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ARTICLE

Pairwise comparison of hydrochlorothiazide and chlorthalidone responses among hypertensive patients

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Abstract

This study conducted a pairwise comparison of antihypertensive and metabolic effects of hydrochlorothiazide (HCTZ) and chlorthalidone (CTD) at 25 mg/day in the same individuals to address the clinical dilemma on preferred thiazide for hypertension (HTN) management. We included 15 African American (AA) and 35 European American (EA) patients with HTN treated with HCTZ and CTD as part of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) and PEAR-2 trials, respectively. Mean reduction in systolic/diastolic blood pressure (SBP/DBP) with HCTZ versus CTD was 8/5 versus 16/8 mmHg among EA patients ($p < 1.0e^{-5}$ SBP, $p = 0.002$ DBP) and 11/8 versus 20/11 mmHg among AA patients ($p = 0.03$ SBP, $p = 0.22$ DBP). While CTD showed clinically meaningful benefit over HCTZ in two-thirds of participants with respect to SBP reduction and half of EA patients with respect to DBP reduction, a majority of AA patients (53%) showed similar DBP reduction with both thiazides. Sixty percent of AA patients and 29% of EA patients attained blood pressure (BP) <140/90 mmHg with both thiazides. Mean potassium (K+) reduction was greater with CTD compared to HCTZ both in EA patients (mean difference = 0.35, $p = 0.0002$) and AA patients (0.49, $p = 0.043$). While 31% of AA patients developed severe hypokalemia on CTD, <5% of others developed severe hypokalemia. Although 46% of AA patients on CTD required K+ supplementation, only 6%–11% of others required supplementation. Overall, in the majority of EA patients, CTD was superior to HCTZ, whereas among AA patients, it was superior in a minority, and was associated with significant potassium-related risk, suggesting that guideline preferences for CTD over HCTZ are reasonable in EA patients but may be less reasonable in AA patients, particularly if the target is <140/90 mmHg.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Hydrochlorothiazide (HCTZ) is the most frequently prescribed thiazide for blood pressure (BP) lowering in hypertension (HTN), but recent guidelines favor the

longer-acting chlorthalidone (CTD). It remains unclear if HCTZ or CTD is better as few studies compare them at currently used low doses and fewer in the same individuals.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aims to address the clinical dilemma on preferred thiazide for HTN management.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

By comparing HCTZ and CTD at the clinically used 25 mg/day doses, in the same individuals, this study aims to identify the thiazide with the best efficacy and safety profile without the confounding factor of interindividual variability in antihypertensive responses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our study can help physicians choose the best thiazide for their patients. Data in this study suggest that in a majority of European American (EA) patients, CTD was superior to HCTZ, whereas among African American (AA) patients, it was superior in a minority, and was associated with significant potassium-related risk. Thus, the guideline preferences for CTD over HCTZ is reasonable in EA patients, but in AA patients with a BP target of <140/90 mmHg, initiation with HCTZ might be the safest approach.

INTRODUCTION

Thiazide diuretics have been among the preferred first-line drugs for the management of essential hypertension (HTN) for decades.[1–4] But there is a long-standing debate[5–8] about the preferred diuretic among the two primary drugs in this category – hydrochlorothiazide (HCTZ) and chlorthalidone (CTD), each belonging to a different subtype within the class of thiazide diuretics. Although the recent US and Canadian guidelines[9,10] recommend the preferred use of long acting "thiazide-like diuretics," such as CTD, HCTZ remains the preferred clinical choice based on prescriptions written.[11–13] CTD is estimated to be twice as potent as HCTZ, and to have a better pharmacokinetic (PK) profile compared to HCTZ, with a longer duration of action.[14] But there are no head-to-head clinical outcomes trials testing the two drugs and there are limited studies comparing their blood pressure (BP) lowering efficacy,[15] making the selection of the optimal thiazide diuretic difficult. The available comparisons are across non-equipotent or pooled doses and with limited data at the current clinically recommended low doses. Higher potency and its PK properties are also attributed to higher rate of adverse effects with CTD, although some argue that the effects are not clinically relevant at low doses. Considering the significant differences in the dose–response relationship[16] of the two drugs, and the confounding effect of interindividual differences in response to various antihypertensive drugs,[17,18] it is imperative to compare them at the commonly used equal milligram doses and in the same patients for an accurate estimate of the relative efficacy/safety of the two drugs. While the interindividual differences in response to different classes of antihypertensive drugs is well-established, variation within a drug class is not well studied. Herein, we report data on hypertensive study participants treated with both HCTZ and CTD. We compared the antihypertensive and metabolic responses of 50 patients with HTN from the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) clinical trial upon treatment with HCTZ and responses to CTD in the PEAR-2 clinical trial. We separated the analysis by genetically defined ancestry into European American (EA) and African American (AA) patients using principal component analysis on the genome-wide genotype data from the subjects, because our previous work[17] identified differences in the relative efficacies of the drugs between AA patients and EA patients.

