BP at 19 and 20 mmHg respectively. BP reductions were similar in those with eGFR >60. Laboratory abnormalities and adverse events occurred in 15% of patients; these included hypokalemia, hyponatremia, and hyperuricemia.
9. The last study is ours and is discussed in preliminary data.

Randomized controlled trials on the of use of thiazides in CKD

Literature search revealed only 4 randomized controlled trials (RCTs) evaluating the response to thiazides among participants with CKD. All were small; the largest being of 23 participants.

1. Fliser et al reported the first single-blind, cross-over RCT in 10 participants with advanced CKD; natriuresis was the end-point [32]. Inulin clearance averaged 13.1 mL/min/1.73 m^2. After a low Na diet (150 mmol/d) a sham infusion of 50 ml 5% dextrose was given on Day 6 and Day 13. On the days following the sham infusion (days 7 and 14), participants received either torsemide 50 mg IV alone or torsemide 50 mg in combination with butizid 20 mg IV (equal to ~30 mg of HCTZ) in a cross-over fashion. With torsemide alone, Na excretion rate increased from 154 mEq/d to 232 mEq/d. With torsemide + thiazide, Na excretion rate increased significantly more from 156 mEq/d to 290 mEq/d.
2. Knauf and Mutschler performed a single-blind RCT (n=19) of loop diuretic or a combination of loop diuretic plus a thiazide in participants with moderately severe renal failure (Ccr 39.5 mL/min) [33]. After establishment of a steady state of urinary electrolyte excretion, a single oral dose of HCTZ (25 mg) induced an increase in the urinary excretion of Na, K, Cl, Ca, and Mg over the subsequent 12 h, which was significantly and inversely related to the GFR for each electrolyte. Doubling the dose of either HCTZ or furosemide produced statistically insignificant increases in Na excretion. In contrast, when the lower doses of each (25 mg HCTZ + 40 mg furosemide) were co-administered, there was a substantial and a statistically significant increase in Na excretion. Thus, a combination of low doses of diuretics acting at different functional sites of electrolyte reabsorption in the nephron may be superior in natriuretic potency to increasing the dose of either diuretic alone.

3. Dussol et al, reported the first double-blind, RCT of furosemide and HCTZ in 2005 (n=7, Ccr <40 mL/min) [34]. Long-acting furosemide (60 mg/d) or HCTZ (25 mg/d) was given in a cross over manner for 30 days with a washout of 1 month. Both diuretics were equally effective in reducing clinic oscillometric supine mean arterial BP. Somewhat surprisingly, HCTZ was more effective than furosemide in causing natriuresis. Perhaps, this was because once daily dosing of furosemide may not elicit persistent natriuresis and therefore may appear to be weaker than HCTZ. The combination of the two drugs was more effective than either therapy given alone.
4. Dussol et al, in 2012 reported the second double-blind, cross-over RCT of furosemide and HCTZ among 23 participants with stage 4 and 5 CKD [35]. They found that both the natriuretic and the antihypertensive response to the standard dose of furosemide and HCTZ were similar. But the combination of furosemide and HCTZ had an additive effect on both natriuresis and BP.

Taken together, the above studies, although small, demonstrate the potential for the use of thiazide-like diuretics in patients with CKD. A functioning kidney and a negative Na balance are both needed to produce an antihypertensive effect. There does not appear to be an independent effect of thiazides on vasculature and peripheral vascular resistance. None of the above studies, even when considered collectively, provide enough support to firmly recommend the routine use of these drugs in advanced CKD.

Risks and benefits of thiazides in CKD

There are several problems that may be associated with thiazide use in CKD. These include volume depletion, hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia, hyperglycemia, dyslipidemia, and idiosyncratic events (e.g., rash, pancreatitis etc.). Like with other BP lowering agents, transient creatinine elevation and orthostatic hypotension may be seen. Thus, the use of these agents requires close monitoring, especially when initially prescribed or when their dose is increased. These risks can be assessed only in larger and longer studies.

Thiazides may augment the natriuretic effect of loop diuretics and in doing so may improve the control of BP. This may be especially true among individuals who may have been on diuretics for a long time and consequently developed a hypertrophied distal nephron. By increasing K excretion, thiazides may be valuable in the setting of hyperkalemia such as people with diabetic nephropathy and Type IV renal tubular acidosis.

Preferred thiazide diuretic use in CKD

There are important differences between thiazide diuretics in potency, duration of action, side effects, and costs. In a recent meta-analysis of trials comparing the antihypertensive effects of thiazides among patients with hypertension, Peterzan et al reported markedly different potencies of hydrochlorothiazide, chlorthalidone (CTD), and Bendroflumethiazide [36]. Potency followed a log-linear relationship Bendroflumethiazide > CTD > HCTZ. The estimated dose of each drug predicted to reduce systolic BP by 10 mm Hg was 1.4, 8.6, and 26.4 mg, respectively. Thus, CTD has nearly three times the potency compared to the commonly used

HCTZ. However, at ceiling doses of different thiazides, the maximum reduction in systolic BP was similar. Given the higher potency, a longer duration of action, and a lower cost, CTD may be preferred to other thiazides. In studies that have compared ambulatory BP with HCTZ or CTD, the latter appears to provide a more consistent reduction in 24-hour BP i.e., both during the day and during the night. For example, in a cross-over study of 30 participants, of which 24 completed 8 weeks of treatment with both agents, 50 mg HCTZ produced 7.4 mmHg reduction in 24-hour systolic BP, whereas 25 mg CTD produced 12.4 mmHg decline (p=0.054) [37]. More significant were the differences in nighttime BP; 50 mg HCTZ produced a 6.4 mmHg reduction whereas 25 mg CTD produced 13.5 mmHg reduction (p=0.009). Reductions in clinic BP were similar between agents. Post-hoc analysis of the Multiple Risk Factor Intervention Trial suggests that compared to HCTZ, CTD may more effectively cause regression of left ventricular hypertrophy [38] and fewer cardiovascular events [39]. However, CTD is also most likely to cause hypokalemia. For example, in the Multiple Risk Factor Intervention Trial when compared to HCTZ, CTD use was associated with lower serum potassium and a higher serum uric acid [39].

Additionally, metolazone is also effective in CKD, but it costs nearly ten times that of generic thiazides. Also, the bioavailability of metolazone depends on the formulation. Thus, in comparison to others, it appears that CTD would be the preferred thiazide.

A reduced intake of dietary Na, diuretic use, or both may protect the kidney

In a cross-sectional study, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, the interactive relationship between dietary Na and body mass index on albuminuria was evaluated [40]. In 30,239 adults aged ≥45 years and among obese participants, a higher dietary Na intake or a higher urinary Na/K ratio was associated with albuminuria. Among 3,680 participants in the Chronic Renal Insufficiency Cohort study, the relationship between 24-hour urinary sodium or potassium on 24-hour urine protein excretion was examined [41]. Urinary sodium excretion was associated with increasing proteinuria even after and adjustment for demographic and clinical factors, including 24-hour urinary potassium.

A high dietary salt intake may accelerate the progression of CKD independent of angiotensin II and systemic blood pressure. A high dietary salt intake activates the vascular endothelium and provokes the release of transforming growth factor-beta1 (TGF-β1) [42]. Additionally, a high dietary salt intake provokes nitric oxide production, which attenuates TGF-β1. In this model, the overproduction of TGF-β1 permits excess biological activity of this important fibrogenic growth factor with subsequent development or acceleration of vascular and kidney damage. In patients with diseases whose pathogenesis is related to excess production of TGF-β1, such as chronic allograft nephropathy and diabetic nephropathy, increased salt intake may hasten loss of function, particularly if nitric oxide production does not increase.

