Are there head to head studies of chlorthalidone versus hydrochlorothiazide? People seem to be mostly using chlorthalidone now?

Chlorthalidone and hydrochlorothiazide (HCTZ) are thiazide-type diuretics that are commonly used to treat hypertension. The eighth report of the Joint National Committee (JNC8) for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2014) recommends thiazide-type diuretics as first-line treatment for patients with hypertension without diabetes or chronic kidney disease.[1] The JNC8 further asserts that there is stronger clinical evidence regarding use of chlorthalidone. A review of the literature was conducted in order to determine whether active comparative trials have been conducted between chlorthalidone and HCTZ.

Until recently, no head-to head prospective comparative trials have been conducted between chlorthalidone and HCTZ. Pareek et al conducted a randomized, double-blind, multi-center trial comparing the efficacy of low-dose chlorthalidone and HCTZ on blood pressure (BP) in patients in India.[2] The primary efficacy endpoint was the change in mean 24-hour ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline up to weeks 4 and 12. Additional secondary endpoints were changes in mean office SBP and DBP and any change in mean ambulatory daytime and nighttime SBP and DBP from baseline up to weeks 4 and 12. This trial included patients between the ages of 18 and 65 years with stage 1 hypertension. Exclusion criteria included (amongst the many): secondary hypertension, diabetes, gout, recent cardiovascular disease/accident, pregnancy, abnormal renal/liver function, etc.

A total of 54 patients were randomized to chlorthalidone 6.25 mg daily (n=16), HCTZ 12.5 mg daily (n=18), or an extended-release HCTZ (HCTZ-CR) 12.5 mg daily (n=20).[2] Compared to baseline, all treatments significantly reduced office BP at weeks 4 and 12 ($p<0.01$). However, only chlorthalidone-treated patients showed a significant decrease in 24-hour ambulatory and nighttime SBP and DBP at weeks 4 and 12 ($p<0.01$) when compared to HCTZ-treated patients (note: only significant for immediate-release HCTZ, not the HCTZ-CR formulation). For secondary endpoints, all groups showed a significant decrease in mean office SBP (HCTZ: $p<0.001$; HCTZ-CR: $p<0.001$; chlorthalidone: $p=0.002$) and DBP (HCTZ: $p<0.006$; HCTZ-CR: $p<0.001$; chlorthalidone: $p=0.005$) at weeks 4 and 12. For changes in ambulatory daytime SBP, all groups had a significant reduction by week 12 (HCTZ: $p=0.017$; HCTZ-CR: $p=0.034$; chlorthalidone: $p=0.001$); however, only the chlorthalidone and HCTZ-CR groups had a significant reduction in ambulatory daytime DBP (HCTZ: $p=0.058$; HCTZ-CR: $p=0.014$; chlorthalidone: $p=0.002$). In terms of safety, there were no serious adverse events or tolerability issues.

The authors concluded that unlike HCTZ, low-dose chlorthalidone significantly decreased mean 24-hour ambulatory BP; this was also observed for the secondary endpoints: daytime and nighttime BP.[2] The authors stated that HCTZ's short duration of action accounted for its lack of

effect on mean 24-hour ambulatory BP values. Limitations of the study included its small sample size, lack of external validity (only conduced in India), and its retrospective design.

In a retrospective, observational cohort study, Dhalla et al compared the effectiveness and safety of chlorthalidone versus HCTZ for treatment of hypertension in older adults in Canada.[3] The primary endpoint was a composite of death or hospitalization for heart failure (HF), stroke, or myocardial infarction (MI). Additional safety outcomes included hospitalization due to hypokalemia or hyponatremia. Patients were included in the study if they were treatment-naïve to chlorthalidone or HCTZ, aged ≥66 years, and had not experienced hospitalization due to HF, stroke, or MI in the past year. Using propensity score matching, each patient who received chlorthalidone was matched to 2 HCTZ patients based on age at index date, sex, and several other factors. Data were extracted from several Canadian healthcare databases and patients were followed for up to 5 years.

A total of 29,873 were included in the study.[3] The primary outcome occurred in 510 chlorthalidone-treated patients (3.2 events per 100 person-years of follow-up) and 1,265 HCTZ-treated patients (3.4 events per 100 person-years of follow-up). After adjustment for baseline differences, patients treated with chlorthalidone were not at a lower risk of experiencing the primary outcome (adjusted hazard ratio (HR)=0.93, 95% confidence interval (CI), 0.81 – 1.06). In terms of safety compared to HCTZ, chlorthalidone-treated patients experienced more hospitalizations due to hyponatremia (adjusted HR=1.68, 95% CI, 1.24 – 2.28) and hypokalemia (adjusted HR=3.06, 95% CI, 2.04 – 4.58).