METHODS

Study design

PEAR and PEAR-2 clinical trials (NCT00246519 and NCT01203852, www.clinicaltrials.gov) were prospective, open-label, multicenter clinical trials designed to evaluate the genetic determinants of BP responses to two classes of antihypertensive drugs, namely thiazides and beta-blockers. The design and objectives of both studies have been published previously.[19,20] In brief, PEAR was a randomized controlled trial in individuals ≤65 years of age with uncomplicated mild–moderate essential HTN.

Individuals with diabetes and known cardiovascular diseases were excluded. After a 4-week washout period, study participants were randomized to receive HCTZ (12.5 mg/day for 3 weeks, titrated to 25 mg/day for 6 weeks if BP >120/70 mmHg) or atenolol. BP and fasting blood samples for determining various electrolyte and metabolite levels were collected at baseline (visit 1), at 2–3 weeks (visit 2), and after 8–9 weeks of treatment (visit 3). PEAR-2 was a sequential monotherapy trial with the same inclusion and exclusion criteria and study protocols as PEAR, whereas CTD (15 mg/day for 2 weeks, titrated to 25 mg/day for 6 weeks if BP was >120/70 mmHg) and metoprolol were tested.

The current study is a post hoc comparative subgroup analysis of the thiazide (TZD) monotherapy arms of PEAR and PEAR-2 trials. Analyses involved a paired comparison of safety and efficacy outcomes between HCTZ and CTD treatments in 50 individuals who were part of both the PEAR and PEAR-2 trials and hence received treatment with HCTZ and CTD at different points in time. Genetically determined race using principal component analysis was used to categorize subjects as AA patients or EA patients, as previously described.[21]

Trial conduct and ethics

Both PEAR and PEAR-2 studies were approved by the institutional review boards at the participating clinical trial sites (University of Florida in Gainesville, FL; Mayo Clinic in Rochester, MN; and Emory University in Atlanta, GA). All participants provided written informed consent.

Blood pressure measurement

BP was measured two ways: office BP and home BP (plus 24-h ambulatory monitoring in PEAR). Here, we present analyses of home BP (details in Supplementary File) following several international guidelines that recommend out-of-office measurements for confirmation and management of HTN,[22] considering its reproducibility and stronger associations with cardiovascular outcomes.

Antihypertensive effect

BP change. "Response" to each drug was calculated by subtracting the pretreatment (visit 1) BP from the post-treatment (visit 3) BP.

We also evaluated certain clinically relevant outcomes as follows:

Percentage of population that responded better to one TZD. Percentage of population that responded better to HCTZ; percentage of population that responded better to CTD with "better response" defined as at least a 3 mmHg greater systolic BP (SBP) or diastolic BP (DBP) response to one drug over the other; and percentage of population that showed similar response to both drugs within 3 mmHg. We considered a minimum 3 mmHg difference in SBP or DBP as clinically meaningful to avoid any spontaneous or non-pharmacologic BP reductions. Although there is no consensus on a BP threshold that is considered clinically meaningful, we identified a previous study where 3 mmHg DBP reduction was used as an arbitrary cutoff to avoid any spontaneous BP changes or measurement errors, based off of many HTN clinical trials,[23] whereas another study arbitrarily used 5 mmHg SBP or 2.5 mmHg DBP.[24] Further, a study on BP reductions with non-pharmacologic isometric hand grip exercises used a 2 mmHg SBP and DBP to be clinically meaningful[25] based on a large meta-analysis of studies that showed that BP reductions as low as 2 mmHg to reduce the incidence of cardiovascular disease (CVD) in both hypertensive and normotensive individuals,[25–27] and a different study showed a mean change of 3 mmHg SBP and 3 mmHg DBP upon aerobic exercise among normotensive individuals.[28] Considering the above literature, we chose a cutoff of 3 mmHg SBP or DBP as a level where few would dispute that was a clinically meaningful difference.

