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Design and Baseline Characteristics of the Chlorthalidone in Chronic Kidney Disease (CLICK) Trial

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Abstract

Background: Hypertension often accompanies chronic kidney disease (CKD), and diuretics are widely prescribed to reduce blood pressure (BP). Chlorthalidone (CTD) is a thiazide-like diuretic and an effective antihypertensive drug, yet little data exist to support its use in treating hypertension in individuals with advanced CKD.

Methods: Chlorthalidone in Chronic Kidney Disease (CLICK) is a phase II, single-institution, multicenter, double-blind randomized control trial to test the hypothesis that CTD improves BP, through reduction of extracellular fluid volume, and results in target organ protection in patients with stage 4 CKD and poorly controlled hypertension. After a single-blind placebo run-in for two weeks and confirmation of hypertension by 24-hour ambulatory blood pressure (ABP), patients are randomized to either placebo or CTD 12.5mg once daily (QD) followed by dose escalation. Randomization is stratified by prior loop diuretic use, and the double-blind phase lasts 12 weeks. With a total of 160 patients, the study will have ≥80% power to detect a 6 mm Hg difference in systolic ABP between the two treatment groups.

Results: Between June 2016 and October 2019, 131 patients have been randomized. The baseline characteristics are as follows: average age 65.8 years, 79% men, 36% black, and 79% with diabetes, mean eGFR 23.2 mL/min/1.73m^2, median urine albumin/creatinine ratio (UACR) 923 mg/g, average number of BP medications 3.4, 60% on loop diuretics, and 24-hour ABP averaged 141.7/73.8 mmHg.

Conclusion: Among patients with stage 4 CKD and uncontrolled hypertension, CLICK should answer the question whether CTD is safe and effective.

Keywords

Chronic Kidney Disease; Hypertension; Thiazide Diuretics; Ambulatory Blood Pressure Monitoring

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Introduction

Worldwide 10–15% of the population has chronic kidney disease (CKD) [1]. Given the kidney's role in regulating blood pressure (BP), it is not surprising that compared to those without CKD, hypertension is more prevalent among individuals with CKD [2]. Furthermore, compared to those without CKD, although hypertension is more often treated in individuals with CKD, BP is often less well controlled [3]. This is due to many factors, including a hypervolemic state. To control both hypertension and hypervolemia, diuretics are frequently prescribed.

Loop diuretics are effective in treating hypervolemia but at the expense of causing acute kidney injury (AKI). As examples, compared to the administration of saline or mannitol, a randomized trial noted that the administration of furosemide prior to intravenous contrast administration was associated with a greater increment in serum creatinine at 48 hours [4]. Among patients with heart failure, higher doses of loop diuretics were associated with a higher incidence of worsening kidney failure [5] and reduction in the dose of loop diuretics was associated with an improvement in glomerular filtration rate [6]. Conversely, thiazide diuretics are less potent and longer acting, which may induce a more consistent reduction in BP over 24 hr. To date, there are no firm data that support the use of thiazides in improving BP in advanced CKD. In a review of 13 studies on the use of thiazide diuretics either alone or in combination with loop diuretics in advanced CKD [7], nine studies were observational, whereas 4 were randomized clinical trials (ranging between 7–23 patients). Observational studies showed that thiazides lowered seated clinic BP by 10–15 mmHg systolic and 5–10 mmHg diastolic, whereas randomized trials lowered the mean arterial pressure by about 15 mmHg reduction in mean arterial pressure. Our own preliminary study supported the use of CTD in advanced CKD [8]. Given the promising preliminary data, we see the need for a larger and more definitive trial to establish the safety and efficacy of thiazide diuretics in advanced CKD.

The unacceptably high rates of cardiovascular morbidity and mortality in individuals with advanced CKD are the main impetus for the CLICK trial [9]. To our knowledge, few clinical trials have been completed that are adequately powered for cardiovascular outcomes in individuals with advanced CKD [10]. We hypothesize that among patients with advanced CKD and treated but uncontrolled hypertension, CTD will result in lowering of 24-hour ambulatory systolic BP primarily due to a reduction in extracellular fluid volume. Furthermore, CTD will improve albuminuria over 12 weeks and therefore provide preliminary evidence for target organ protection.

Methods

Overall Trial Design

The CLICK study is a single-institution, multicenter, placebo-controlled, double-blind, randomized control trial of CTD vs. placebo in patients with advanced CKD and treated but poorly controlled hypertension. The study is designed to test the hypothesis that CTD, when added to the current regimen of antihypertensive drugs, improves BP in patients with stage 4 CKD and uncontrolled hypertension. The study was approved by the Institutional Review

Board of Indiana University and the Research and Development Committee of the Richard L Roudebush Veterans Administration Medical Center, Indianapolis, IN and all patients provided written informed consent prior to participation.

