Indian Health Service
National Pharmacy and Therapeutics Committee

Hydrochlorothiazide vs. Chlorthalidone for HTN
April 2012

Introduction:
Hypertension (HTN) affects approximately 76.4 million individuals in the United States. Currently, one in every three adults has HTN, a major risk factor for heart disease, stroke, congestive heart failure, and kidney disease. By the year 2030, hypertension is projected to grow by an additional 27 million individuals. Furthermore, real total direct medical costs of cardiovascular disease (CVD), including hypertension, are projected to triple from $272 billion in 2010 to $818 billion in 2030.[1]

Hypertension is common in American Indian/Alaska Natives (AI/AN), affecting approximately 30% of individuals. AI/AN are 1.3 times more likely to have HTN than white adults.[2] Among American Indian men 45 to 75 years of age, the incidence of CVD ranges from 15 to 28 per 1000 population. Among women, it ranges from 9 to 15 per 1000.[1] Heart disease is the leading cause of mortality in AI/AN, reaching approximately 18.4% in 2007.[3] As such, life expectancy for AI/AN is 5.2 years less compared to all races in the United States (72.6 years to 77.8 years, respectively; 2003-2005 rates).[4]

Health disparities among AI/AN remain an issue. Preventing risk factors that can lead to heart disease is the primary goal. However, once the patient develops a risk factor, such as HTN, controlling the chronic condition becomes imperative. Thiazide diuretics offer significant reductions in stroke and cardiovascular events based on evidence from the Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT) and other hypertension studies.[5-7] Given the conclusive evidence, low cost, and favorable side effect profile for thiazides, the Joint National Committee on the prevention, detection, evaluation and treatment of high blood pressure (JNC 7) recommends using thiazides such as hydrochlorothiazide (HCTZ) and thiazide-like diuretics such as chlorthalidone (CTD) as initial preferred agents for uncomplicated HTN. The ultimate goal of treatment with antihypertensive therapy is to reduce CVD morbidity and mortality (JNC 7).[8]

Historically, CTD was the most commonly prescribed and studied thiazide-like diuretic.[6,7] However, over the last 20 years for reasons unknown there has been a preferential shift towards the use of HCTZ. Some researchers have hypothesized this prescribing shift may be due to the potential risk of hypokalemia seen with CTD in past studies or the lack of combination products available on the market that contain CTD.[9-11] Accordingly, a comprehensive literature review comparing the two agents is warranted to further validate the use of one thiazide diuretic over the other.

This monograph provides an overview of two diuretic agents in the United States: HCTZ and CTD.

Pharmacology/Pharmacokinetics:[12-14]
HCTZ:
Mechanism of action: reabsorption of sodium and chloride are blocked in the distal tubule, which therefore decreases the reabsorption of water and increases diuresis.

CTD:
Mechanism of action: a monosulfamyl diuretic that increases the excretion of sodium and chloride by decreasing the reabsorption in the distal tubule.

Table 1. Pharmacokinetic properties

Drug	Absorption	Distribution	Metabolism	Excretion
HCTZ	Rapidly absorbed Bioavailability: 60-80% Food: decreased plasma drug levels	Cmax 1.5-2.5 hours Vd=3-4 L/kg T1/2=5.6-14.8 hours	Not significantly metabolized	Renal: 50-70%; 61% unchanged
CTD	Bioavailability: 65%	Cmax=1.5-6 hours Vd=3-13 L/kg T1/2=40-89 hours	Unidentified metabolites	Renal: 50-74%

FDA Approved Indications: [12,13]

HCTZ:

- Hypertension when used alone or as an adjunct
- Edema associated with heart failure, renal dysfunction, cirrhosis, and corticosteroid and estrogen therapy

CTD:

- Hypertension when used alone or as an adjunct
- Edema associated with heart failure, renal dysfunction, cirrhosis, and corticosteroid and estrogen therapy

Current National Core Formulary Alternatives: [15]

HCTZ is currently on the IHS National Core Formulary (NCF)

Dosage and Administration: [12-14]

Table 2. Dosage and Administration:

Agent	Indication	Dosage	Special Considerations
HCTZ	Edema	25-100 mg daily orally	Pregnancy Cat. B
	Hypertension	25 mg daily orally initially; may increase to 50 mg daily	No dosage adjustment for hepatic impairment. Use caution in severe hepatic impairment. No dosage adjustment in mild to moderate renal impairment. Use caution in severe renal disease. Note: Patients in renal failure are usually refractory to thiazides

Note: Information within this document is current as of this writing and should not replace clinical judgment.