Target BP attainment rate. Patients who attained a target BP of <140/90 mmHg at the end of therapy were considered to have reached the BP goal. A BP <140/90 mmHg was defined as the target because all participants in these trials had uncomplicated HTN, and target BP based on existing guidelines[2] at the time of the conduct of the trial. Additional analysis is provided with a target of <135/85 mmHg considering home BP targets based on the recent international guidelines[22,29,30] and <130/80 mmHg based on recent US guidelines that suggest this target may be reasonable for those with uncomplicated HTN.[9]

We further compared clinical and demographic characteristics at baseline among subjects who showed a better clinical response to HCTZ versus those who showed a better clinical response to CTD with respect to SBP, to identify potential clinical factors associated with differential response to the compared TZDs.

Safety

Metabolic parameters, including serum potassium, glucose, cholesterol, triglycerides, and uric acid, were measured centrally at a core research laboratory at the Mayo Clinic, Rochester, MN, at visits 1, 2, and 3.[31] For clinical safety, serum potassium was also monitored locally during the titration visit (visit 2). Study physicians could elect to replace potassium based on their clinical judgment,

with a protocol mandated prescription of oral potassium chloride 40 mEq/day for serum potassium <3.2 mEq/L (clinically measured). Hypokalemia was defined as values <3.5 mEql/L (normal: 3.5–5) and severe hypokalemia as values <3.0 mEq/L, which is often considered as the threshold for manifestation of clinical symptoms of hypokalemia.[32] For the purposes of comparison between HCTZ and CTD treatments, we compared the treatment associated changes in metabolite levels between visits 3 and 1. We tested the rates of incident hypokalemia at visit 3, and the number of subjects who had potassium supplementation initiated following visit 2 and visit 3.

Statistical analysis

Homogeneity in the baseline characteristics and the comparison between HCTZ and CTD responses was tested using the paired Student *t*-test for continuous variables and Fisher test for categorical variables. Paired *t*-test was used to compare delta BP between HCTZ and CTD. A sensitivity analysis for antihypertensive and metabolic effects of drug response, adjusted for baseline levels, age, and waist circumference, was conducted using linear mixed effect models, with change in BP/metabolite levels as dependent variable and, baseline BP/metabolite levels, treatment arm, age, and waist circumference as fixed effects and subjects as random effect. Risk of developing hypokalemia/severe hypokalemia on TZD treatments was presented as odds ratio, considering CTD as control. Unpaired Student *t*-test was used to identify clinical factors associated with one or the other thiazide. A two-sided *p* value <0.05 was regarded as significant.

Because these data arise from a larger clinical trial, we conducted a post hoc power analysis to define the power for this analysis based on participants who completed both trials. Based on a delta delta DBP of 3 mmHg (delta delta DBP = change in BP due to HCTZ – change in BP due to CTD, which we defined 3 mmHg as clinically significant) and a standard deviation (SD) of difference of 5.7 mmHg as observed among EA patients in this study, we have 86% power to detect the stated difference, with an alpha of 0.05 using a two-sided paired *t*-test in 35 EA patients. We had only 17% power to detect the same differences in AA patients ($n = 15$), based on SD = 10.8 mmHg as observed in this study among AA patients.

RESULTS

Sample demographics and baseline characteristics of the study population are presented in Table 1: 35 EA patients and 15 AA patients received both thiazides: HCTZ during the PEAR trial and CTD during the PEAR-2 trial. We did not perform a statistical comparison for age because PEAR was conducted from 2005 to 2010 and PEAR-2 was conducted from 2010 to 2014. Hence, by definition all patients