Recruitment Criteria

Inclusion and exclusion criteria are listed in Table 1. To qualify, patients had stage 4 CKD (eGFR<30 mL/min/1.73m^2 but ≥15 mL/min/1.73m^2) and treated but uncontrolled hypertension. All patients underwent a 2-week period of single-blind placebo run-in during which patients were administered a placebo which was known only to the investigators but not the patients. Following this run-in, confirmed cases of uncontrolled hypertension were randomized. Herein, uncontrolled hypertension was defined as an average 24-hour ambulatory blood pressure of ≥130 mmHg systolic or ≥80 mmHg diastolic among patients receiving at least one drug for treating hypertension [11].

Study Protocol

Figure 1 shows the overall conduct of the study. There were nine study-related visits, 4 prior to randomization over three weeks, 4 after randomization over 12 weeks, and a final visit 2 weeks after the end of the study. We first enumerate the procedures performed at each visit, followed by the description of procedures.

Description of Intervention Prior to Randomization—Patients were instructed to delay their blood pressure medications for all visits except for visit 1 and fast for all visits except for visit 1, visit 2, visit 4, and visit 8.

Visit 1, Week -3: At visit 1, after written informed consent, seated clinic BP measurement were obtained on both arms to determine the arm that would be used for the measurement of BP. For BP measurement in the clinic, the non-dominant arm was generally used, unless the dominant arm had systolic BP that was ≥5 mmHg more than the non-dominant arm. After explaining the methodology of home blood pressure (HBP) monitoring, patients were scheduled to return one week later.

Visit 2, Week -2: At visit 2, clinic BP was recorded, and the HBP recordings were downloaded to a computer. Using a standard questionnaire, we collected the demographics and medical history, and reconciled the medications. If the patient's average systolic clinic BP was <110mmHg, participation was terminated. Following a focused physical exam, single-blind run-in of a placebo was administered, and antihypertensive regimen was standardized. All patients were provided written instructions in sixth grade language on how to follow a diet containing <100 mEq Na/day.

Visit 3, Day -1: Visit 3 took place two weeks after visit 2. HBP was collected. Serum electrolytes, glucose, creatinine, blood urea nitrogen, uric acid, lipid profile, hemoglobin A1C, and spot urine for albumin and creatinine were measured by the local lab. Body volume was measured by using air displacement plethysmography. Ambulatory blood pressure was monitored over 24h. Patients were asked to keep a sleep diary and were

instructed to collect a 24-hour urine specimen. In addition, patients were administered a questionnaire to elicit adverse effects that may potentially be related to the study medication.

Visit 4, Day of randomization: At visit 4, 24 hours after visit 3, the 24-hour ambulatory monitor, 24-hour urine jug, and sleep diary were collected. On the 24-hour urine, the following analytes were measured: sodium, potassium, chloride, calcium, albumin, and creatinine. The 24-hour urine volume was measured using a graduated cylinder. An electrocardiogram (EKG) was performed if the patient was found eligible for further participation. Randomized patients were dispensed the double-blind study medication for four weeks with instruction to take one pill every day upon waking up. A home BP monitor was provided.

Description of Visits After Randomization

Visits 5 and 6, Weeks 4 and 8, respectively: Visit 5 (4 weeks after visit 4) and visit 6 (4 weeks after visit 5) were similar procedurally, therefore are discussed together. Home BP monitor was collected and clinic BP measured. Serum electrolytes, glucose, creatinine, blood urea nitrogen, uric acid and spot urine for albumin and creatinine were measured by the local lab. Body volume was measured. A structured questionnaire was used to elicit study medication-related adverse effects, and medications were reconciled. The study drug dose was doubled based on the home BP threshold of 135/85 mmHg, to 25mg CTD vs. placebo at visit 5 and a maximum of 50mg CTD vs. placebo at visit 6. A 30-day supply of study medication and the home BP monitor were dispensed.

Visits 7 and 8, Week 12, day 1 and 2.: The procedures and labs at visit 7 and visit 8 were identical to visit 3 and 4. and occurred four weeks after visit 6. However, an EKG was not obtained, and the patients were not prescribed study medication because visit 8 marked the start of the two-week wash-out period. A home BP monitor was provided.