The effects of modest salt restriction on BP and urine protein excretion in nondiabetic black hypertensive participants were examined in a randomized, double blind, and placebo-controlled, cross-over study [43]. After the run-in period, on their usual diet and on reduced salt, participants continued to restrict their salt intake and then received either “slow Na” tablets, designed to bring their salt intake back to normal, or placebo tablets for 4 weeks. In the 40 who completed the study, switching “slow Na” to placebo caused urinary Na excretion to fall from 169 to 89 mmol/d. BP fell from 159/101 to 151/98 mm Hg (P<0.01). Protein excretion fell from

93 mg to 75 mg per 24 hours (P<0.008). Therefore, reducing salt intake from approximately 10 to 5 g per day reduced both BP and urine protein excretion among black hypertensives. Furthermore, this reduction in urine protein was seen within a few weeks.

Vogt et al performed a randomized, double-blind, placebo-controlled trial to determine the separate and combined effects of a low-Na diet and hydrochlorothiazide (HCTZ) on proteinuria and BP [44]. In 34 proteinuric patients, without diabetes, mean baseline proteinuria was 3.8 g/d, and this was reduced by 22% with a low-Na diet alone. Losartan monotherapy reduced proteinuria by 30%, and the addition of a low-Na diet led to a total reduction by 55% and the addition of HCTZ to 56%. The combined addition of HCTZ and a low-Na diet reduced proteinuria by 70% from baseline (all P < 0.05). The reduction in urine protein was seen within a few weeks. Reductions in mean arterial pressure showed a similar pattern (all P < 0.05).

Thus, the benefits of reducing dietary Na intake, diuretics, or both may extend to protecting the kidney, above and beyond reducing BP.

Pilot Study

To gauge the feasibility of this protocol we implemented a pilot, open-label study of CTD [64]. To test the hypothesis that CTD effectively lowers BP in moderate to advanced CKD after confirming poorly controlled hypertension with 24-hour ambulatory BP monitoring in 14 men (age 67.5 y, diabetes mellitus in 12, median number of antihypertensive drugs 4), with stage 3B (n=4) or 4 CKD (n=10) (eGFR 26.8 ± 8.8 mL/min/1.73m^2) we added CTD in a dose of 25 mg/d and doubled its dose every 4 weeks if BP remained elevated. Mixed modeled mean prescribed CTD dose at 4 weeks was 34 mg, at 8 weeks 55 mg, and at final visit 51 mg/d. Over 12 weeks of treatment 24-hour BP which was 143.1/75.1 mmHg at baseline was reduced by 10.5/3.1 mmHg (p = 0.01/p=0.17, **Figure 2**). Home BP at baseline was 152.4/82.6 mmHg and fell at 4, 8, and 12 weeks by 10.2/4.8, 13.4/6.0, and 9.4/3.7 mmHg (all p<0.05, **Figure 3**). Clinic BP was 137.7/65.4 mmHg and was significantly reduced only at 8 weeks. Maximal reduction in body weight and total body volume was seen at 8 weeks concurrent with the maximal elevation in serum creatinine concentration and plasma renin activity (**Figure 4**). Albuminuria was significantly reduced by 40-45% from baseline. Adverse events following CTD therapy occurred in 7 participants: hypokalemia (n=4), hyperuricemia (4), hyponatremia (3), transient creatinine changes (3), dizziness (2), hyperglycemia (1), and constipation (1). One subject had ischemic stroke during the study. In conclusion, in advanced CKD, CTD has the potential to control hypertension; an RCT is now needed.