TABLE 1 Demographics and baseline characteristics

	EA patients			AA patients		
	HCTZ	CTD	*p* Value	HCTZ	CTD	*p* Value
Age, years	48.7 ± 7.4	51.7 ± 7.3	-	46.9 ± 9.3	49.1 ± 9.5	-
Gender, *n*, %						
Female	17			12		
Male	18			3		
BMI, kg/m^2	29.6 ± 4	29.9 ± 4	0.24	32.4 ± 5.9	31.6 ± 6.6	0.51
Waist circumference	96.3 ± 9.7	99.4 ± 9.8	0.0036	93.2 ± 12.3	95.1 ± 14.6	0.18
Baseline DBP, mmHg	93.9 ± 5.8	95.6 ± 5.3	0.12	94.5 ± 6.6	95.55 ± 6.09	0.59
Baseline SBP, mmHg	146.8 ± 8.8	152.1 ± 8.6	0.0016	143.6 ± 15.8	147.5 ± 14.3	0.15
Smoking, *n*						
Current	4	3	ns	5	5	-
Never/former	31	32		10	10	
Baseline potassium, mEq/L	4.4 ± 0.4	4.4 ± 0.3	0.14	4.2 ± 0.6	4.0 ± 0.7	0.64
Baseline glucose, mg/dl	94.9 ± 9.2	94.8 ± 8.2	0.93	89.7 ± 10.4	92.6 ± 8.5	0.08
Baseline uric acid, mg/dl	5.7 ± 1.4	6.0 ± 1.3	0.03	4.7 ± 1.6	4.9 ± 1.7	0.31

Note: A statistical comparison of age is not relevant because all participants took CTD after HCTZ and so age differences by definition must exist. Continuous variables are presented as mean ± SD and categorical variables are presented as counts (*n*). The *p* values correspond to paired student *t*-test between HCTZ and CTD groups.

Abbreviations: AA, African American; BMI, body mass index; CTD, chlorthalidone; DBP, diastolic blood pressure; EA, European American; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

were older when treated with CTD compared to when they received HCTZ. Older age could explain the higher waist circumference and increased SBP in CTD compared to the HCTZ group, both in EA patients and AA patients, although statistical significance was observed only in EA patients.

Antihypertensive effect

Our data showed that at equal milligram doses of 25 mg/day, CTD produced greater systolic and diastolic home BP reduction compared to HCTZ, with a mean difference of 7.9/3.3 mmHg in EA patients and 9.0/3.6 mmHg difference in AA patients (Table 2). Although the differences between the drugs were statistically significant for both SBP and DBP among EA patients, the difference was not statistically significant for DBP among AA patients. Given the baseline differences in SBP, age, and waist circumference among EA patients, we conducted a sensitivity analysis for change in SBP adjusting for baseline SBP, age, and waist circumference (Table S2). The trends for differences in drug responses in the adjusted analysis were similar to that of the unadjusted analysis.

Figure 1 presents a comparison of BP response to CTD and HCTZ in each study participant. We observed wide interpatient variability in the comparative BP reductions between the two drugs. CTD did not provide numerically greater BP reduction compared to HCTZ in all patients. Table 3 presents the frequencies of patients who showed a clinically meaningful benefit of treatment with one drug over the other, presented as ≥3 mmHg difference between the treatment responses. Although CTD showed clinically meaningful benefit over HCTZ in approximately two-thirds of AA patients and EA patients with respect to SBP reduction, 40% of EA patients and 53% of AA patients showed similar DBP reduction with the two drugs.

TABLE 2 Mean BP reduction

	EA patients				AA patients			
	HCTZ	CTD	μ of diff	*p* Value	HCTZ	CTD	μ of diff	*p* Value
Δ home DBP	−4.5 ± 4.0	−7.8 ± 5.3	3.3	0.0014	−7.6 ± 5.5 *(−6.2 ± 6.4)*[a]	−11.1 ± 7.1 *(−9.9 ± 6.1)*[a]	3.6	0.22
Δ home SBP	−7.8 ± 7.1	−15.7 ± 8.9	7.9	$1.01e^{-05}$	−10.5 ± 9.0 *(−9.9 ± 10.2)*[a]	−19.5 ± 10.3 *(−16 ± 13)*[a]	9.0	0.028

Note: Delta BP = (end of treatment BP − baseline BP). Values are mean ± SD. The *p* values correspond to paired Student *t*-tests.

Abbreviations: AA, African American; BP, blood pressure; CTD, chlorthalidone; DBP, diastolic blood pressure; EA, European American; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; μ, mean of difference.

[a](Median ± interquartile range) is also provided for CTD treated African American patients as the data is non-normally distributed.

