



Q/ How do hydrochlorothiazide and chlorthalidone compare for treating hypertension?

EVIDENCE-BASED ANSWER

A/ BOTH MEDICATIONS REDUCE THE INCIDENCE OF CARDIOVASCULAR EVENTS in patients with hypertension, but chlorthalidone may confer additional cardiovascular risk reduction (strength of recommendation [SOR]: **B**, conflicting network meta-analysis and cohort studies). (No head-to-head studies of hydrochlorothiazide [HCTZ] and chlorthalidone have been done.)

Serious hypokalemia and hyponatremia can occur with either medication; it is unclear if the rates of these adverse effects are the same at equivalent doses. Patients taking chlorthalidone are less likely to need a second antihypertensive medication but more likely to be nonadherent than patients taking HCTZ (SOR: **B**, cohort studies).

Evidence summary

A network meta-analysis—designed to compare 2 interventions that haven't been studied head-to-head—examined 9 trials that evaluated cardiovascular outcomes in 18,000 patients taking HCTZ and 60,000 patients taking chlorthalidone against outcomes for placebo or other antihypertensive agents.¹ Daily doses ranged from 12.5 to 25 mg for HCTZ and 12.5 to 100 mg for chlorthalidone (although most patients taking chlorthalidone were on 12.5-25 mg).

In a drug-adjusted analysis using shared comparator medications, chlorthalidone proved superior to HCTZ in reducing the risk of both heart failure (relative risk [RR]=0.77; 95% confidence interval [CI], 0.61-0.98) and combined cardiovascular events—myocardial infarction (MI), stroke, a new diagnosis of coronary artery disease, and new-onset congestive heart failure (RR=0.79; 95% CI, 0.72-0.88).

After adjusting for achieved blood pressure, chlorthalidone was still associated with lower rates of cardiovascular events than HCTZ (RR=0.82; 95% CI, 0.70-0.97). Relative to HCTZ, the number needed to treat with

chlorthalidone to prevent 1 additional cardiovascular event over 5 years was 27. Because network meta-analyses draw from a wider body of research than standard meta-analyses, they may be weakened by increased variability in study design and patient demographics.

But another study shows no significant difference in cardiovascular outcomes

A subsequent retrospective cohort study didn't find a significant difference in cardiovascular outcomes between HCTZ and chlorthalidone. The study compared pooled cardiovascular outcomes (MI, heart failure, and stroke) in 10,400 patients recently started on chlorthalidone and 19,500 started on HCTZ.² Initial doses were typically either 25 mg chlorthalidone (70% of patients on chlorthalidone) or 12.5 mg HCTZ (67% of patients on HCTZ). The median follow-up was about a year, but lasted as long as 5 years in some cases.

The 2 groups showed no significant difference in cardiovascular events (3.2 events per 100 person-years for chlorthalidone compared with 3.4 for HCTZ; adjusted hazard ratio [aHR]=0.93; 95% CI, 0.81-1.06).

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➤ **Chlorthalidone may reduce the risk of cardiovascular events in patients with hypertension more than HCTZ.**

Serious hypokalemia and hyponatremia are risks

Patients taking chlorthalidone were more likely to be hospitalized for hypokalemia (0.69 per 100 person-years vs 0.27 for HCTZ; aHR=3.1; 95% CI, 2.0-4.6; number needed to harm [NNH]=238 in 1 year) or hyponatremia (0.69 per 100 person-years vs 0.49 for HCTZ; aHR=1.7; 95% CI, 1.2-2.3; NNH=434 in 1 year).² However, the all-cause hospitalization rates for the 2 drugs were the same (aHR=1.0; 95% CI, 0.93-1.07).

Lower systolic BP and serum potassium found with chlorthalidone

A smaller retrospective cohort analysis (6441 participants who received either chlorthalidone or HCTZ starting at 50 mg and stepped once to 100 mg) also assessed the difference in cardiovascular events between patients taking the 2 drugs.³ (Cardiovascular events were defined as pooled MIs, onset of angina or peripheral artery occlusive disease, or need for coronary artery bypass.) Although significant reductions in pooled events occurred in both groups over the 7-year study, these reductions were significantly lower in the chlorthalidone group than in the HCTZ group (aHR=0.79; 95% CI, 0.68-0.92).

Systolic blood pressures were statistically lower in the chlorthalidone group during Years 1 through 5 but not in Years 6 and 7 (difference 2-4 mm Hg). Serum potassium was also lower in patients taking chlorthalidone (3.8 mEq/L on chlorthalidone vs 4.0 mEq/L on HCTZ after 7 years; $P<.05$).

Chlorthalidone users more responsive, but less adherent than HCTZ users

A retrospective cohort study investigated

medication tolerance in veterans who had recently started either HCTZ (120,000 patients) or chlorthalidone (2200 patients) and were followed for a year.⁴ Most received doses between 12.5 and 25 mg of active drug.

One primary outcome was “nonpersistence,” defined as failure to refill the medication after double the number of days as the initial prescription. The other was “insufficient response,” defined as the need to start another antihypertensive medication. Chlorthalidone users were less likely than HCTZ users to have an insufficient response (odds ratio [OR]=0.71; 95% CI, 0.63-0.80) but more likely to exhibit nonpersistence (OR=1.6; 95% CI, 1.5-1.8).

Recommendations

For primary hypertension, the United Kingdom’s National Institute for Health and Care Excellence (NICE) recommends diuretic monotherapy in patients older than 55 years who are poor candidates for calcium channel blockers.⁵ If a diuretic is to be initiated or changed, NICE recommends chlorthalidone (12.5-25 mg daily) or indapamide (1.5-2.5 mg daily) in preference to HCTZ.

The guideline set forth in the eighth annual report of the United States Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure makes no distinction between chlorthalidone and HCTZ; it refers only to “thiazide-type diuretics.” Thiazide-type diuretics are listed as one option (along with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers) for initial monotherapy in nonblack patients.⁶

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References

1. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension*. 2012;59:1110-1117.
2. Dhalla IA, Gomes T, Yao Z, et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. *Ann Intern Med*. 2013;158:447-455.
3. Dorsh MP, Gillespie BW, Erickson SR, et al. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*. 2011;57:689-694.
4. Lund BC, Ernst ME. The comparative effectiveness of hydrochlorothiazide and chlorthalidone in an observational cohort of veterans. *J Clin Hypertension*. 2012;14:623-629.
5. Hypertension: clinical management of primary hypertension in adults. (NICE Clinical Guideline 127). National Institute for Health and Care Excellence Web site. London, UK: National Institute for Health and Care Excellence; 2011. Available at: www.nice.org.uk/guidance/CG127. Accessed December 16, 2013.
6. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8). *JAMA*. 2014;311:507-520.