Visit 9, Week 14: Visit 9 took place two weeks after the end of treatment visit (visit 8). Home BP monitor was collected and clinic BP was measured. Serum electrolytes, glucose, creatinine, blood urea nitrogen, uric acid, and spot urine for albumin and creatinine were measured by the hospital lab. Body volume was measured and symptoms potentially related to study medications are collected using a standardized questionnaire. At this visit, the home BP average was compared to the home BP average from visit 7, two weeks prior. If the patient's blood pressure increased by ≥7 mmHg systolic or ≥4 mmHg diastolic, the patient was prescribed at least 12.5mg of CTD in an open-label manner. Further follow-up was provided by the patient's own physician.

Method of Randomization—Patients were randomized at a 1:1 ratio to either CTD or placebo, stratified by patient's being on loop diuretics. Random block sizes were used to avoid imbalance in the number of patients receiving each treatment assignment. The study pharmacist, who did not interact with patients, maintained the blind and dispensed the medication according to the randomization sequence for the appropriate stratum after confirming eligibility with the principal investigator. Drug assignment was masked for the investigator, treating physician, patient and the outcome assessor.

Safety Assessments and Variables—This was a placebo-controlled titrate to endpoint study. The dose of the study drug was escalated if goal home BP was not achieved. We asked patients to measure BP at home in triplicate twice a day for one week, and the average of these was used to inform decision making. However, if a patient failed to record at least 3 days of BP at home, decision making was based on BP recorded in the clinic.

The dose of study medication was not increased if the patient had one of the following: home BP was not ≥135 mmHg systolic or ≥85 mmHg diastolic, symptomatic orthostatic hypotension, hypercalcemia, hypomagnesemia, moderate hypokalemia (K<3 mEq/L), acute gout, or recent hospitalization for poorly controlled diabetes. In these instances, the study drug dose was either maintained or decreased based on the investigator's judgment.

Stopping parameters—There were four stopping rules in place to ensure the safety. 1) The study medication was stopped, or the dose was reduced if a patient experienced a drug-induced rash, acute kidney injury (AKI), or other adverse events that are attributable to the drug. 2) If home BP averaged over one-week was ≥180 mmHg systolic or ≥110 mmHg diastolic, the dose of the study drug was increased, and the patient returned to clinic in 7 days with a week's worth of home BP recordings. If home BP recordings were ≥180/110 mmHg, the patient was withdrawn from the study. 3) Over one week, if the average home BP was 160–179 mmHg systolic or 100–109 mmHg diastolic, the dose of the study drug was further increased, and the patient returned to clinic in two weeks with a week's worth of home BP readings. If BP was not <160/100 mmHg within 4 weeks, the patient was withdrawn from the trial. 4) If, in the PI's judgment, the risks of taking the medication outweighed the benefits for a patient, then the patient was withdrawn.

Observational Annual Follow-Up—Patients who complete all post-randomization visits were invited to participate in an observational cohort sub-study with annual follow-up visits for up to 3 years. Those who agreed to do so were contacted once every 12 months to consent to the follow-up visits. The follow-up procedures consisted of 2 consecutive visits, much like visit 3/visit 4 and visit 7/visit 8. At visit 1, clinic blood pressure and anthropometric measurements were taken as well as serum electrolytes, glucose, creatinine, uric acid, lipid profile, hemoglobin A1C, and spot urine for albumin and creatinine measured in the hospital lab. Concomitant medications and changes in health status using a questionnaire were reviewed. Patients underwent body volume measurement using air displacement plethysmography. Patients monitored 24-hour ambulatory blood pressure, collected urine over 24-hours, kept a sleep diary, and returned the following day for visit 2. At visit 2, clinic BP was recorded, and the results of the 24-hour ambulatory BP recording reviewed. Like in the previous visits, 24-hour urine was measured in the hospital lab for the following analytes: sodium, potassium, chloride, calcium, urea nitrogen, albumin, and creatinine. The 24-hour urine volume was measured using a graduated cylinder.

Procedures

Clinic Blood Pressure—Clinic BP measurements were obtained by a trained technician. The patient rested in a closed room, in a chair for 5-minutes with both feet on the ground, back resting, and without any electronic devices such as cell phones. The blood pressure was

taken in triplicate in both arms after applying an appropriately sized cuff using a digital oscillometric sphygmomanometer (Model HEM-907, Omron Healthcare, Inc, Vernon Hills, IL) following the recommendation of the European Society of Hypertension [12]. No observer was present in the room. Inflations occurred 30 seconds apart. The arm and the forearm were supported at the level of the heart (mid-sternal level) and the oscillometric BP was averaged over three readings, which was used as that clinic visit BP. The non-dominant arm was used for all measurements, unless the between arm reading exceeded 5 mmHg systolic for the dominant arm. If so, the dominant arm was designated the clinic BP arm and was used for all subsequent clinic BP measurements. If patients had dialysis access (AV fistula or AV graft), the non-access arm was used for clinic BP measurements.