	Diuresis and Hypertension in infants and children	1-2 mg/kg/day in 1 or 2 divided doses (not to exceed 37.5 mg/day in infants up to 2 years or 100 mg/day in children 2-12 years). Infants <6 months 3 mg/kg/day in 2 divided doses may be used.	
CTD	Edema	50-100 mg daily orally or 100 mg on alternate days; may increase up to 150-200 mg daily. Maintenance doses may be lower than initial doses.	Pregnancy Cat. B
	Hypertension	25 mg daily orally initially as a single dose; may be increased to 50 mg-100 mg daily. Maintenance doses may be lower than initial doses.	No dosage adjustment for hepatic impairment. Use caution in severe hepatic impairment. No dosage adjustment in mild to moderate renal impairment. Use caution in severe renal disease. Note: Patients in renal failure are usually refractory to thiazides

Guideline/Systematic Reviews:

A Cochrane Systematic review was done to determine the relative benefits of major first-line antihypertensive drugs on mortality, stroke, and coronary heart disease.[16] Studied drugs included thiazides, beta blockers, angiotensin-converting enzyme inhibitors (ACE-Is), and calcium-channel blockers (CCBs). Included studies compared these antihypertensive drug classes with placebo or no treatment in hypertensive patients who had taken the drug class for greater than 1 year. Cardiovascular benefit was most evident with low-dose thiazides (defined as the equivalent of $\leq$ 50 mg/day of hydrochlorothiazide) followed by angiotensin-converting enzyme inhibitors. Based on this systematic review, authors recommend beginning with thiazides or ACI-Is as first-line antihypertensive treatment. Differentiation between specific thiazides and thiazide-like diuretics were not discussed.

JNC 7 [8]

JNC 7 guidelines for the prevention, detection, evaluation, and treatment of HTN provided evidence-based recommendations based on scientific literature between 1997 to 2003. JNC 7 recommends initial therapy with lifestyle modifications. However, if blood pressure (BP) goals are not achieved (< 140/90 mmHg or < 130/80 mmHg with chronic kidney disease), thiazides* or thiazide-like diuretics* should be initiated for most patients with uncomplicated HTN, either alone or in combination with another class (ACE-Is, ARBs, BBs, CCBs). Selection of other agents as initial therapy should be utilized if thiazide diuretics cannot be used or if the patient has a compelling indication where a specific class is warranted. (i.e. heart failure, post myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention).

*Guidelines do not advocate between a specific thiazide but listed HCTZ and CTD as acceptable preferred first line agents.

NICE[17]

In August 2011, the National Institute for Health and Clinical Excellence (NICE) updated the clinical guidelines for managing hypertension in adults. One new update includes the recommendation of using a thiazide-like diuretic (i.e. CTD) over a thiazide diuretic (i.e. HCTZ) when initiating or changing diuretic therapy. However, they also recommend that those patients currently stable and well controlled on HCTZ should continue treatment with HCTZ. These recommendations are based on the limited evidence available to support thiazides compared to the demonstrated benefits of thiazide-like diuretics. The Guideline Development Group (GDG) also comments that limited clinical outcomes data is available to support the use of thiazide diuretics including low dose HCTZ and bendroflumethiazide (the preferred diuretic in the UK). However, results comparing thiazide-like diuretics, including CTD, showed statistically significant clinical outcomes including CV events, stroke, CHD event, but not significant outcomes in terms of mortality.

Overall, the GDG emphasizes that the head to head comparison trials were too underpowered to show a statistical difference in blood pressure lowering.

