

Long-Term Care Updates

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Chlorthalidone vs. Hydrochlorothiazide – New Updates and Guidance



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Introduction:

Thiazide diuretics are generally a first line option for providers when considering antihypertensive therapy. The 2017 American College of Cardiology (ACC) and American Heart Association (AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults specifically recommends chlorthalidone as the preferred thiazide diuretic for the treatment of hypertension due to its extended half-life and history of clinical cardiovascular disease (CVD) reduction. The guideline states that chlorthalidone should be used with caution in patients with a history of gout and patients should be monitored for electrolyte disturbances such as hyponatremia and hypokalemia. Chlorthalidone is recommended over other widely available and cost-effective thiazides such as hydrochlorothiazide (HCTZ) due to its pharmacokinetic profile and clinical evidence.¹

However, the recommendation for chlorthalidone over HCTZ has not been widely adopted in clinical practice, particularly in the geriatric population. According to the Centers for Medicare and Medicaid Services (CMS), Medicare Part D services paid claims for 4.6 million chlorthalidone prescriptions compared to 16.5 million HCTZ prescriptions in 2021. This indicates that CMS pays for approximately four times as many claims for HCTZ as opposed to chlorthalidone in Medicare patients.² There have also been recent clinical studies evaluating the cardiovascular benefit of chlorthalidone versus HCTZ that showed no statistically significant difference between the two.³⁻⁴ The purpose of this newsletter is to review recent evidence from clinical trials regarding the cardiovascular benefit of chlorthalidone compared to HCTZ in adult and geriatric patients.

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Clinical Evidence:

In a study published in the Journal of the American Medical Association in 2020, Hripcsak et al. assessed the safety and efficacy of chlorthalidone compared to HCTZ using real-world data. The design of this study was a retrospective, observational, comparative cohort utilizing Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND). Data from January 2001 to December 2018 indicating inpatient or outpatient care episodes of first-time users of antihypertensive monotherapy of HCTZ or chlorthalidone were included. The primary outcomes included acute myocardial infarction, hospitalization for heart failure, ischemic or hemorrhagic stroke, and a composite of cardiovascular disease including the first three outcomes and sudden cardiac death. Safety data was also evaluated. A total of 730,225 patients were included with 36,918 patients prescribed chlorthalidone and 693,337 prescribed HCTZ as initial antihypertensive therapy. Most participants were between the ages of 40 to 64 years with 61% being of female sex. The most common cardiovascular co-morbidity in each group was heart disease (6%). Other common conditions included acute respiratory disease (26%), hyperlipidemia (around 26%), and visual system disorders (15%). The chlorthalidone group reported 149 composite outcome events compared to 3,089 in the HCTZ group. It was found that there was no significant difference in the risk of myocardial infarction (Hazard Ratio [HR] 0.92; 95% CI, 0.64 to 1.31), hospitalization for heart failure (HR 1.05; 95% CI 0.82 to 1.34), stroke (HR 1.10; 95% CI, 0.86 to 1.41), or the composite outcome (HR 1.00; 95% CI, 0.85 to 1.17) with chlorthalidone versus HCTZ. Regarding safety, chlorthalidone was shown to have an increased risk of hypokalemia (HR 2.72; 95% CI, 2.38 to 3.12), hyponatremia (HR 1.31; 95% CI, 1.16 to 1.47), acute renal failure (HR 1.37; 95% CI, 1.15 to 1.63), chronic kidney disease (HR 1.24; 95% CI, 1.09 to 1.42), and type 2 diabetes mellitus (HR 1.21; 95% CI, 1.12 to 1.30) compared to HCTZ. Chlorthalidone showed a lower risk of abnormal weight gain (HR 0.73; 95% CI, 0.61 to 0.86).³

More recently, a December 2022 study published in The New England Journal of Medicine evaluated chlorthalidone versus HCTZ in preventing major adverse cardiovascular events in patients with hypertension. This multicenter, open-label trial was sponsored by the Veterans Administration Cooperative Studies Program. Patients were at least 65 years old and had hypertension managed with HCTZ 25 to 50 mg daily. Participants were randomized to continue their current regimen with HCTZ or to switch to chlorthalidone 12.5 to 25 mg daily. The primary outcome was a composite of nonfatal myocardial infarction, stroke, heart failure leading to hospitalization, urgent coronary revascularization for unstable angina, and non-cancer related death. The safety of each agent was also evaluated and analyzed. The trial had a sample size of 13,523 participants who underwent randomization. The average age in both groups was 72 years and about 97% of participants were male (77% being white). After 2.4 years, it was found that there was minimal difference in the occurrence of the primary outcome events in each treatment group. The HCTZ group had a 10% occurrence compared to 10.4% in the chlorthalidone group (HR 1.04; 95% CI, 0.94 to 1.16; $P = 0.45$). Regarding individual events, no significant differences were identified between the groups. Myocardial infarctions occurred in 2.1% in each group (HR 1.02; 95% CI, 0.80 to 1.28), strokes in 1.2% of each group (HR 1.00; 95% CI, 0.74 to 1.36), hospitalizations due to heart failure in 3.6% of participants in the chlorthalidone group versus 3.4% in the HCTZ group (HR 1.04; 95% CI, 0.87 to 1.25), urgent coronary revascularization for unstable angina in 0.3% of the chlorthalidone group versus 0.2% in the HCTZ group (HR 1.54; 95% CI, 0.77 to 3.10), and non-cancer related death in 5.3% of the chlorthalidone group versus 5.2% in the HCTZ group (HR 1.01; 95% CI, 0.88 to 1.17). In terms of safety, the chlorthalidone group did have higher incidence of hypokalemia with 6% incidence versus 4.4% in the HCTZ group ($P < 0.001$).⁴

Conclusion:

Despite the recommendation of chlorthalidone as the preferred thiazide diuretic in the most recent ACC/AHA guideline for the management of hypertension, prescribing practices among providers, particularly in the elderly patient population, do not reflect this preference. There are various reasonable explanations as to why HCTZ is the most prominently prescribed thiazide in this patient population including drug cost, availability, convenient combination antihypertensive products available with HCTZ, and preference on insurance formularies. However, recently, there has also been clinical evidence that suggests that when studied head-to-head against HCTZ, chlorthalidone does not show cardiovascular benefit. In addition to this lack of clinical benefit, chlorthalidone was associated with an increased risk of adverse effects such as hyponatremia, hypokalemia, acute renal failure, chronic kidney disease and type 2 diabetes when compared to HCTZ.

With the publication of these recent clinical trials, there may be a gray area in practice where recent clinical evidence does not support the guidelines. As with managing chronic disease states in all patients, it is essential to practice evidence-based medicine, considering patient specific factors; particularly in elderly patients who may be more prone to adverse effects.

References:

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