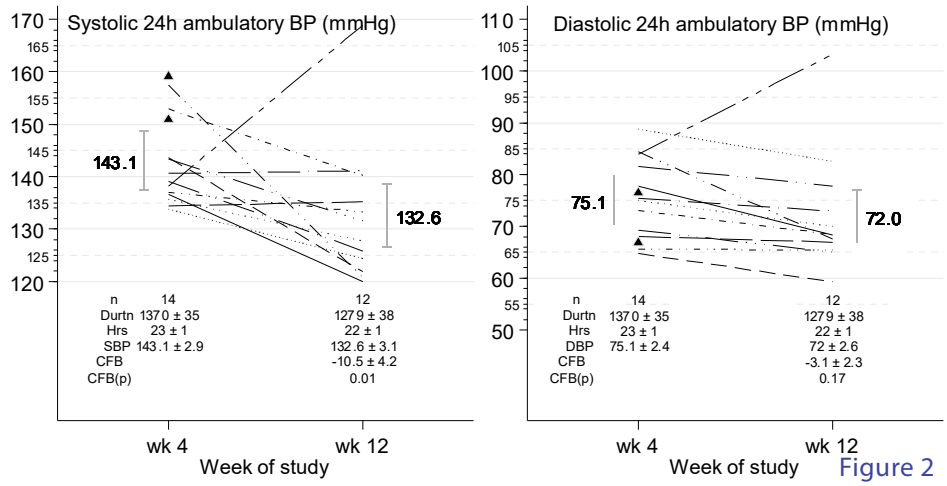


Figure 2

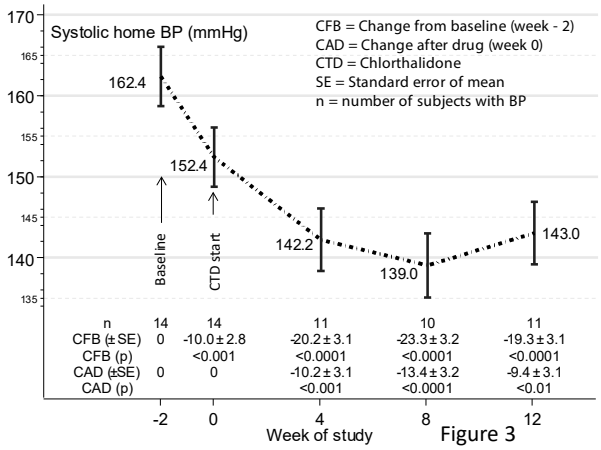


Figure 3

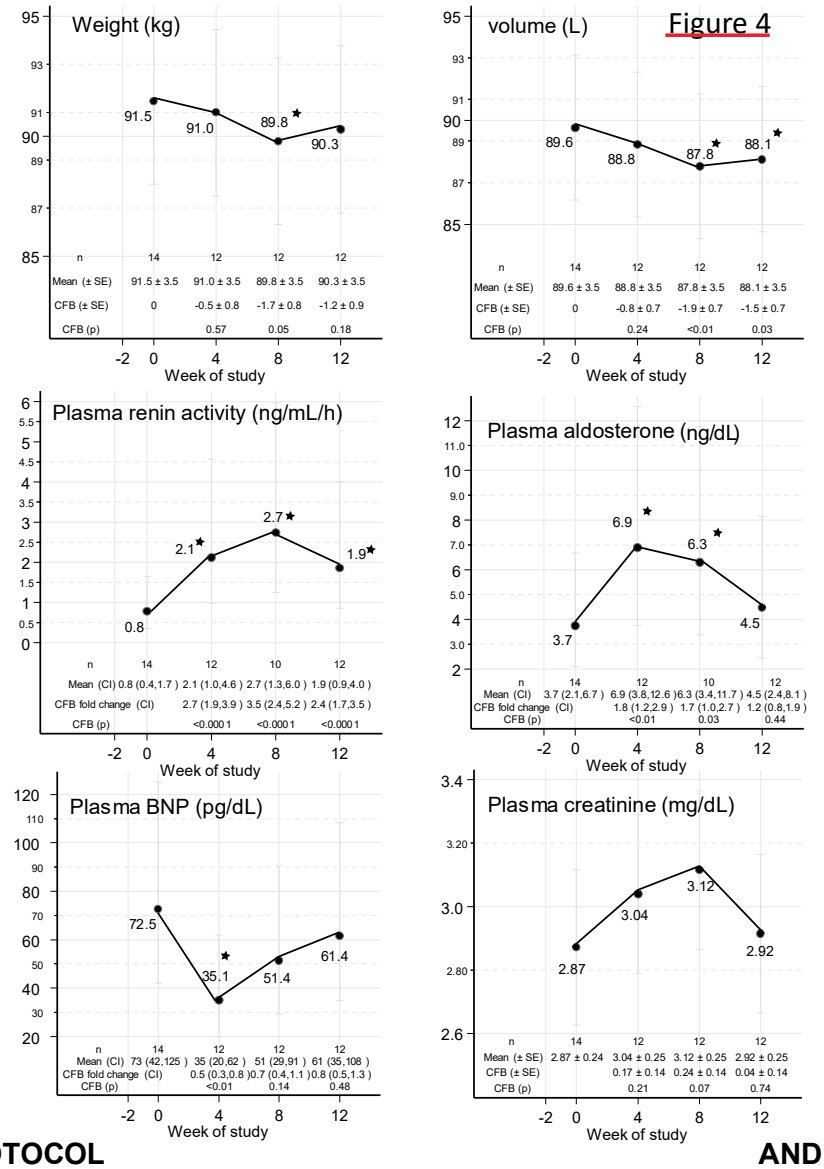


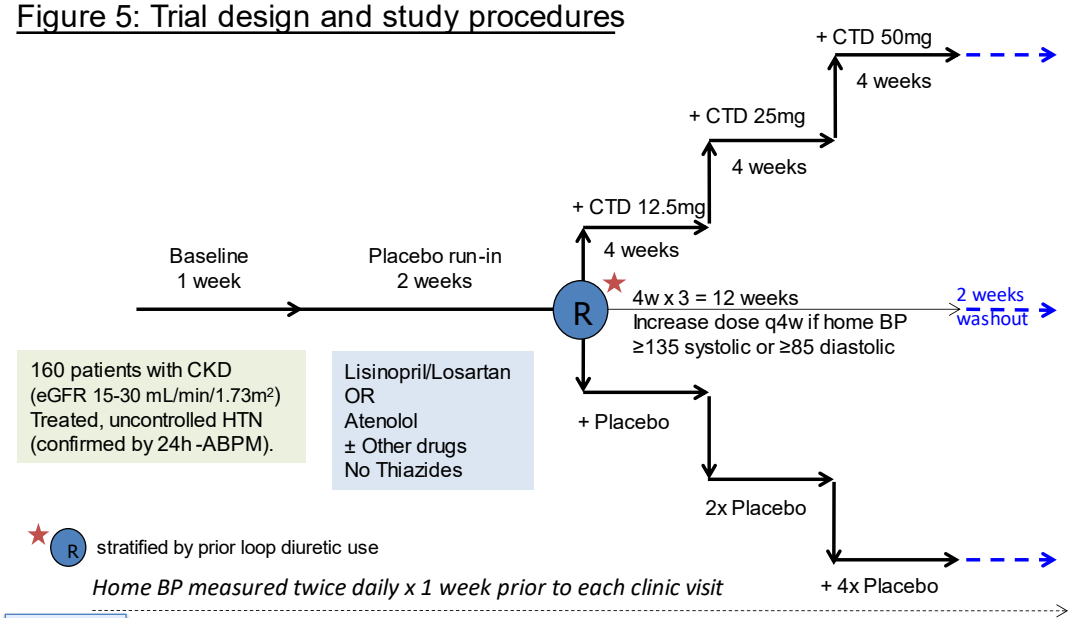
Figure 4

RESEARCH PROTOCOL AND TRIAL DESIGN

CLICK will provide evidence for the specific role of thiazide diuretics in the management of hypertension in those with advanced CKD. BP control is the backbone of renal and cardiovascular protection, yet control rates are dismal. Furthermore, the use of CTD has increased after publication of ALLHAT. This study will examine the benefits of CTD in a vulnerable group of patients including albuminuria and providing surrogate evidence for target-organ protection. The wider use of this specific thiazide diuretic may also improve CV outcomes in CKD. The results will help support the use of a low-cost, but potentially effective, antihypertensive drug in this high-risk group.

Overall Trial Design and Plan

Figure 5: Trial design and study procedures



Measurements	Time →	Week 0	Week 4	Week 8	Week 12	Week 14
24h ambulatory BP + 24 h urine		x			x	
Home BP (BID x 1w), Clinic BP		x	x	x	x	x
Markers of target organ damage		x	x	x	x	x
Markers of volume		x	x	x	x	x

To test the notion that CTD added to the regimen of antihypertensive drugs will improve BP in those with advanced CKD and uncontrolled hypertension, we propose a placebo-controlled, double-blind, randomized controlled trial (**Figure 5**). This trial will assess the effects of CTD in patients with CKD and poorly controlled hypertension. According to the European Society of Hypertension (ESH 2013) guidelines, poorly controlled hypertension is defined as the average 24-hour ambulatory blood pressure of ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic[45]. During the study, doubling the dose of the diuretic or placebo will occur every 4 weeks if home BP remains above ≥135/85 mmHg. This level of BP was chosen because it roughly approximates to the clinic BP of ≥140/90 mmHg, which is the current target for treatment for people with CKD. The effects will be assessed by change in ambulatory BP measured over 24 hours from baseline to 12 weeks.

At baseline and every 4 weeks thereafter, we will also evaluate changes in albuminuria and markers of volume (renin, aldosterone, NT-proBNP, and body volume). Home BP will be measured prior to each clinic visit for one week, twice daily. The final visit will be two weeks after stopping the study drug to have a proper wash out period. At the post-termination visit, if the increase in home BP from drug discontinuation is ≥7/4 mmHg open label CTD of at least 12.5 mg/d will be administered. Further follow up will be provided by the participant's physician.

At week 14, we will measure albuminuria and volume markers to provide a stronger mechanistic basis for the effect of CTD on these outcomes.

Study Intervention

Participants with CKD and poorly controlled hypertension, confirmed by ambulatory BP monitoring after the two-week run-in, who meet the inclusion and exclusion criteria will be administered the study drugs in increasing doses. There are 9 study related visits at week -3, -2, 0, 4, 8, 12, and 14. Visits occurring before randomization (week 0) will have a ± 2-day visit window. Any visit occurring after randomization will have a ± 3-day window. At both weeks 0 and 12, visits on two consecutive days are to perform 24h ambulatory BP monitoring and 24-hour urine collection. Participants will be identified in the renal clinic on the basis of estimated GFR and BP. If they are on any antihypertensive medications excluding a thiazide-like diuretic in the prior 12 weeks (HCTZ, CTD, or metolazone), they will be sent home with a BP monitor. If the average systolic clinic blood pressure is <110 mmHg, they will not be further considered for participation. This is based on our prior study that suggests the prevalence of uncontrolled hypertension is less than 2% in persons with a clinic systolic blood pressure of 90-110mmHg [46].

At the beginning of the run-in, all participants will receive a standard regimen of antihypertensive medications from various classes of drugs, e.g., ACE inhibitors (lisinopril 20-40 mg/d), angiotensin receptor blocker (losartan 50-100 mg/d if intolerant to ACE inhibitors), dihydropyridine calcium channel blockers (amlodipine 10 mg/d), beta blockers (atenolol 25-100 mg/d) and/or a loop diuretic (torsemide 10-20 mg/d). The nature of the antihypertensive used will depend on their existing regimen. Thus, if they are on a beta-blocker and a diuretic, they will receive atenolol and torsemide. Doses will be selected based on what the patient is currently prescribed. For those on furosemide, 20 mg of furosemide will be considered equivalent to 10 mg torsemide. Atenolol is renally cleared and has a long half-life in those with CKD. For those on metoprolol, 100 mg atenolol will be considered equivalent to 200 mg metoprolol. For those on clonidine or minoxidil as fifth and sixth drugs, the doses of these drugs will be left unchanged. Some participants receive alpha-blockers for prostatic symptoms. The dose of alpha-blockers will not be changed to avoid precipitating acute urinary retention. Those on K-sparing diuretics (e.g., amiloride, spironolactone, or eplerenone) will continue taking the same dose with the drug remaining unchanged. The final dose of the standardized medication regimen will be determined by the study physician. All participants will be provided written instructions to consume a diet containing <100 mEq Na/day. 24-hour urine Na will be measured to assess dietary sodium intake.