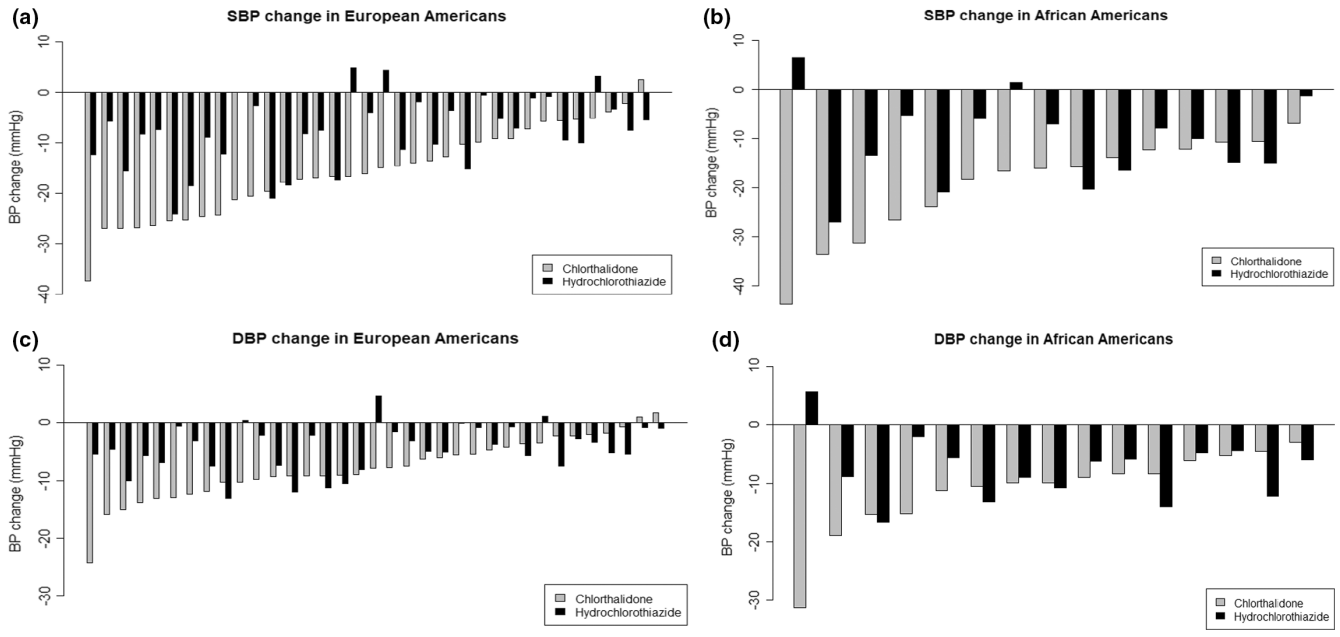

FIGURE 1 Comparison of responses to HCTZ and CTD treatment in each patient. Figures present the change in blood pressure after 8–9 weeks of therapy with HCTZ and CTD at 25 mg/day. BP, blood pressure; CTD, chlorthalidone; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure. (a) and (b) represent SBP changes in European Americans and African Americans respectively; (c) and (d) represent D changes in European Americans and African Americans respectively.

TABLE 3 HCTZ versus CTD one-on-one comparison

	EA patients (%) $N = 35$	AA patients (%) $N = 15$
Comparison based on SBP response		
Clinically meaningful benefit with HCTZ over CTD (≥3 mmHg)	5 (14)	3 (20)
Similar response with both drugs	6 (17)	2 (13)
Clinically meaningful benefit with CTD over HCTZ (≥3 mmHg)	24 (69)	10 (67)
Comparison based on DBP response		
Clinically meaningful benefit with HCTZ over CTD (≥3 mmHg)	3 (9)	3 (20)
Similar response with both drugs	14 (40)	8 (53.3)
Clinically meaningful benefit with CTD over HCTZ (≥3 mmHg)	18 (51)	4 (27)

Note: Values are *n (%)*. Similar response = magnitude of difference between BP change on HCTZ and BP change on CTD is <3 mmHg.

Abbreviations: AA, African American; BP, blood pressure; CTD, chlorthalidone; DBP, diastolic blood pressure; EA, European American; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure.