The authors concluded that there was no difference between chlorthalidone and HCTZ in terms of preventing stroke, MI, HF, or death in older adults with hypertension.[3] Patients treated with chlorthalidone were also more likely to experience hospitalization due to hypokalemia or hyponatremia. Limitations of the study include its design, as there is the possibility that the groups differed in terms of characteristics that were not accounted for. Also, the study only included older patients, so the results may not apply to a younger patient population.

Another retrospective study was conducted in order to compare the effectiveness of chlorthalidone compared to HCTZ in a cohort of Veterans.[4] Primary outcomes included the persistence of thiazide use for up to 1 year (i.e., pattern of refills did not have significant interruptions), adequate response to the thiazide diuretic (i.e., patient did not start a new antihypertensive within 1-year of initiating the thiazide), and a composite outcome of persistence and adequate response. Patients were naïve to thiazide diuretic treatment and could not have transferred into VA care during the study period. Data were extracted from the United States National Veterans Administration pharmacy data from 2003 – 2008.

A total of 126,808 patients were included in the study.[4] For the primary outcomes, persistence of use was lower in chlorthalidone-treated patients compared to HCTZ-treated patients (62.0%

and 72.0%, respectively; p<0.001). However, more patients using HCTZ needed additional antihypertensive treatment versus chlorthalidone (76.4% and 70.1%, respectively; p<0.001). The composite outcome favored HCTZ-treated patients when compared to chlorthalidone (50.7% and 47.4%, respectively; p=0.002). The results remained unchanged after multivariable logistic regression.

The authors concluded that chlorthalidone may have greater efficacy than HCTZ for those patients that remain persistent to treatment.[4] Potential reasons for lower persistence included better tolerability of HCTZ and use of low-doses of HCTZ (fewer side effects) than the more potent chlorthalidone. Limitations of the study include its retrospective design and that the study did not examine BP measurements or other cardiovascular outcomes. Lastly, given the patient population, enrolled patients were mostly male precluding application of the result to female patients with hypertension.

In addition to these reviewed studies, several meta-analyses were identified which indirectly compared chlorthalidone to HCTZ.[5-7] See Table 1 below for a summary of the studies.

Table 1: Meta-analyses comparing chlorthalidone and HCTZ.

Study	Objective	Methods	Results	Author conclusions
Peterzan et al (2012)[6]	Determine dose-response relationships for B, C, & HCTZ on BP, K, urate	-Included R, DB, parallel, PC trials (1950-2010) with ≥2 different monotherapy arms, FU duration of ≥4w -Included adults with HTN	-Included 29 trials (C=3, HCTZ=26); 4,693 pts -Potency in ↓SBP: B>C>HCTZ (estimated dose to ↓SBP by 10 mm Hg: 1.4, 8.6, 26.4 mg, respectively) -No potency differences for DBP, K, urate	-Considerable differences in potency of B, C, & HCTZ may account for differences in SBP lowering
Roush et al (2012)[7]	Determine whether C or HCTZ is superior in reducing CVEs	-Included RCTs (1948-2011) which evaluated antihypertensive effect on all-cause mortality or CVEs (MI, new dx of CHD, stroke, or CHF) -Included adults with HTN	-Included 9 trials (C=6, HCTZ=3) -Drug-adjusted analysis (n=50,946): % risk reduction in CHF for C vs. HCTZ=23 (95% CI, 2-39; p=0.032) -For all CVEs: % risk reduction for C vs. HCTZ=21 (95% CI, 12-28; p<0.0001) -Office systolic BP-adjusted analysis (n=78,350): % risk reduction in CVEs for C vs. HCTZ=18 (95% CI, 3-30; p=0.024)	-C is superior to HCTZ in prevention of CVEs
Ernst et al (2010)[5]	Compare dose-response characteristics of C & HCTZ on SBP & K	-Included all trials (1948-July 2008) using C or HCTZ monotherapy and reported SBP and K -Included adults with HTN	-Included 137 trials (C=29, HCTZ=108) -Pooled analysis: C caused greater ↓SBP & K compared to HCTZ (compared on a mg-per-mg basis) -For lower doses (12.5-25 mg): reductions in SBP were not equivalent between C and HCTZ (reductions in K were equivalent)	-SBP lowering is not equivalent between C & HCTZ in the recommended dosing range of 12.5-25 mg -Reductions in K are equivalent

B=bendroflumethiazide; BP=blood pressure; C=chlorthalidone; CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CVE=cardiovascular events; DB=double-blind; DBP=diastolic BP; dx=diagnosis; FU=follow-up; HCTZ=hydrochlorothiazide; HTN=hypertension; K=potassium; MI=myocardial infarction; PC=placebo-controlled; pts=patients; R=randomized; RCTs=randomized controlled trials; SBP=systolic BP; w=weeks