Treatment Compliance

We recognize the limitations of pill count, however, we will assess treatment compliance with the study drug by performing pill count at each of the study visits.

Protocol for managing blood pressure

This is a forced-titration study, thus the study drug will be increased if goal BP is not achieved. Goal BP is defined by home BP monitoring. We will ask participants to provide BP

readings in triplicate twice a day for one week. The average of these will be used for decision making when it comes to medication management. However, if fewer than 3 days of readings are available, we will make a decision based on clinic BP.

The dose of study medication will not be increased if the patient has the following symptoms: home BP of <135 mmHg systolic, symptomatic hypotension, hypercalcemia, hypomagnesemia, moderate hypokalemia (K<3 meq/L), acute gout, or a recent hospitalization for poorly controlled diabetes. In these instances, the dose of the drug will be maintained or down-titrated based on investigator's judgment.

Stop points

1. The study medication will be stopped, or the dose reduced, at the discretion of the PI if the patient experiences significant acute kidney injury, drug-induced rash, or other adverse event attributable to the drug, or in the PI's judgment the benefits of taking the medication outweigh the risks.
2. If home BP averaged over one week exceeds either 179 mmHg systolic or 109 mmHg diastolic, the dose of the study drug will be increased, and participant will be called in 1 week with home BP recordings. If home BP recording remain ≥180/110 mmHg, the participant will be withdrawn from the study.
3. If home BP averaged over one week is 160-179 mmHg systolic or 100-109 mmHg diastolic, the dose of the study drug increased, and participant will be called in two weeks. If BP is not <160/100 mmHg within 4 weeks, the participant will be withdrawn from the trial.

Outcome Variables

The outcome variables are as follows.

Primary outcome:

The primary outcome variable is the change from baseline to 12 weeks in systolic ambulatory BP in the CTD group compared to placebo.

Secondary outcomes:

1. Change from baseline at each 4 week visit in the log transformed albumin/creatinine ratio in the CTD group compared to placebo.
2. Change from baseline at each 4 week visit in
    a. log of aldosterone to renin ratio
    b. log of NT-proBNP,
    c. and body volume

    in the CTD group compared to placebo. No adjustments will be made for multiple comparisons.

Safety Assessments and Variables

Harms will be assessed by monitoring changes in eGFR, potassium, calcium, uric acid and hemoglobin A1C. For more definitive assessments, the frequency of acute kidney injury (using AKIN definition), symptomatic orthostatic hypotension (fall >20 mmHg within 3 min of standing with symptoms), hypokalemia (mild <3.5 mEq/L, moderate to severe <3.0 mEq/L), need for K replacement, hypercalcemia (>10.5 mg/dL), hypomagnesemia (<1.8 mg/dL), gout (clinical diagnosis), and hospitalization for hyperglycemia will be examined in the two groups. A screening 12 lead EKG will be completed for all qualifying patients prior to randomization. A pregnancy test will be required for women of childbearing potential. A survey of symptoms commonly linked to antihypertensive drug use in general, thiazides in particular, will be administered at the time of enrollment and every 4 weeks thereafter. Safety of continued participation will be assessed at each study visit. The stop-points will be treatment-emergent severe adverse events that precludes further exposure to the drug, such as an allergic drug reaction, initiation of renal replacement therapy, or death. If the study drug is stopped, the subject will be continued to be studied so as to not violate the intention-to-treat principle.

Subjects

Inclusion and exclusion criteria

Inclusion Criteria

1. Age greater than 18 years.
2. Calculated GFR by 4-component MDRD formula < 30 ml/min/1.73m2 but ≥15 mL/min/1.73m2. Our hospital laboratory uses IDMS-calibrated creatinine, and the appropriate formula is used to estimate GFR.
3. Hypertension, which is defined as BP of either ≥130 systolic or ≥80 mmHg by 24-hour ambulatory BP monitoring.
4. Treatment with antihypertensive drugs, which requires the use of at least one antihypertensive drug. One of the drugs should be either an ACE inhibitor or angiotensin receptor blocker. If these are contraindicated, then use of a beta-blocker is required prior to randomization.

Exclusion Criteria

1. Use of thiazide or thiazide-like drugs in the previous 12 weeks.
2. Use of furosemide in a dose >200 mg/d.
3. BP of either ≥160 systolic or ≥100 mmHg by 24-hour ambulatory BP monitoring.
4. Expected to receive renal replacement therapy within the next 3 months.
5. Myocardial infarction, heart failure hospitalization, or stroke ≤3 months prior to randomization.
6. Pregnant or breastfeeding women or women who are planning to become pregnant or those not using a reliable form of contraception (oral contraceptives, condoms and diaphragms will be considered reliable).
7. Known hypersensitivity to thiazide or sulfa drugs.
8. Organ transplant recipient or therapy with immunosuppressive agents.

Retention of Subjects

Nine study related visits are required. We will offer them $150 for participation in the trial. This amount will be prorated based on the number of visits performed.

Optional Annual Follow Up

Participants who complete all post-randomization visits will be invited to participate in an observational cohort sub-study with follow up visits once a year for 3 years. Those who respond in the affirmative will be contacted once every 12 months to consent to the follow up visits. The follow up sub-study consists of two consecutive visits. At Visit 1, clinic blood pressure and anthropometric measurements will be taken, blood and urine specimens will be obtained for analysis, concomitant medications and changes in health status will be reviewed, and participants will undergo body composition measurement using air displacement plethysmography. Participants will then begin 24-hour ambulatory blood pressure monitoring and complete an overnight urine collection, returning the following day for Visit 2. At Visit 2, clinic blood pressure measurements will again be obtained and the results of the 24-hour ambulatory blood pressure monitoring study will be reviewed. These data will provide valuable insight into longitudinal outcomes for the randomized cohort. If the participants are unable to come for the visits, we will ask for their verbal consent to obtain access to their medical records and conduct a health questionnaire over the phone.

Methods

Method of Randomization

Participants will be randomized in a 1:1 ratio to either CTD or placebo with stratification for prior loop diuretic use. A random permuted block design will be used to avoid imbalance in assignment to the study drugs over time. Random sequence will be generated by the statistician and the randomization sequence will be concealed individually in opaque envelopes. The study pharmacist, who will not interact with participants and maintain the blind, will dispense medication according to the randomization sequence for the appropriate stratum after confirming eligibility with the principal investigator.

Measurement of clinic BP

At Visit 1, clinic BP measurements will be obtained by a trained observer after 5-minute rest in triplicate in both arms after applying an appropriately sized cuff using a digital oscillometric sphygmomanometer (Model HEM-907, Omron Healthcare) following the recommendation of the European Society of Hypertension [47]. The arm and the forearm will be supported at the level of the heart (mid-sternal level) and the oscillometric BP averaged over three readings will be used as that clinic visit BP. The left arm will be used for all measurements, unless between arm reading exceed 5 mmHg systolic. If so, the arm with the higher BP will be designated the “BP arm” and will be used for all subsequent clinic BP measurements. If subjects have a dialysis access (AV fistula or AV graft), we will use the non-access arm for clinic blood pressure measurements.

Measurement of 24-hour Ambulatory BP

Ambulatory BP monitoring will be performed in all participants at baseline prior to randomization and at the end of the 12 weeks of treatment. We will use the Spacelabs 90207 monitor which has been shown to be accurate by both the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instruments (AAMI) [47]. Appropriately sized cuffs will be used with bladder sizes that encircle 80–100% of arm circumference and widths that are at least 40% of arm circumference. We will measure ABP every 20 minutes from 06:00 – 22:00 and every 30 minutes from 22:00 – 06:00 based upon a prior protocol [48]. Participants will be asked to record their wake and sleep times into a diary which will be used to calculate diurnal ambulatory BP. At least 16 total recordings will be required to call 24h ambulatory BP adequate (excluding readings taken for monitor validation during ambulatory dispensing). All ambulatory BP measurements taken on subject's non-dominant arm. If subject has dialysis access, all measurements completed on non-access arm.