Orthostatic Clinic Blood Pressure—After completing the seated oscillometric BP, patients stood for 30 seconds, with arm supported at mid-sternal level by a tray table. Standing BP was compared to the seated oscillometric clinic BP. If standing systolic BP decreased by >20 mmHg and the patient felt dizzy or lightheaded, then an adverse event (AE) for orthostatic hypotension was noted. Conversely, if the patient felt dizzy without the systolic BP decreasing by >20 mmHg in comparison to seated oscillometric blood pressure, an AE for dizziness was recorded. Lastly, if the ortostatic systolic BP declined by >20 mmHg, but there were no complaints of dizziness or lightheadedness, then an AE for asymptomatic orthostatic hypotension was recorded.

Home Blood Pressure (HBP)—Home blood pressure measurements were performed with a home digital sphygmomanometer that has an automatic inflator (Model BP791IT, Omron Healthcare, Inc, Vernon Hills, IL). Patients were provided a cuff size appropriate for arm size. This monitor stored up to 200 measurements in memory which were downloaded to a computer. At a minimum, three days of home BP monitoring was required for a valid home BP recording [13]. Thus, patients were asked to record BP after 5 minutes of seated rest in triplicate twice daily for one week prior to clinic visit. All patients were instructed in use of the monitor at their first visit. All home BP were measured on the non-dominant arm. If patient has dialysis access, all measurements were measured on non-access arm.

Ambulatory Blood Pressure (ABP) Monitoring—Ambulatory blood pressure (ABP) monitoring was performed over a 24-hour period using a Spacelabs 90207 monitor, which is shown to be accurate by both the British Hypertension Society (BHS) and the Association for the Advancement of Medical Instruments protocols [14]. Appropriately sized cuffs were used with bladders sizes that encircled 80–100% of arm circumference and widths that were at least 40% of arm circumference. The monitors were initialized before the patient left the clinic by taking three seated readings manually followed by one standing reading after the patient had been standing for 30 seconds. ABP was measured every 20 minutes from 06:00–20:00 and every 30 minutes from 20:00–06:00. Over the 24-hour period, patients were instructed to record their wake and sleep times in order to calculate diurnal ABP. At least 16 total recordings were required to call 24h ambulatory BP adequate (excluding readings taken for monitor validation during ambulatory dispensing). All ambulatory BP measurements were taken on the non-dominant arm. If the patient had dialysis access, then the non-access arm was used.

Air Displacement Plethysmography (ADP) to Assess Total Body Volume—Air displacement plethysmography (ADP) was used to assess total body volume using a BOD POD Gold Standard Body Composition Tracking System (Life Measurement, Inc, Concord, CA). The ADP system consists of an air plethysmograph, a digital scale, and computer software (BOD POD version 4.2+). Each patient was asked to change into compression shorts (for men) or a swimsuit (for women). Both men and women were instructed to wear a swim cap and remove jewelry. Body mass was measured to the nearest 0.001 kg using an electronic scale prior to the body volume measurement. Height was measured using a Seca 222 measuring rod (Seca group, Hamburg, Germany). Body volume measurements were completed using manufacturer recommended procedures. Body fat percentage was calculated using sex and race-specific equations as follows: for non-blacks, we used the Siri equation [15], for black men the Schutte equation [16], and for black women the Ortiz equation [17].

Standardization of Blood Pressure Regimen—All patients were required to be on an ACEi/ARB or, if contraindicated, a β-blocker. The standardized regimen was dependent on the nature of the antihypertensive drugs already prescribed. The preferred drugs were as follows: 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), β-blocker (atenolol 25–100 mg/d) and loop diuretic (torsemide 10–20 mg/d). For example, if a patient was on a β-blocker and a diuretic, atenolol and torsemide were prescribed. Doses were selected based on what the patient was currently prescribed. For those on furosemide, 20 mg was considered equivalent to 10 mg of torsemide. Due to atenolol being renally cleared, its half-life is prolonged in those with CKD. For those on metoprolol, 100 mg of atenolol was considered equivalent to 200 mg of metoprolol. Clonidine or minoxidil as fifth and sixth drugs were left unchanged. Likewise alpha-blockers for prostatic symptoms were left unchanged to avoid precipitating acute urinary retention. Those on K-sparing diuretics (e.g., amiloride, spironolactone, or eplerenone) were also left unchanged.