TABLE 4 Target BP achievement rate

	On both drugs	Only on HCTZ	Only on CTD	On neither drug
Target BP attainment rate: <140/90 mmHg				
EA patients (35)	10 (29%)	3 (9%)	11 (31%)	11 (31%)
AA patients (15)	9 (60%)	1 (7%)	3 (20%)	2 (13%)
Target BP attainment rate: <135/85 mmHg				
EA patients (35)	4 (11%)	5 (14%)	4 (11%)	22 (63%)
AA patients (15)	6 (40%)	1 (7%)	3 (20%)	5 (33%)
Target BP attainment rate: <130/80 mmHg				
EA patients (35)	0	2 (6%)	3 (9%)	30 (86%)
AA patients (15)	1 (7%)	1 (7%)	3 (20%)	10 (67%)

Note: Tables present the number and percentage of patients who achieved the given BP target after 8–9 weeks of TZD therapy.

Abbreviations: AA, African American; BP, blood pressure; CTD, chlorthalidone; EA, European American; HCTZ, hydrochlorothiazide; TZD, Thiazide.

Comparisons of HCTZ and CTD for target BP are shown in Table 4, which indicates that among AA patients, a majority (60%) attain target BP of <140/90 mmHg with either drug, and <15% fail to achieve target BP on either drug. In contrast, about one-third of EA patients do not achieve target BP with either drug, one-third achieve with CTD only and one-third with either drug. About 40% of AA patients also attained a 135/85 mmHg BP target with either drug, and a third failed to reach this target on either drug. In contrast, a majority of EA patients (63%) failed to achieve this target on either drug, and only 11% achieved the target BP on both drugs. Very few patients achieved a BP <130/80 on monotherapy of either drug (2 on HCTZ and 3 on CTD among 35 EA patients and 2 on HCTZ and 4 on CTD among AA patients), suggesting that attainment of this lower BP target will typically require two antihypertensive drugs.

Safety

The results of the comparison of the metabolic effects of the two drugs are shown in Table 5 and a one-on-one comparison of the drugs' potassium lowering effect is shown in Figure S1. The baseline metabolic features of the study participants did not differ between the treatment groups except for baseline uric acid in EA patients, as shown in Table 1. In ~25% of the cases, HCTZ showed greater potassium lowering than CTD (in 9 of 35 EA patients and 4 of 15 AA patients). On average, CTD showed significantly greater potassium reduction than HCTZ, both in EA patients and AA patients, with a mean difference of 0.35 mEq/L in EA patients and 0.49 mEq/L in AA patients. Incident hypokalemic events were higher in the CTD-treated cohort versus HCTZ both in EA and

TABLE 5 Metabolic effects of thiazide treatment one-to-one comparison

	EA patients (paired *t*-test)				AA patients (paired *t*-test)			
	HCTZ	CTD	μ of diff	*p* Value	HCTZ	CTD	μ of diff	*p* Value
Δ potassium	−0.31 ±0.42	−0.66 ±0.4	0.35	0.00016	−0.17 ±0.43	−0.62 ±0.52	0.49	0.034
Incident hypokalemia, <3.5 meq/L	2 (5.71% 2 of 35)	12 (34% 12 of 35)	OR = 0.12	0.0057*	3 (21% 3 of 14)	5 (45% 5 of 11)	OR = 0.34	0.39*
Severe hypokalemia, <3.0 meq/L	1 (2.86% 1 of 35)	1 (2.86% 1 of 35)			0	4 (31% 4 of 13)		
K supplementation initiated at mid-visit	0	2 (5.7%)			0	3 (20%)		
K supplementation initiated at visit 3	4 (11.4%)	2 (5.7%)			3 (20%)	7 (46.7%)		
Δ glucose	3.53 ±10.18	6.14 ±12.92	−2.6	0.39	1.6 ±11.65	7.42 ±15.65	−5	0.4
Δ uric acid	0.91 ±0.72	1.29 ±0.88	−0.38	0.029	0.99 ±0.86	1.02 ±1.56	−0.03	0.95

Note: Continuous variables are compared using paired *t*-test. Frequencies are compared using Fisher's Exact test*; μ, mean of difference; K, potassium.
Abbreviations: AA, African American; CTD, chlorthalidone; EA, European American; HCTZ, hydrochlorothiazide; OR, odds ratio; μ, mean of difference.