Measurement of home BP

Home BP measurements will be performed with a home digital sphygmomanometer with an automatic inflator and printer for recording (Model HEM790IT or the newer model BP791IT, Omron Healthcare, Inc, Vernon Hills, IL) with a cuff size appropriate for arm size. This monitor stores up to 200 measurements in memory that can be retrieved. A similar device (Omron HEM705CP) was used to monitor BP in the large Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) for the purposes of BP monitoring [49]. At minimum at least three days of home BP monitoring is required for valid home BP recordings [50, 51]. Thus, participants will be asked to record their BP after 5 minutes of seated rest in triplicate twice daily for one week prior to clinic visit. All participants will be instructed on how to use the monitor prior to participation in the study. All home BP measurements will be taken on subject's non-dominant arm. If subject has dialysis access, all measurements completed on non-access arm.

Chemical Determinations

Chemical determinations on research samples will be conducted on those frozen at -80C for analysis of NT-proBNP, plasma renin, plasma aldosterone, and urinary albumin and creatinine. Routine safety laboratory tests will be done in the hospital laboratory.

Air displacement plethysmography

Air displacement plethysmography (ADP) will be measured using the BOD POD Gold Standard Body Composition Tracking System (Life Measurement, Inc, Concord, CA). The ADP system consisted of the air plethysmograph, a digital scale, and computer software (BOD POD version 4.2+). Each participant will be asked to change into compression shorts (for men) or a swimsuit (for women) and a swim cap and to remove any jewelry. Body mass will be measured to the nearest 0.001 kg using the electronic scale prior to the body volume measurement. Height will be measured using a Seca 222 measuring rod (Seca Group, Hamburg, Germany). Manufacture recommended procedures will be used to measure body volume. Body fat percent

will be calculated using gender and race-specific equations as follows: for non-blacks we will use the Siri equation [52], for black men the Schutte equation [53], and for black women the Ortiz equation [54]. Pilot data (see below) suggest that this method is very sensitive in detecting changes in body volume in the time of the study.

STATISTICAL METHODS

Sample Size

The primary objective of the study is to assess CTD-induced lowering of systolic BP. Sample size estimation was based on our pilot data using change from baseline to 12 weeks in average 24-hour ambulatory systolic BP. There was 1 patient who stopped taking his medication and suffered a stroke. In contrast to all others, this patient showed an increase in SBP of 31 mm Hg. We believe this outlier markedly increases the variability and reduces the estimated change in BP. Table 1 below shows the mean changes (standard deviation) and estimated sample size based on ambulatory SBP achieved by CTD, with and without this person and estimated sample size:

Table 1: Estimates of change in 24-hour ambulatory systolic BP, variability, and sample size

	SBP including outlier	SBP excluding outlier
Change in average 24-h SBP	-8.5	-12
STD DEV of Change	16.0	10.7
Sample Size to detect this change	57	13

We recognize that ignoring the outlier assumes this won't occur and we do not believe that to be a safe assumption. However, the outlier has undue influence in the pilot sample especially with respect to the estimation of variability in ambulatory BP monitoring. While we don't expect the impact of such cases in the larger Phase II study planned, we do accept that the -12 mm Hg reduction maybe optimistic for two reasons. One is regression toward the mean or other placebo effects (the pilot is a single group) and the second is that there will be a few outliers that may impact the mean difference. From an ongoing study of patients with CKD (with clinical characteristics similar to one proposed in this trial) who had ABPM performed 4 weeks apart, in 63 pairs of recordings with average 24-hour ambulatory BP of 141 mmHg, the SD of difference was 10.5 mmHg. We expect the SD at 12 weeks to be larger by about 10% or 12 mmHg. With these assumptions, two tailed test and 80% power, the required sample size to detect a between group difference of 6 mmHg is 63 subjects completing the study in each group. Assuming 80% of those randomized complete the trial we would need to randomize 63/0.80 = 79 subjects per group.

For Aims 2 and 3 we will use similar techniques and evaluated the confidence intervals of the changes. For the change in albumin/creatinine ratio from the 24 hours urine collections, the observed decline was consistent and between 40-45% regardless of whether daytime or nighttime collection of urine was evaluated. Power exceeded 99% for both daytime excretion as well as nighttime based on our pilot results with 63 subjects per group based on the observed

changes on the natural log scale of 0.48 (0.613) nighttime and 0.57 (0.694) daytime from baseline to 8 weeks. With 63 completed subjects in each group, we can detect at least 27% decline in UACR, which is clinically meaningful and an effect size that is more likely to be seen in the larger phase 2 trial. We also note that we will have repeated measures over time and using longitudinal data methods will greatly increase our power.

From the pilot, the mean change between baseline and final visit in Body Volume using Air Displacement Plethysmography was 1.234 (sd 2.88) with a similarly small within person standard deviation. Repeated measures analyses using Proc Mixed in SAS showed and estimated change of 1.54 with a standard error of 0.7375, slightly larger due to the fitting of the model to all data points. A repeated measures design with two treatment arms and 4 assessments over time with 60 subjects per group achieves the following power (computed using simulations with PASS) for various differences in the groups:

Table 2: Power to detect minimum detectable difference in body volume with air displacement plethysmography

Minimum detectable difference	0.9	1.0	1.1	1.2	1.3
Power	0.64	0.73	0.82	0.88	0.92

Each subject is measured 4 times. This design achieves 82% power to test the treatment difference in volume is at least 1.54 with a 5% significance level assuming the variance of the volume assessments is 6 and the correlation amongst the volume measurements is 0.75. If the true mean difference were only 1.234 instead of the model estimated 1.54, the power would still exceed 60%.

Analyses

The analyses will begin with descriptive statistics. Overall and by group descriptive statistics will be calculated and examined graphically. Tests for differences in demographics between the randomized group; characteristics of dropouts will be computed using t-tests, chi-square (or fisher's exact tests) to understand if potential differences exist, although such differences are not expected.

Primary Analysis

To test the hypothesis that CTD will improve the 24-hour SBP assessed by change from baseline to 12 weeks. A mixed model will be used to analyze the results. The outcome variable will be the 24h ambulatory systolic BP. The predictors will be indicator variables for group (placebo or CTD), time (baseline and 12 weeks), stratum (loop diuretics use or not) and all their interactions. The random component of the mixed model will include subject and time. Unstructured covariance will be used with estimation of marginal means by maximum likelihood. We expect the interaction between group x time to be significant. If the 3-way interaction term is significant, then results will be reported by each stratum. Confirmatory analyses will utilize the home systolic BP change from baseline. The random coefficient analysis does not require baseline systolic BP as a covariate.

Ambulatory BP recording, the gold-standard to assess BP, is carried out only twice during the trial, but home BP measurements occur every 4 weeks. Patients who drop out but have some post baseline measures of home BP (which will occur every 4 weeks) will be used in the analyses, thus minimizing the losses to follow up. We will impute ambulatory BP as follows: we will use the complete data to build a model that relates the follow up mean 24hour ambulatory systolic BP from the baseline 24-hour ambulatory systolic BP and the home measures using repeated measures Mixed Model regression - then use the expected value from the model for the missing value - and use PROC MI (which generates maybe 5 replicate values to insert variability into the imputation so that there is a price to pay for imputing.

Comparison of the cohort with these measurements will also be done to understand if the inferences based on the ambulatory BPs accurately reflect the differences between the treatment groups using the home BPs. Repeated measures mixed models (PROC MIXED in SAS) will be utilized to assess the overall differences between the treatment group using the home blood pressures. Additional analyses will explore the nocturnal patterns between the groups in the ambulatory blood pressures as well as the pattern over time given the once a day dosing proposed in this study using circadian models of blood pressure in each group

The null hypothesis we intend to reject is that there is no between group change from baseline in albumin excretion rate. Measurements of these markers will occur at weeks 0, 4, 8, and 12. The outcome variable will be the log transformed urine albumin/urine creatinine ratio (UACR). The predictors will be an indicator variable for group (placebo or CTD), a continuous variable of time (baseline, 4, 8 and 12 weeks), stratum and all interaction terms. The random component of the mixed model will include subject and time. Unstructured covariance will be used with estimation of marginal means by maximum likelihood.