Once BP medications are standardized, they are held constant through the 12 weeks of the trial.

Statistical Analyses—All analyses will be carried out in an intention-to-treat framework. The analysis will use a mixed model with the 24-hour ambulatory systolic BP measured at baseline and 12 weeks serving as response variables. The model will include the treatment assignment indicator (placebo or CTD), time (4 and 12 weeks), and loop diuretics at baseline (yes/no) as independent variables as well as the following interactions: treatment x time loop diuretics x treatment x time. The model will include a random subject effect, with an unstructured variance-covariance matrix, to accommodate the potential correlations among the repeated measures within the same patient. We will first examine the statistical significance of the treatment's interaction with loop diuretic and time. If the three-way interaction is significant, we will report the treatment×time effect by loop diuretics. If the three-way interaction is not statistically significant, we will remove the term from the model and report the time trend of the BP change by treatment groups.

In addition to the two ambulatory BP recordings, the gold-standard of BP assessment, we also assessed home BP and measurements in the clinic every 4 weeks. The more frequently measured home BP and clinic BP provides an opportunity for a more careful examination of the time course of the treatment effect. Graphical methods will be used to depict the mean BP level at each assessment time. As in the analysis of the primary outcome, a mixed effect model analysis for home BP measurements and clinic BP measurement will be conducted. The intention-to-treat analysis only excludes participants with no BP recordings at any post-randomization assessment. We will examine the missing data patterns and impute the outcome as appropriate. If necessary, sensitivity analyses will be conducted to validate the main analyses.

Similar mixed models with random subject effect will be used to assess the treatment effects on the secondary outcomes, including urinary albumin/creatinine, aldosterone-to-renin ratio (ARR), levels of B-type natriuretic peptide (BNP), as well as body volume. We will examine the distributions of these outcome measures and perform necessary transformations prior to the modeling exercise.

Pre-specified sub-group analysis—Pre-specified sub-group analysis for BP responses planned to be performed are as follows:

1. Effect of age: the effect of age 65 or more and <65
2. Effect of sex
3. Effect of race: Black vs non-Black
4. Effect of loop diuretic use: presence or absence.
5. Effect of albuminuria (>300 mg/g cr at baseline, presence or absence)
6. Effects of volume overload: which will be classified according to the median values of B-type natriuretic peptide levels, median aldosterone:renin ratio, and body volume.
7. Effect of dietary Na intake: which will be classified by the baseline median 24-hour urine Na excretion rate.

We will examine the outcome on ambulatory systolic BP of each of the above outcomes using interaction effects.

Safety Analysis—A safety analysis will be performed to assess the number of patients who experience hypokalemia, hypercalcemia, gout, hospitalization for diabetes mellitus, transient elevations in serum creatinine concentration, and symptomatic orthostatic hypotension. The rates 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. 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.

Power and Sample Size—The primary objective of the study was to assess the BP-lowering effect of CTD. We designed the trial to ensure adequate power for testing the primary hypothesis - patients receiving CTD will have a greater reduction in ambulatory systolic BP from baseline than patients in the control group. Assuming 20% attrition, a total sample size of 160 will ensure at least 128 subjects with complete follow-up (i.e., 64 subjects per treatment group). Based on our preliminary data, we estimate that a sample size of 64 per group will give us at least 80% power to detect a 6 mm Hg difference in BP change from baseline by using a two-sided t-test at 0.05 significance level.

Results

Recruitment occurred both by screening from renal clinics as well as searching computerized databases for eligible patients at three hospitals affiliated with Indiana University School of Medicine: Richard L. Roudebush VA Medical Center, Eskenazi Hospital, and Indiana University, Indianapolis, IN, USA. The study started in July 2016. The number of patients randomized from these 3 sites is through October 2019.

In total, 131 patients have been randomized. Baseline characteristics are shown in Table 2. The sample is predominantly male (79%) with a mean age of 65.8 years. Blacks constitute 36% of the overall sample. All patients have stage 4 CKD with a mean eGFR of 23.2 mL/min/1.73m^2 with a median urine albumin/creatinine ratio (UACR) of 923 mg/g creatinine. As may be expected from a sample of patients with advanced CKD, cardiovascular comorbidity was high: 34% of patients had been hospitalized for CHF, 25% had a past medical history of myocardial infarction, 20% had a stroke, 18% had a coronary stent, 12% had a coronary artery bypass graft, and 7% have had a peripheral vascular bypass operation. The etiology of CKD was diabetes mellitus in 54%, and hypertension in 30%.