Table 3. Summary of Studies Comparing HCTZ and CTD [17]

Study	N	Intervention	Control	Follow-up	Results
Bowlus (1964)	29	CTD 50 mg/day	HCTZ 100 mg/day	6 weeks treatment, 2 weeks washout	NS difference in BP between groups
Finnerty (1976)	54	CTD 50 mg/day (plus placebo)	HCTZ 100 mg/day	2 weeks no treatment, followed by 4 weeks of treatment in either arm	NS difference in BP between groups
Ernst (2006)	30	CTD 12.5 mg/day; force titrated to 25 mg/day	HCTZ 25 mg/day; force titrated to 50 mg/day	8 weeks treatment, 4 weeks washout, 8 weeks treatment	NS difference (office BP and 24 hour ABPM) between groups

In 2011, the American College of Cardiology and the American Heart Association (ACC/AHA) provided "expert consensus" for treating hypertension in the elderly.[18] Thiazide diuretics including HCTZ and CTD are recommended for initial treatment of hypertension based on several studies, which demonstrated a reduction in cardiovascular, cerebrovascular, and renal adverse outcomes in the elderly. Overall, no studies looking at the comparative efficacy between HCTZ and CTD were mentioned. The author's commented that since CTD has a longer duration of action and increased potency, elderly patients may be at higher risk for metabolic adverse effects. There are no recommendations for which thiazide to initiate.

In May 2005, the National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents updated the guidelines on treatment of hypertension in pediatric patients.[19] Overall, there was limited data available on the use of pharmacological treatment of hypertension in this population. All drug classes including diuretics are appropriate therapy and the initial choice should remain under the discretion of the physician. However, long-term safety data has been demonstrated with the use of diuretics in pediatric patients. The guidelines did not address any differences or preference to HCTZ or CTD.

Efficacy:

ALLHAT[20]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) studied the effects of CCBs or ACEIs versus diuretics* on the incidence of combined fatal CHD and non-fatal MI. Secondary outcomes included all-cause mortality, fatal and nonfatal stroke, combined CHD (the primary outcome, coronary revascularization, hospitalized angina), and combined CVD (combined CHD, stroke, other treated angina, HF and peripheral arterial disease). The multicentered randomized, double-blind, active controlled trial was conducted from February 1994 through March 2002 and included 33,357 patients aged 55 years or older with hypertension and at least 1 other CHD risk factor (previous > 6 months MI or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 diabetes, current cigarette smoker, high-density lipoprotein cholesterol of less than 35 mg/dl or documentation of other atherosclerotic CVD). Mean follow-up was 4.9 years. Combined fatal and nonfatal MI and all-cause mortality did not differ between treatment groups. In contrast, blood pressures were significantly higher in the amlodipine (0.8 mm Hg, p=0.3) and lisinopril (2 mmHg, p<0.001) groups compared to the CTD group. Other secondary endpoints revealed a 38% higher risk of HF (p<0.001) with amlodipine compared with CTD. The lisinopril group had a 15% higher risk of stroke (p=0.02) and a 10% higher risk of combined CVD (p<0.001) compared with CTD.

*Chlorthalidone was the only studied diuretic in the ALLHAT trial

MRFIT: Blood Pressure Intervention[21]

The Multiple Risk Factor Intervention Trial (MRFIT), conducted by Cohen and colleagues (1981), was a randomized primary prevention trial using multiple interventions to determine the effect on mortality from CHD. This trial included 22 centers where men 35 to 57 years old (N=12,866) were included and randomly assigned to either the special intervention (SI) program (N=6428) or usual care (UC) (N=6438) provided from health care facilities in their community. The SI program included smoking cessation counseling, dietary recommendations to decrease cholesterol, and treatment for hypertension. Subjects were defined as hypertensive based on a diastolic blood pressure of 90 mmHg or greater. Hypertension was managed in a stepwise procedure. Step 1 of the 4 total steps included the use of CTD or HCTZ 50-100 mg daily based on the physician's preference. Following Step 1, reserpine, hydralazine, guanethidine, or specific alternate drugs were added if goal BP was not reached. One-third of the SI subjects were on a diuretic alone.