The null hypothesis we intend to reject is that there is no between group change from baseline in markers of extracellular fluid volume as measured by (i) N-terminal pro B-type natriuretic peptide (NT-proBNP), (ii) plasma aldosterone to renin ratio (ARR) and (iii) body volume. Measurements of these markers will occur at weeks 0, 4, 8, and 12. Thus, three different models will be fitted. In the first model, the outcome variable will be the log transformed NT-proBNP. The predictors, fixed variables, and random variables will be as noted above. Similar analyses will be performed for ARR and body volume. To test the hypothesis that CTD is causal in this improvement in BP via a reduction in extracellular fluid volume, we will evaluate changes from baseline in the following extracellular fluid volume markers: NT-proBNP, seated plasma renin, and plasma aldosterone. That is, we will test if the improvement is a mediation effect using the technique described by Judd and Kenny[55] and elaborated by MacKinnon[56]. The technique, expanded here for more than one potential mediator (simultaneously NT-proBNP, seated plasma renin, and plasma aldosterone = mediators), employs three regression equations:

$$Y = \beta_0 + \tau X_p + \varepsilon$$
$$X_i = \beta_0 + \alpha_i X_p + \varepsilon$$
$$Y = \beta_0 + \tau' X_p + \beta_1 X_1 + \ldots + \beta_i X_i + \ldots + \beta_k X_k + \varepsilon \text{ for all mediators together}$$
$$\text{or } Y = \beta_0 + \tau' X_p + \beta_i X_i \ \varepsilon \text{ for each mediator separately}$$

Y is the outcome result (e.g., change in 24-hour ambulatory systolic BP), X_p is the treatment and X_i represent the k purported mediators. the total effect of the treatment on the outcome (measured by the coefficient, τ) is the sum of direct effect (τ') of the treatment and the mediated, or indirect, effects ($\alpha_i\beta_i$). Mediation is established when four conclusions are met: (1) the treatment predicts the outcome variable (supported by a test of statistical significance of τ in equation [A]); (2) the treatment causes the potential mediator (α_i is significant in [B]); (3) the mediator causes the outcome variable controlling for the treatment (β_i is significant in [C] and $\tau' < \tau$ which provides evidence for mediation rather than suppression); and (4) the mediated effect is statistically significant. For mediators that satisfy conclusions 1 through 3, the significance of the mediation (conclusion 4) will be determined via interval estimation of the mediated effect using the asymptotic variance derivation of Sobel[57], since the outcomes are the continuous measures. Additional analyses that look at thresholds of change (binary, successful reduction in SBP or not) will utilize the bootstrap methods[4] for binary outcomes successful reduction in SBP or not when logistic regression is utilized. The proportion of the effect mediated is calculated as the ratio of the indirect effect to the total effect, or $\alpha\beta/\tau$.

Pre-specified sub-group analysis for BP response

- Effect of age: The effect of age 65 or more and <65 will be tested using interaction effects.
- Effect of sex, presence/absence of albuminuria (>300 mg/g cr at baseline) will be assessed as above.
- Effect of volume overload: Volume overloaded subjects are more likely to show improvement with CTD therapy. In people with volume overload, renin and aldosterone levels are expected to be low, N-terminal pro B-type natriuretic peptide levels elevated and 24-hour urine Na high. We will dichotomize the baseline levels of these markers and examine the outcome on ambulatory BP using interaction effects.

Safety analysis

The number of subjects who experience hypokalemia, hypercalcemia, gout, hospitalization for diabetes mellitus, transient elevations in serum creatinine concentration, and symptomatic orthostatic hypotension will be counted for each group and compared using a Poisson regression model using terms for treatment and treatment x stratum. The statistical significance of the treatment term will be used to indicate differences between CTD and placebo. If the interaction term is significant then the event rates will be reported for each stratum. The mean change from baseline in serum potassium, calcium, estimated GFR, uric acid, HgbA1C, PTH intact, and orthostatic BP will be calculated using mixed models as noted above.

Secondary analysis

1. The mean change from baseline in 24-hour diastolic BP.

2. The proportion of subjects who achieve at least a 10-mmHg reduction in ambulatory systolic BP or a 5-mmHg reduction in diastolic BP will be called responders. Responders will be compared by group.
3. The proportions of responder subjects who achieve final ambulatory BP of <130/80mmHg by group.
4. Some data support lowering of nocturnal BP with the use of diuretics. We will analyze the dipping state by treatment. Dipping will be defined as at least 10% drop in systolic BP with sleep. Between group differences in the above analyses will be compared using interaction tests in a logistic regression model.
5. The time-course of systolic home BP will be analyzed using week as a continuous variable. It is expected that the drop in BP in the initial 4 weeks will be steep in the CTD group and then will taper off. In contrast, the placebo group is expected to have a flat response or a linear decline. Accordingly, we will use a term for week and square of the week in the CTD group only. Between group differences will be tested using marginal means.

Alternative study design considerations and clarifications

Choice of CTD: CTD was selected over HCTZ since it has a longer half-life (40-60 hrs versus 2.5 hrs in those with normal renal function) and potentially greater BP lowering effects. According to KDOQI, compared to hydrochlorothiazide, CTD may be effective at a lower GFR (KDOQI provides no reference). Although metolazone has been used in high doses in people with CKD, but it is nearly 10 times as expensive as CTD. CTD is generic and inexpensive and therefore we have selected it over others

Choice of torsemide as loop diuretic: Compared to furosemide, torsemide has more predictable bioavailability. Whereas the bioavailability of furosemide can vary from 10-100% [58], the bioavailability of torsemide is between 78-92% [59]. Among those with renal failure, the bioavailability of torsemide is 100% [60]. Thus, with torsemide use, more predictable absorption and less inter-individual variation in diuretic responses are expected [61]. Although bumetanide has more predictable bioavailability than furosemide, it is less natriuretic than furosemide [62]. Furthermore, torsemide has a longer half-life and its use as once daily diuretic is likely to enhance adherence. In a RCT that we performed among participants with CKD, the anti-hypertensive effect of torsemide given once a day was similar to furosemide given twice daily [63]. Accordingly, we have chosen torsemide as the agent of choice for a loop diuretic.

Choice of fixed-dose versus forced-titration study: Since we do not know the dose at which chlorthalidone will produce a decline in BP, we have designed this as a forced-titration study. It is quite likely, that the BP lowering effects will vary according to the GFR. Therefore, titration of dose may be required. Thus, the dose at which CTD improves BP will be individualized in this protocol.

TIMETABLE/MILESTONES

We expect to recruit and randomize a total of 160 participants in the first 4.5 years and complete the study in 5 years.

DATA SAFETY MONITORING BOARD (DSMB)

A DSMB will meet periodically to review the progress of the trial. Should signal of harms emerge, the trial can be terminated early. This will be in addition to periodic and mandatory reporting requirement to the IRB. No interim efficacy analysis is planned.

HUMAN SUBJECTS

Protection of Human Subjects

The trial has been designed to reflect current clinical practices. The titration scheme of the drugs reflects current clinical practice. After completion of the 12 weeks of active drug or placebo, the medication will be stopped. To protect against excessive rise in blood pressure, subjects will be called 2 weeks after stopping medication such that open label chlorthalidone can be prescribed should the home BP rise 7/4 mmHg or more.