Table 3 shows that, on average, patients were taking 3.4 antihypertensive medications at baseline. Of the 131 patients, 60% were on a loop diuretic, 63% were taking an ACE inhibitor or ARB, and only 7% were taking spironolactone.

Table 4 displays baseline ambulatory BP monitoring data. At baseline, an average of 56.2 readings over a 24-hour period were available. Average 24h ambulatory BP was 141.7/73.8 mmHg, and only a fraction (22%) of randomized patients meet the criteria for nocturnal dipping.

Discussion

Despite hypertension control being the backbone of renal and cardiovascular protection, in advanced CKD, poorly controlled hypertension is very common in part because volume expansion is causally important, but the use of thiazide diuretics in these patients is not recommended. As examples, the 2017 AHA/ACC hypertension guidelines recommend using loop diuretics over thiazides in patients with moderate-to-severe CKD such as those with GFR <30 mL/min [18]. The 2014 Eighth Joint National Committee had no position on thiazides in advanced kidney disease [19]. However, the 2003 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC7) recommended that increasing doses of loop diuretics be used in combination with

other drug classes in those with advanced renal disease [20]. Conversely, 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 support the use of loop diuretics but not thiazide diuretics in advanced CKD.

Thiazide diuretics are less potent in comparison to loop diuretics, and their use may be associated with less AKI, yet there are no firm data to support that thiazide diuretic therapy can improve BP in advanced CKD. Therefore, it is understandable that the present guidelines do not support the use of thiazides or thiazide-like diuretics in patients with stage 4 CKD. Nonetheless, a narrative review suggests that thiazide diuretics may be useful even among people with advanced CKD [21].

There are important differences between thiazide diuretics in potency, duration of action, side effects, and costs. CTD has nearly three times the potency compared to the commonly used hydrochlorothiazide (HCTZ) [22]. Given the higher potency, a longer duration of action, and a lower cost, CTD may be preferred to other thiazides. Ambulatory 24h systolic BP with 50mg of HCTZ is reduced 7.4 mmHg in contrast to 25mg CTD reducing it by 12.4 mmHg [23]. Thus, the CLICK study using CTD has the potential of changing existing practice using an inexpensive therapy that can impact a large number of people with CKD.

There are several strengths of the study design. CLICK utilizes state-of-the-art methods such as direct measurement of body volume with air displacement plethysmography and indirect measurements of volume with BNP and plasma renin and aldosterone activity. We measure target organ damage through frequent measurements of urinary albumin and creatinine. Routine laboratory tests are taken to test for common problems associated with thiazide diuretics such as volume depletion, serum electrolyte abnormalities, dyslipidemia, and AKI. ABP monitoring is performed twice, once to confirm uncontrolled hypertension and a second reading to determine response after patients have been on either CTD or placebo for 12 weeks. Measurments of a large number of BP recordings over a 24h period will provide a comprehensive picture of a patient’s blood pressure. In our study so far, only about half the patients, after receiving a single-blind placebo run-in, continued to have confirmed stage 4 CKD, but had either too low (ABP <130/80 mmHg) or too high (ABP ≥160/100 mmHg) a BP. Thus, ABP monitoring removed both the white coat effect as well as patients whose BP was too high to participate. In CLICK, 36% of the patients are Black, providing valuable information on a vulnerable subpopulation likely to progress to end stage renal disease (ESRD). A weakness of CLICK is that it is being conducted at a single institution. A multi-institutional model would have been more generalizable, but this limitation was ameliorated by recruiting individuals from three different hospitals broadening the social and demographic characteristics.

Conclusions

Preliminary studies support the use of CTD in advanced CKD, but better studies are needed to evaluate the safety and efficacy of thiazide diuretics in advanced CKD. CLICK is innovative because it will further our understanding of the role of excess volume in the pathogenesis of hypertension in CKD. CLICK focuses on the potential mechanisms by

which thiazides reduce BP and provides evidence for the specific role of thiazide diuretics in the management of hypertension in those with advanced CKD, which to date, has not been adequately evaluated. A randomized control trial of this nature is rare in nephrology and it aims to address treating hypertensive patients with CKD using an inexpensive and effective medication. Furthermore, CLICK assesses the shrinking of extracellular fluid volume by CTD and provides evidence on whether a decrease in albuminuria over 12 weeks leads to target organ protection. The study population is diverse, and the study will provide information about important subgroups such as women, Blacks, non-diabetics, elderly, as well as patients who are on loop diuretics.