AA patients, although it was only significant in EA patients. Whereas the severe hypokalemia cases (potassium <3.0 mEq/L) among EA patients were <3% with either HCTZ and CTD, 31% of AA patients on CTD developed severe hypokalemia versus none on HCTZ. Additionally, 6% of EA patients versus 20% of AA patients required potassium supplementation on CTD treatment whereas none on HCTZ required supplementation, when measured at mid-visit. At the end of therapy, 6% of EA patients versus 46% of AA patients required potassium (K+) supplementation on chlorthalidone treatment whereas 11% of EA patients and 6% of AA patients on HCTZ required supplementation.

Studying the hypokalemia rates in the subset of population who achieved target BP with both the drugs (as shown in Table 4), we observed that among EA patients, four of 10 patients (40%) had hypokalemia with CTD and none on HCTZ. In contrast, among AA patient s, five of nine patients (56%) developed hypokalemia on CTD and two of nine (22%) on HCTZ.

Although mean glucose and uric acid changes were greater in CTD treated cohorts versus HCTZ, both in EA patients and AA patients, the differences were nonsignificant, except for uric acid change in EA patients, which was also nonsignificant when adjusted for baseline uric acid, age, and waist circumferance (Table S3).

DISCUSSION

To the best of our knowledge, our study is the first to compare HCTZ and CTD at equal milligram doses of the clinically used 25 mg/day in the same patients, stratified by race. This paired analysis allows for better comparison of the drug effects without the confounding effects of inter-patient variability in responses. To date, there is only one head-to-head crossover study that compared monotherapies of HCTZ and CTD.[33] The study had a small sample size (n = 30) and compared CTD and HCTZ at 1:2 dose ratio. Although that study[33] identified greater night-time systolic BP reduction with CTD, no difference was found between the drugs with respect to SBP or DBP reduction or adverse effects after 8 weeks of therapy. Our current study aimed to conduct a paired comparison of the two drugs at equal milligram doses and stratified by race.

Overall, 25 mg CTD showed greater reduction in SBP and DBP compared to 25 mg HCTZ. The difference in BP response between CTD and HCTZ was highly significant in EA patients but only moderately significant in AA patients for SBP and nonsignificant for DBP. Similar results were observed in a previous study that compared CTD and HCTZ at 1:1 doses, but in combination with Azilsartan, which showed significantly higher clinical

SBP reduction with CTD compared to HCTZ among EA patients, and higher but nonsignificant difference in AA patients.[34] Despite treatment with a presumably more potent thiazide, CTD (accepted by many to be 1.5–2 times more potent than HCTZ and estimated as ~2 to 3 times in a systematic meta-analysis of dose–response studies[16]), 31% of EA patients and 33% of AA patients showed equal or better SBP reduction with HCTZ; and 49% of EA patients and 73% of AA patients showed equal or better DBP reduction with HCTZ.

When the focus is on the more clinically relevant phenotype of target BP achievement, a majority of AA patients attained target BP with both HCTZ and CTD, whereas EA patients were much more likely to achieve the target on CTD. Although it is convenient to recommend initiation of treatment with CTD in all, the relative advantage of shifting the current prescription trends from HCTZ to CTD needs to be considered both in terms of net gain in BP reduction, balanced against the adverse metabolic effects. CTD showed greater reduction in potassium and higher incidence of hypokalemia compared to HCTZ, both in EA patients and AA patients (although a nonsignificant difference in AA patients due to small sample size) with higher frequencies of hypokalemic events observed among AA patients compared to EA patients, with both drugs. Inherently lower baseline potassium levels among AA patients, combined with the longer acting, highly potent characteristics of CTD could be the cause of higher frequencies of hypokalemia and significantly more common occurrence of severe hypokalemia with CTD among AA patients.[17] This is in line with population-based studies that observed higher frequencies of hypokalemia with CTD even at 1:2 dose comparisons with HCTZ.[35,36] Our study also showed that patients who attained target BP with both drugs, showed higher adverse hypokalemic effects with CTD, with highest rates in CTD treated AA patients. Hence, considering that a majority of AA patients have a high rate of target BP attainment rate with both drugs, when taken in light of higher adverse effects with CTD, one might question the recommendation of CTD as the preferred TZD when treating AA patients. In patients with uncomplicated HTN, and depending on the treatment goal (<140/90 or <130/80 mmHg), these data suggest clear benefit of using CTD in EA patients. In contrast, for AA patients where there is a less aggressive BP target (e.g., <140/90 mmHg), the optimum strategy among AA patients might be to start with HCTZ, given its greater safety profile, and then transition to CTD in case of insufficient BP response. In patients for whom the BP target is <130/90 mmHg, then it is reasonable to start all patients on CTD, but our data suggest that a minority will achieve this BP target with a single drug (whether CTD or HCTZ).