Risks

1. Risks associated with taking chlorthalidone include drop in blood concentrations of various electrolytes such as potassium, sodium, and chloride. This drug can aggravate diabetes, gout, and increase blood calcium. Other side effects include excessive drop in blood pressure especially when standing and impotence.
2. Risks related to blood pressure changes and blood pressure medication changes. Risks of blood pressure drop include: light headedness, dizziness, kidney injury, or rarely stroke or myocardial ischemia or infarction. The risks of blood pressure rising excessively include stroke, heart failure, myocardial ischemia or infarction, or epistaxis.
3. Pain, bruising, and rarely infection from drawing blood from a vein in the arm
4. Lower quality of sleep and discomfort while sleeping while wearing the 24-hour blood pressure monitor.
5. Discomfort from the blood pressure machine cuff.
6. Discomfort from being enclosed within the BODPOD for body composition measurement. Patients will be asked if they have a fear of closed spaces before starting the measurement.
7. Risks related to possible loss of confidentiality.

Protection against risks and reporting of adverse events

To protect against risks, we are only recruiting subjects, who have poorly controlled hypertension by ambulatory BP monitoring.

1. Subjects will be closely monitored while receiving chlorthalidone and they will be questioned about possible side effects.

2. Blood pressure will be monitored continuously, and other possible side effects will be monitored through blood tests we are obtaining.
3. Blood will be drawn by a trained phlebotomist and whenever possible it will be obtained at a time when blood is being obtained for other tests the subject's doctor has ordered.
4. All patient charts are kept in an office locked after normal working hours and when no one is in the office. All electronic databases are password protected.
5. We will make sure all subjects are wearing the correct cuff size.
6. The automatic blood pressure monitor will be set for the sound to be turned off at night to minimize the disruption of sleep.

Adverse experience will be recorded to include the date and time of onset, description, severity, duration and outcome, etiology, relationship to study drug, and action taken.

Should a serious adverse experience (defined as death, hospitalization or prolongation of hospitalization, life-threatening or permanently disabling) occur at any time and is deemed possibly, probably, or definitely related to the study drug, the Investigator will report the incident to the IRB following the locally accepted regulations.

Adverse events of special interest

Due to the relatedness of many adverse events with use of thiazide diuretics we will use the following list as adverse events of special interest (AEOSI)

Acute gout: clinical diagnosis in the presence of symptoms.

Acute kidney injury (AKI)

Mild AKI: an increase in serum creatinine of ≥ 25% but < 50% from baseline value.

Severe AKI: an increase in serum creatinine of ≥ 50% from baseline value.

Dizziness: symptoms with observed decrease in blood pressure < 20 mmHg systolic while standing. If decrease in blood pressure is > 20 mmHg, see orthostatic hypotension .

Orthostatic hypotension: greater than 20 mmHg drop in systolic blood pressure within 3 minutes of standing when in the presence of symptoms.

Hypercalcemia: serum calcium concentration > 10.5 mg/dL.

Hyperglycemia: in patients without diabetes when random glucose is > 200 mg/dL or in patients with diabetes when random glucose > 300 mg/dL (mild/moderate); severe when random glucose is > 400 mg/dL.

Hyperkalemia: serum potassium concentration > 5.5 mmol/L.

Hyperuricemia: serum uric acid concentration > 12.0 mg/dL in patients with a serum creatinine concentration > 2.0 mg/dL.

Hypokalemia: serum potassium concentration < 3.5 mmol/L but ≥ 3.0 mmol/L (mild); serum potassium concentration < 3.0 mmol/L (moderate to severe).

Hypomagnesemia: serum magnesium concentration < 1.80 mg/dL

Hyponatremia: serum sodium concentration < 135 mmol/L.

SIGNIFICANT PROTOCOL AMENDMENTS

Table 3: Listing of significant protocol amendments and rationale of amendments

Date amended	Description of amendment	Rationale for amendment
7/28/2016	Add home BP diary and modify exclusion criteria for two weeks run in (formerly home BP < 130/80, now clinic BP < 110 systolic).	Less restrictive exclusion. Only those with clinic BP of <110 mmHg at visit 2 will be excluded from the trial. Prior to this amendment, those with home BP <130/80 mmHg were excluded.
10/14/2016	The threshold for randomization to the treatment arm (chlorthalidone vs. placebo) is revised from an average 24-hour ambulatory blood pressure of ≥135 mmHg systolic or ≥85 mmHg diastolic to a new threshold of ≥130 mmHg systolic or ≥80 mmHg diastolic.	To make 24h ambulatory BP thresholds for the diagnosis of poorly controlled hypertension consistent with prevailing guidelines
1/17/2017	Updated the definitions of adverse events of special interest.	Definitions were amended to reflect the relatedness of adverse events to use of thiazide diuretics.
2/2/2017	The protocol is amended to include a follow-up sub-study and informed consent documents are added for the sub-study. Further, the informed consent statements are amended to include fasting for blood draw and delayed blood pressure medication administration as visit procedure. IU Health is added as a recruitment site and the relevant	Broaden the recruitment site to increase trial recruitment. Follow up to assess long-term consequences of participation in the trial

	sections of the questionnaire are updated to include these changes.	
6/7/2017	This amendment removed an external site for the trial.	The external site was closed due to nonperformance, thus the informed consent statements will be amended to state that 160 subjects (e.g., enrollment target for this study) will be recruited locally.
10/5/2017	Dr. Wanzhu Tu of the IU Department of Biostatistics is added as key study personnel as he will serve as an unblinded statistician for the study and provide interim reports to the data and Safety Monitoring Board (DSMB) and will assist with results reporting at the conclusion of the trial.	External site was also the data coordinating center. With external site closure, data needed to be moved to Indiana University.
12/14/2018	Questionnaire being used to collect data from the subject for the substudy over the phone uploaded to the notes and attachment tab. We will get verbal consent from the subjects that do not want to come into the office.	Some subjects are unable to come in for the sub study due to advanced illness or time commitment issues but are interested in allowing us to ask them questions and review their medical records.
12/14/2019	Instead of BNP, changed volume marker to NT-proBNP.	NT-proBNP is more stable in freezer than BNP which is why we have changed this biomarker

REFERENCE LIST

(1) Coresh J, Wei GL, McQuillan G et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2001;161(9):1207-1216.

(2) Jones SS, D'Andrea AD, Haines LL, Wong GG. Human erythropoietin receptor: cloning, expression, and biologic characterization. *Blood* 1990;76(1):31-35.

(3) Coresh J, Selvin E, Stevens LA et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298(17):2038-2047.

(4) Sarafidis PA, Li S, Chen SC et al. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med* 2008;121(4):332-340.

(5) http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6004a4.htm

(6) Plantinga LC, Miller ER, III, Stevens LA et al. Blood pressure control among persons without and with chronic kidney disease: US trends and risk factors 1999-2006. *Hypertension* 2009;54(1):47-56.

(7) He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens* 2002;16(11):761-770.

(8) Sacks FM, Svetkey LP, Vollmer WM et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;344(1):3-10.

(9) Strategies to Reduce Sodium Intake in the United States. Henney JE, Taylor CL, Boon CS, editors. 1-506. 2010. Washington,D.C., The National Academies Press.

Ref Type: Serial (Book,Monograph)

(10) Bibbins-Domingo K, Chertow GM, Coxson PG et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med* 2010;362(7):590-599.

(11) Pimenta E, Gaddam KK, Oparil S et al. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension* 2009;54(3):475-481.

(12) Agarwal R, Andersen MJ. Correlates of systolic hypertension in patients with chronic kidney disease. *Hypertension* 2005;46(3):514-520.

(13) Crews DC, Plantinga LC, Miller ER, III et al. Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension* 2010;55(5):1102-1109.

(14) Peralta CA, Hicks LS, Chertow GM et al. Control of hypertension in adults with chronic kidney disease in the United States. *Hypertension* 2005;45(6):1119-1124.

(15) Agarwal R, Weir MR. Dry-weight: a concept revisited in an effort to avoid medication-directed approaches for blood pressure control in hemodialysis patients. *Clin J Am Soc Nephrol* 2010;5(7):1255-1260.