Overall, after 4 years, both CTD and HCTZ lowered blood pressure to a similar degree. However, the overall intervention was multifactorial and it is unknown if there were true statistical differences among the 2 drugs after 4 years. Additionally, the data for the UC group was not published.

Table 4. Systolic BP change from baseline to 48 months for the SI group

Step 1: drug regimen	N	Mean baseline systolic BP (mmHg)	48-Month mean systolic BP (mmHg)	Difference (mmHg)
CTD	396	140.8 (13.4)[a]	119.0 (11.2)	-21.8 [0.74][b]
HCTZ	622	139.8 (13.8)	121.0 (11.8)	-18.8 [0.60]

Table 5. Diastolic BP change from baseline to 48 months for the SI group

Step 1: drug regimen	N	Mean baseline diastolic BP (mmHg)	48-Month mean diastolic BP (mmHg)	Difference (mmHg)
CTD	396	94.4 (8.0)[a]	81.7 (6.7)	-12.7 [0.49][b]
HCTZ	622	93.5 (7.6)	82.4 (6.9)	-11.1 [0.37]

[a] Standard deviation
[b] Standard error

MRFIT: Risk Factor Changes and Mortality Results[22]
Patients were followed for a minimum of 6 years. Overall, significant differences were observed between the SI and UC group in improving control of hypertension and cholesterol and cessation of cigarette smoking. Overall, there were no significant differences in mortality due to CVD or CHD between the 2 groups and the mortality rate of both groups was much lower than predicted. This may be because significant outcomes were not seen in the follow up period, favorable outcomes may have been significant in the SI subgroups but not as a comprehensive intervention, or the SI group has no effect on the primary outcome.

Table 6. Mortality by frequency and cardiovascular cause

	SI	**Percentage of total deaths in SI group**	**UC**	**Percentage of total deaths in UC group**
Total	265		260	
Other CVD	23	8.7%	21	8.1%
CHD	115	43.4%	124	47.7%

Mortality after 10 1/2 Years for Hypertensive Participants in MRFIT[23]
An extended follow up trial was conducted on all patients who were classified as hypertensive (N=8012). After 10.5 years, overall mortality rates and those due to CHD were lower in the SI group but not significant (15%, p=0.19 and 11%, p=0.13 respectively). Mortality during post-trial years following 1982 (March 1982 through December 1985) were also compared to the preceding years in the original trial (through February 1982). All deaths were significantly lower in the SI group compared to the UC group from 1982-1985 (22.8% difference*, p=0.02). Only significant decreases in mortality related to all causes (not CHD) were noted in patients that had a diastolic BP of ≥100 mmHg. No significant decreases in mortality were found in patients who had a diastolic BP between 90-99 mmHg (on no treatment) or in those who were on treatment when starting the trial.

Table 7. Mortality due to all causes for patients with diastolic BP ≥100 mmHg (p<0.01)

Years	**SI**		**UC**		**Difference (%)***
	N	Rate	N	Rate	
Through Feb 1982	25	4.71	45	8.95	-48.4
Mar 1982 through Dec 1985	24	8.51	44	17.02	-50.6
Through Dec 1985	49	6.03	89	11.70	-49.8

*Defined as (RR-1) x100%; RR estimated from proportional hazards regression model

Significant increases in mortality due to all causes and CHD were seen in hypertensive patients with resting ECG abnormalities only through 1982, but were not seen following 1982. The authors hypothesized that these post-trial changes may be due to changes in diuretic therapy in the SI group 5 years after randomization. After 5 years, it was recommended that CTD be the only diuretic therapy for step 1 control of HTN. This change was based on favorable outcomes seen in clinics using CTD and unfavorable outcomes in other clinics using HCTZ. Therefore, beneficial mortality outcomes post-trial may have been due to this change in protocol. However, several other factors may have influenced these outcomes including the continued interventions targeting smoking cessation and cholesterol lowering.