Strengths and limitations

Our study has an advantage of a paired comparison of CTD and HCTZ in the same patients and hence each patient can act as his/her own control. The data herein arise from two controlled trials: HCTZ data from the PEAR trial and CTD data from the PEAR-2 trial. A more optimal dataset would have arisen from a single trial. However, this concern is mitigated by the fact that both trials were designed and conducted by the same group of investigators, at the same centers, with the same overarching goal; had similar study design, identical inclusion and exclusion criteria, similar demographic populations, and nearly identical data collection approaches and, hence, are comparable. Another potential limitation is that in all cases, the study participants received HCTZ before CTD, thus all were older when they received CTD. However, in our analysis of clinical and demographic factors that might influence differential response, age was not significant (data in Table S1). The smaller sample size, particularly in AA patients, limits interpretations of statistical comparisons, particularly those that are nonsignificant and might represent type 2 errors. The data at visit 3 (post-treatment visit) for serum potassium must be interpreted with potassium supplementation in mind. The threshold to start potassium supplementation at visit 2 (titration visit) was left to the physicians' digression, unless clinically measured potassium was 3.2 mEq/L, which, in most cases, is when potassium supplementation was initiated. Thus, any observed differences in hypokalemia or severe hypokalemia in AA patients at visit 3 were in the face of a higher rate of potassium supplementation with CTD than HCTZ. Thus, the differences in the visit 3 hypokalemia data would likely have been more extreme between CTD and HCTZ in the absence of potassium supplementation. Collectively, these issues bias the potassium data toward the null, and yet large differences were observed. Additionally, it is to be noted that the current study was conducted in the context of older HTN guidelines, with a target BP of 140/90 mmHg, although the study protocol advanced dosing in all whose BP remained >120/70 mmHg. This allowed us to test attainment of lower BP targets (including the class IIb recommendation in lower CVD risk hypertensives of 130/80 mmHg), and the data herein show that how one approaches selection of HCTZ versus CTD may be influenced by the BP target for the patient.

CONCLUSION

Here, we presented a comparison of effects of HCTZ and CTD among individuals treated with both diuretics, to address the current clinical dilemma of the preferred

diuretic. Although recent guidelines recommend CTD for longer duration of action and better cardiovascular risk reduction potential, there is limited evidence directly comparing the two drugs for outcomes at clinically recommended doses and inconsistencies exist with respect to their comparative BP lowering potential. Considering that BP lowering and adverse safety profile are immediate drivers of therapy selection in HTN management in clinics, it is important to accurately compare the two drugs for their efficacy and safety without the confounding factors of race and interindividual variability. We have previously published race-specific comparisons of HCTZ and CTD[17] from a large cohort suggesting that although CTD as preferred TZD is reasonable in EA patients, it may be less appropriate in AA patients, due to similar achievement of BP targets with the two drugs and greater adverse effects with CTD. However, population data mask the interpatient variability and, here, we report data on 50 patients who took both drugs, to provide additional guidance to clinicians on selection of TZD in individual patients. These paired data also suggest that while CTD is numerically better at BP lowering in both EA patients and AA patients, the relevance of this might be much less in AA patients as the majority of AA patients achieved a BP target of 140/90 mmHg with both drugs, whereas potassium risk is consistently higher with CTD. As in our larger unpaired analysis,[17] these data suggest TZD initiation with CTD in EA patients seems appropriate, regardless of BP target, whereas use of HCTZ as the first TZD in AA patients may be a safer approach if the BP target is <140/90 mmHg. Neither drug was highly effective at achieving a BP target <130/80 mmHg, thus the numerically greater BP lowering with CTD may make it the more appropriate choice in all patients with a lower BP target.

AUTHOR CONTRIBUTIONS

L.M.S.C. designed the research question, analyzed the data and wrote the manuscript, R.M.C.-D., J.G.G., A.B.C., designed and conducted the clinical trials, and secured funding. J.A.J. designed and conducted the clinical trials, secured funding, oversaw the design of the research question in this manuscript, and edited the manuscript.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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