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Conflicts of Interest

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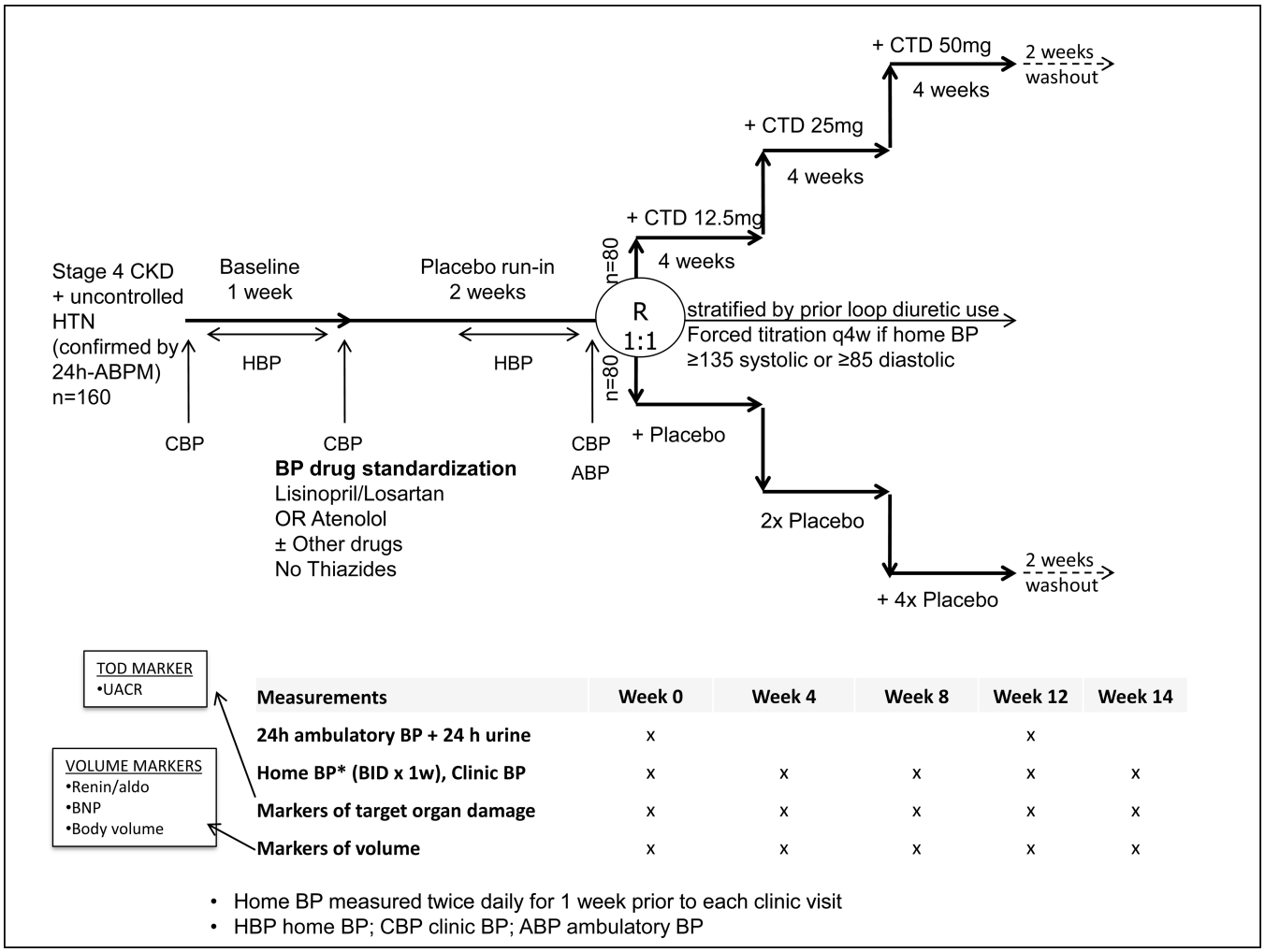

Figure 1.

Description of study procedures and trial flow. R, randomization; CTD, chlorthalidone; TOD, target organ damage; BID, twice daily; HBP, home BP; CBP, clinic BP; ABP, ambulatory BP.