(16) Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension* 2009;53(3):500-507.

(17) Chobanian AV, Bakris GL, Black HR et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-1252.

(18) http://www.kidney.org/professionals/kdoqi/guidelines_bp/guide_12.htm

(19) http://www.cari.org.au/CKD_Prevent_List_Published/Blood_pressure_Control_role_of_specific_antihypertensive.pdf

(20) http://publications.nice.org.uk/hypertension-cg127/key-priorities-for-implementation#choosing-antihypertensive-drug-treatment

(21) http://www.hypertension.ca/hypertension-with-compelling-indications-dp1

(22) http://www.healthquality.va.gov/ckd/ckd_v478_sums.pdf

(23) Agarwal R, Sinha AD. Thiazide diuretics in advanced chronic kidney disease. *J Am Soc Hypertens* 2012;6(5):299-308.

(24) Dargie HJ, Allison ME, Kennedy AC, Gray MJ. High dosage metolazone in chronic renal failure. *Br Med J* 1972;4(5834):196-198.

(25) Bennett WM, Porter GA. Efficacy and safety of metolazone in renal failure and the nephrotic syndrome. *J Clin Pharmacol* 1973;13(8):357-364.

(26) Craswell PW, Ezzat E, Kopstein J, Varghese Z, Moorhead JF. Use of metolazone, a new diuretic, in patients with renal disease. *Nephron* 1974;12(1):63-73.

(27) Dargie HJ, Allison ME, Kennedy AC, Gray MJ. Efficacy of metolazone in patients with renal edema. *Clin Nephrol* 1974;2(4):157-160.

(28) Paton RR, Kane RE. Long-term diuretic therapy with metolazone of renal failure and the nephrotic syndrome. *J Clin Pharmacol* 1977;17:243-251.

(29) Wollam GL, Tarazi RC, Bravo EL, Dustan HP. Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. *Am J Med* 1982;72:929-938.

(30) Bennett WM, McDonald WJ, Kuehnel E, Hartnett MN, Porter GA. Do diuretics have antihypertensive properties independent of natriuresis? *Clin Pharmacol Ther* 1977;22(5 Pt 1):499-504.

(31) Cirillo M, Marcarelli F, Mele AA, Romano M, Lombardi C, Bilancio G. Parallel-group 8-week study on chlorthalidone effects in hypertensives with low kidney function. *Hypertension* 2014;63(4):692-697.

(32) Fliser D, Schroter M, Nerubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. *Kidney Int* 1994;46:482-488.

(33) Knauf H, Mutschler E. Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. *J Cardiovasc Pharmacol* 1995;26(3):394-400.

(34) Dussol B, Moussi-Frances J, Morange S, Somma-Delpero C, Mundler O, Berland Y. A randomized trial of furosemide vs hydrochlorothiazide in patients with chronic renal failure and hypertension. *Nephrol Dial Transplant* 2005;20(2):349-353.

(35) Dussol B, Moussi-Frances J, Morange S, Somma-Delpero C, Mundler O, Berland Y. A pilot study comparing furosemide and hydrochlorothiazide in patients with hypertension and stage 4 or 5 chronic kidney disease. *J Clin Hypertens (Greenwich)* 2012;14(1):32-37.

(36) Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012;59(6):1104-1109.

(37) Ernst ME, Carter BL, Goerdt CJ et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47(3):352-358.

(38) Ernst ME, Neaton JD, Grimm RH, Jr. et al. Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. *Hypertension* 2011;58(6):1001-1007.

(39) Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension* 2011;57(4):689-694.

(40) Aaron KJ, Campbell RC, Judd SE, Sanders PW, Muntner P. Association of dietary sodium and potassium intakes with albuminuria in normal-weight, overweight, and obese

participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Clin Nutr* 2011;94(4):1071-1078.

(41) Weir MR, Townsend RR, Fink JC et al. Urinary sodium is a potent correlate of proteinuria: lessons from the chronic renal insufficiency cohort study. *Am J Nephrol* 2012;36(5):397-404.

(42) Sanders PW. Effect of salt intake on progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2006;15(1):54-60.

(43) Swift PA, Markandu ND, Sagnella GA, He FJ, MacGregor GA. Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives: a randomized control trial. *Hypertension* 2005;46(2):308-312.

(44) Vogt L, Waanders F, Boomsma F, de ZD, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;19(5):999-1007.

(45) O'Brien E, Parati G, Stergiou G et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013;31(9):1731-1768.

(46) Agarwal R, Pappas MK, Sinha AD. Masked Uncontrolled Hypertension in CKD. *J Am Soc Nephrol* 2016;27(3):924-932.

(47) O'Brien E, Asmar R, Beilin L et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21(5):821-848.

(48) Agarwal R, Lewis RR, Davis JL, Becker B. Lisinopril therapy for hemodialysis hypertension – Hemodynamic and endocrine responses. *Am J Kidney Dis* 2001;38(6):1245-1250.

(49) Sever PS, Dahlof B, Poulter NR et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens* 2001;19(6):1139-1147.

(50) Stergiou GS, Skeva II, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? *J Hypertens* 1998;16(6):725-731.

(51) Stergiou GS, Baibas NM, Gantzarou AP et al. Reproducibility of home, ambulatory, and clinic blood pressure: implications for the design of trials for the assessment of antihypertensive drug efficacy. *Am J Hypertens* 2002;15(2 Pt 1):101-104.

(52) Siri WE. Body composition from fluid spaces and density: analysis of methods. In: Brozek J, Henschel A, editors. *Techniques for measuring body composition*.Washington,D.C.: National Academy of Science; 1961. 223-244.

(53) Schutte JE, Townsend EJ, Hugg J, Shoup RF, Malina RM, Blomqvist CG. Density of lean body mass is greater in blacks than in whites. *J Appl Physiol* 1984;56(6):1647-1649.

(54) Ortiz O, Russell M, Daley TL et al. Differences in skeletal muscle and bone mineral mass between black and white females and their relevance to estimates of body composition. *Am J Clin Nutr* 1992;55(1):8-13.

(55) Ghafourifar P, Colton CA. Compartmentalized nitrosation and nitration in mitochondria. *Antioxid Redox Signal* 2003;5(3):349-354.

(56) Bendahan D, Confort-Gouny S, Kozak-Reiss G, Cozzone PJ. Pi trapping in glycogenolytic pathway can explain transient Pi disappearance during recovery from muscular exercise. A 31P NMR study in the human. *FEBS Lett* 1990;269(2):402-405.

(57) Klooker P, Bommer J, Ritz E. Treatment of hypertension in dialysis patients. *Blood Purif* 1985;3(1-3):15-26.

(58) Murray MD, Haag KM, Black PK, Hall SD, Brater DC. Variable furosemide absorption and poor predictability of response in elderly patients. *Pharmacotherapy* 1997;17(1):98-106.

(59) Blose JS, Adams KFJ, Patterson JH. Torsemide: A pyridine-sulfonylurea loop diuretic. *Ann Pharmacother* 1995;29:396-402.

(60) Gehr TWB, Rudy DW, Matzke GR, Kramer WG, Sica DA, Brater DC. The pharmacokinetics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther* 1994;56:31-38.

(61) Klutsch K, Grosswendt J, Haecker W. Single dose comparison of torasemide and furosemide in patients with advanced renal failure. *Arzneimittelforschung* 1988;38(1A):200-204.

(62) Voelker JR, Cartwright-Brown D, Anderson S et al. Comparison of loop diuretics in patients with chronic renal insufficiency. *Kidney Int* 1987;32(4):572-578.

(63) Vasavada N, Saha C, Agarwal R. A double-blind randomized crossover trial of two loop diuretics in chronic kidney disease. *Kidney Int* 2003;64(2):632-640.

(64) Agarwal R, Sinha AD, Pappas MK, Ammous F. Chlorthalidone for poorly controlled hypertension in chronic kidney disease: an interventional pilot study. *Am J Nephrol* 2014;39(2):171-182.