Ernst and colleagues compared a 24-hour antihypertensive efficacy profile of HCTZ and CTD in a randomized, single-blinded, 8-week active treatment crossover trial.[6] Treatment-naive study participants 18 to 79 years of age with prehypertension or a new diagnosis of hypertension were included in the study. Patients were initially randomized to receive HCTZ (25 mg) or CTD (12.5 mg) once daily. At week 4, both medications were titrated to double their dose for the remainder of the study. The antihypertensive efficacy of chlorthalidone was significantly greater compared with HCTZ when it was administered first but was not the case when given second. From this, only data from completers of the first active treatment period was analyzed (n=30), therefore changing the study from a crossover to a parallel design. Although not statistically significant, ambulatory BP readings indicated a greater reduction from baseline in SBP with CTD 25 mg/day compared with HCTZ 50 mg/day (24-hour mean = -12.4 $\pm$ 1.8 mmHg and - 7.4 $\pm$ 1.7 mm Hg respectively; p=0.054). Statistical significance was seen in nighttime mean SBP favoring CTD (nighttime mean = -13.5 $\pm$ 1.9 mmHg versus -6.4 $\pm$ 1.8 mm Hg; p=0.009). For DBP and office blood pressures, differences between the two groups from baseline were not statistically significant. No serious adverse reactions were reported other than hypokalemia, which occurred similarly between patients treated with HCTZ and CTD (p=0.76). No patients experienced symptoms of hypokalemia.

In all, CTD demonstrated a greater antihypertensive effect compared to HCTZ for mean 24-hour BP readings, however the results were not statistically significant. The trend observed with the 24-hour mean SBP appeared to result from the statistically significant difference seen at nighttime (p=0.009). Nighttime ambulatory BP readings have been found to be the most predictive of cardiovascular outcomes in one study.[24] Several limitations exist with this trial. The short duration and limited number of study participants lack to represent the general population. Also, the potential for a carryover effect which led to the analysis of data from only the first active treatment period may have reduced the power of the study. Lastly, possible bias may exist due to the single-blinded nature of the study.

Dorsch and colleagues performed a retrospective observational cohort analysis comparing the clinical effects of CTD and HCTZ using data from MRFIT.[11] The primary outcome measure was cardiovascular events (CVEs) that were adjudicated and pre-specified in MRFIT. Nonfatal events consisted of clinical MI, MI determined by annual ECG, stroke, coronary artery bypass surgery, ECG-defined left ventricular hypertrophy, heart failure, angina, and peripheral artery occlusive disease. Results revealed that patients on CTD had significantly fewer CVEs compared with those on HCTZ (adjusted hazard ratio: 0.79 [95% CI: 0.68 to 0.92]; p=0.0016). The individual CVEs that contributed the most to this difference were clinical MI, ECG MI, coronary artery bypass, rose angina, and peripheral artery disease. Patients on CTD had a significantly lower SBP (p <0.0001), total cholesterol (p<0.0001), LDL (p=0.009), and serum potassium (p <0.0003), and higher uric acid over time (p<0.0001) compared to HCTZ. Glucose (p=0.1595) and triglyceride (p=0.2648) levels did not differ between groups.

Adverse Events:[12,13]

HCTZ:

- Cardiovascular: hypotension including orthostatic hypotension
- Digestive: pancreatitis, jaundice, diarrhea, vomiting, sialadentitis, cramping, constipation, gastric irritation, nausea, anorexia
- Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
- Hypersensitivity: anaphylactic reactions (caution with sulfa allergy), necrotizing angitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura
- Metabolic: electrolyte imbalance (hypokalemia), hyperglycemia, glycosuria, hyperuricemia
- Musculoskeletal: muscle spams
- Nervous system/psychiatric: vertigo parasthesias, dizziness, headache, restlessness
- Renal: renal failure, renal dysfunction, interstitial nephritis
- Skin: erythema multiforme including Stevens-Johnson Syndrome, exfoliate dermatitis including toxic epidermal necrolysis, alopecia
- Special senses: transient blurred vision, xanthopsia
- Urogenital: impotence