Table 1:

Recruitment criteria for the clinical trial

Inclusion criteria
1. Age ≥18 years old.
2. eGFR <30 mL/min/1.73m^2 but ≥15 mL/min/1.73m^2 using the MDRD 4-component formula and IDMS-calibrated creatinine.
3. Hypertension defined as BP of either ≥130 mmHg systolic or ≥80 mmHg diastolic by 24-hour ambulatory BP monitoring.
4. Treatment with antihypertensive drugs. This requires the use of at least one antihypertensive medication for 12 continuous weeks prior to randomization. One of the drugs should be either an ACE inhibitor or ARB. 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 >200 mg/d or torsemide >100 mg/d.
3. BP of either ≥160 mmHg systolic or ≥100 mmHg diastolic by 24-hour ambulatory BP monitoring.
4. Myocardial infarction, heart failure hospitalization, or stroke ≤3 months prior to randomization.
5. Expected to receive renal replacement therapy within the next 3 months.
6. Woman who is pregnant or breastfeeding, plans to become pregnant, or those not using a reliable form on 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.
9. Advanced Illness (e.g., terminal cancer, advanced heart failure, or advanced liver cirrhosis).

IDMS isotope dilution mass spectroscopy; eGFR estimated glomerular filtration rate; MDRD Modification of Diet in Renal Disease; ACE angiotensin converting enzyme; ARB angiotensin receptor blocker

Table 2:

Baseline characteristics of the study cohort

Characteristic		n (%) or mean (SD)
Sample size		131
Age		65.8 (11.9)
Men		104 (79.4%)
Ethnicity and Race	Non-Hispanic White	77 (58.8%)
	Non-Hispanic Black	47 (35.9%)
	Hispanic white	1 (0.8%)
	Asian	1 (0.8%)
	American Indian	1 (0.8%)
	Other	4 (3.1%)
Tobacco use	Current User	32 (24.4%)
	Never used	25 (19.1%)
	Past User	74 (56.5%)
Diabetes mellitus		103 (78.6%)
Gout		35 (26.7%)
Sleep Apnea		54 (41.2%)
Myocardial infarction		33 (25.2%)
Stroke		26 (19.8%)
PTCA		24 (18.3%)
CABG		15 (11.5%)
Hospitalization for CHF		44 (33.6%)
Peripheral vascular bypass		9 (6.9%)
Etiology of CKD	diabetes	71 (54.2%)
	hypertension	39 (29.8%)
	glomerulonephritis	5 (3.8%)
	obstructive uropathy	5 (3.8%)
	polycystic kidney disease	1 (0.8%)
	other	10 (7.6%)
eGFR (mL/min/1.73m^2)		23.2 (4.2)
UACR (mg/g) (median, IQR)		923.4 (184.7, 2273.9)
UACR category	<30 mg/g	18 (13.7%)
	30 to <300 mg/g	24 (18.3%)
	>=300 mg/g	89 (67.9%)
Weight (kg)		95.3 (22.3)
Body Mass Index (kg/m^2)		32.0 (6.8)
Pulse rate		64.1 (10.8)
Systolic BP (mmHg)		140.5 (19.0)
Diastolic BP (mmHg)		68.5 (13.2)

SD standard deviation; PTCA percutaneous transluminal coronary angioplasty; CABG coronary artery bypass graft; CHF congestive heart failure; CKD chronic kidney disease; IQR interquartile range; UACR urine albumin to urine creatinine ratio; eGFR estimated glomerular filtration rate; BP and pulse rate were taken in the clinic the day prior to randomization.

Table 3:

Antihypertensive medications

Number of nature of BP medications	n (%) or mean (SD)
Number	3.4 (1.42)
Loop diuretic	78 (59.5%)
ACE inhibitors or ARBs	83 (63.4%)
Dihydropyridine CCBs	85 (64.9%)
Beta-blockers	100 (76.3%)
Vasodilators	26 (19.8%)
Centrally acting agents	11 (8.4%)
Spironolactone	9 (6.9%)

ACE angiotensin converting enzyme; ARB angiotensin receptor blocker; CCB calcium channel blocker

Table 4:

Ambulatory blood pressure

Parameter	Result
Sample size	131
Number of readings	56.2 (7.0)
24h systolic BP (mmHg)	141.7 (8.5)
24h diastolic BP (mmHg)	73.8 (9.4)
24h pulse rate (bpm)	68.8 (10.7)
Awake systolic BP (mmHg)	144.0 (9.0)
Awake diastolic BP (mmHg)	75.8 (9.6)
Awake pulse rate (bpm)	69.8 (10.9)
Sleep systolic BP (mmHg)	136.8 (11.0)
Sleep diastolic BP (mmHg)	69.7 (10.6)
Sleep pulse rate (bpm)	66.4 (11.0)
Dippers n (%)	29 (22.1%)

Dippers defined as ≥10% drop in systolic BP from awake to sleep