CTD:

- Cardiovascular: orthostatic hypotension
- Digestive: pancreatitis, jaundice, diarrhea, vomiting, sialadentitis, cramping, constipation, gastric irritation, nausea, anorexia
- Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
- Hypersensitivity: purpura, photosenstivity, rash, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis)
- Central Nervous system: dizziness, vertigo, parasthesias, headache, xanthopsia
- Other Adverse Reactions: hyperglycemia, hyperuricemia, muscle spasm, glycosurai, restlessness, impotence, weakness

Precautions/Contraindications:[12,13]

HCTZ:

Contraindications

- Anuria
- Hypersensitivity to this product or to other sulfonamide-derived drugs

Precautions

- All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: hyponatermia, hypochloremic alkalosis, and hypokalemia.
- Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.
- In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics.
- The antihypertensive effects of the drug may be enhanced in a post-sympathectomy patient.
- If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.
- Increase in cholesterol and triglyceride levels may be associated with thiazides.

- Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism.
- Thiazides should be discontinued before carrying out tests for parathyroid function.

CTD:
Contraindications
- Anuria
- Known hypersensitivity to chlorthalidone or other sulfonamide-derived drugs

Precautions
- Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH.
- Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
- Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
- Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone.
- Thiazide-like diuretics have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.
- The antihypertensive effects of the drug may be enhanced in a post-sympathectomy patient.
- If progressive renal impairment becomes evident, as indicated by rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Calcium excretion is decreased by thiazide-like drugs.

Look-alike/Sound-alike Error Risk Potential:[25]
None

FDA Risk Evaluation and Mitigation Strategy (REMS):[26]
None

Drug Interactions:[12,13]
HCTZ:
- Alcohol, barbiturates, or narcotics - may potentiate hypotension.
- Antidiabetic drugs - may require dose adjustments
- Antihypertensive drugs - additive effect or potentiation
- Cholestyramine and colestipol resins - absorption of HCTZ of anionic exchange resins
- Corticosteroids, ACTH - intensifies electrolyte depletion, particularly hypokalemia
- Pressor amines - possible decreased response to pressor amines but not sufficient to preclude their use
- Skeletal muscle relaxants, nondepolarizing - possible increased responsiveness to the muscle relaxant

- Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
- Non-steroidal anti-inflammatory drugs - can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

CTD:

- Antihypertensive drugs - additive effect or potentiation
- Digitalis - may influence serum electrolytes
- Insulin - requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes mellitus may become manifest during CTD administration.
- Oral hypoglycemic agents - higher dosages might be required with CTD
- Tubocurarine - CTD and related drugs may increase the responsiveness to tubocurarine
- Norepinephrine - CTD and related drugs may decrease arterial responsiveness to norepinephrine

Conclusions:

Based on the reviewed literature, CTD may be more beneficial in lowering SBP and preventing CVD events compared to HCTZ. Additionally, larger trials including ALLHAT, MRFIT, SHEP, and HDFP show favorable outcomes with CTD when compared with other antihypertensive therapies. CTD possesses a different pharmacokinetic profile from that of HCTZ. Its longer duration of action and higher potency may provide a greater antihypertensive effect, particularly throughout nighttime hours.[27] Moreover, the longer elimination half-life of CTD may result in more sustained BP reduction over 24 hours.[27] Conversely, CTD may have greater effects on lowering potassium and increasing uric acid versus HCTZ.[11] Overall, literature supports the safe and effective use of CTD in patients with HTN, and therefore, should be considered an alternative first line agent alongside HCTZ.

Recommendations:

Based on the available evidence, it is recommended that CTD be considered for addition to the NCF formulary. For patients that are stable and controlled on HCTZ, therapy should be continued. For patients initiating diuretic therapy for the first time, CTD seems a reasonable first line option. Safety and efficacy data should be reevaluated over the next few years to determine the place in therapy for both of these agents.

Authors: LT Jennifer Bongartz, PharmD; LT Deborah A. Gallo, PharmD; CDR Michael Lee, PharmD, NCPS, BCPS

Relevant Acronyms:

ABPM	Ambulatory Blood Pressure Measurement
ACE-Is	Angiotensin Converting Enzyme Inhibitors
ACTH	Adrenocorticotropic hormone
AI/AN	American Indian/Alaska Natives
ARBs	Angiotensin II Receptor Blockers
BBs	Beta Blockers
BP	Blood Pressure
CCBs	Calcium Channel Blockers
CTD	Chlorthalidone
CHD	Coronary Heart Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
GDG	Guideline Development Group
HDFP	Hypertension Detection and Follow-up Program
HCTZ	Hydrochlorothiazide
HTN	Hypertension
JNC 7	Committee on the prevention, detection, evaluation and treatment of high blood pressure
SHEP	Systolic Hypertension in the Elderly Program

References:

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation.* Jan 3 2012;125(1):e2-e220.

2. CDC 2005. Health Characteristics of the American Indian and Alaska Native Adult Population: United States, 1999-2003. Advance Data (356), Table 4.

3. Heron M. Deaths: leading causes for 2004. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.* Nov 20 2007;56(5):1-95.

4. IHS Fact Sheets: Indian Population. http://info.ihs.gov/Population.asp; accessed February 3, 2011.

5. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* May 21 2003;289(19):2534-2544.

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

7. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* Dec 18 2002;288(23):2998-3007.

8. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7). NIH Publication No. 04-5230. 2004 Aug.

9. Carter BL. Implementing the new guidelines for hypertension: JNC 7, ADA, WHO-ISH. *J Manag Care Pharm.* Sep 2004;10(5 Suppl A):S18-25.

10. Sumiye L, Vivian AS, Frisof KB, Podany EC. Potassium loss associated with hydrochlorothiazide versus chlorthalidone. *Clin Ther.* 1981;4(4):308-320.

Note: Information within this document is current as of this writing and should not replace clinical judgment.

11. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension.* Apr 2011;57(4):689-694.
12. Hydrochlorothiazide Package Insert. Miami, FL. Ivax Pharmaceuticals/Teva. 2002.
13. Chlorthalidone Package Insert. Croatia. Pliva/Teva. 2006.
14. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed March 5, 2012.
15. IHS National Core Formulary: http://www.ihs.gov/nptc/index.cfm?module=dsp_nptc_formulary; Accessed March 5, 2012.
16. Shah NR, Ogedegbe G. ACP Journal Club. Review: first-line low-dose thiazides and ACE inhibitors reduce mortality and morbidity in adults with hypertension. *Ann Intern Med.* Jan 19 2010;152(2):JC1-4.
17. National Clinical Guideline Center. Hypertension: The clinical management of primary hypertension in adults. Update of guidelines 18 and 34. http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf. Accessed April 1, 2012.
18. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *Journal of the American Society of Hypertension : JASH.* Jul-Aug 2011;5(4):259-352.
19. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* Aug 2004;114(2 Suppl 4th Report):555-576.
20. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* Dec 18 2002;288(23):2981-2997.
21. Cohen JD, Grimm RH, Jr., Smith WM. Multiple risk factor intervention trial (MRFIT). *Prev Med.* Jul 1981;10(4):501-518.
22. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. *JAMA.* Sep 24 1982;248(12):1465-1477.
23. Mortality after 10 1/2 years for hypertensive participants in the Multiple Risk Factor Intervention Trial. *Circulation.* Nov 1990;82(5):1616-1628.
24. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension.* Jul 2005;46(1):156-161.
25. Institute of Safe Medical Practice: ISMP's List of Confused Drug Names.; http://www.ismp.org/Tools/confuseddrugnames.pdf; accessed April 3, 2012.
26. U.S. Food and Drug Administeration. Approved Risk Evaluation and Mitigation Strategies (REMS). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm?utm_source=fdaSearch&utm_medium=website&utm_term=REMS&utm_content=1; assessed April 4, 2012.
27. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension.* Jan 2004;43(1):4-9.