In the Literature

**Chlorthalidone Versus Hydrochlorothiazide in Hypertension Treatment: Do We Have the Evidence to Decide?**


Pharmacologic treatment of hypertension, including the use of thiazide-type diuretics, has had a major impact on reducing the risk of stroke, heart failure, myocardial infarction, and death in the population. Although it generally is agreed that as a class, thiazide-type diuretics are effective in reducing blood pressure (BP) and preventing cardiovascular disease (CVD) in hypertensive persons, it is not clear whether all drugs in this class are equally safe and effective. This disagreement is reflected in recent hypertension guidelines, some of which specify a preference for certain agents within the class, for example, chlorthalidone or indapamide, whereas others regard all agents in the class as generally equivalent. In the absence of evidence from randomized controlled trials that directly compare different diuretics in the treatment of hypertensive populations, various forms of indirect evidence have been used to inform clinical practice. Several studies, including small trials and one meta-analysis, have demonstrated pharmacokinetic/pharmacodynamic profiles and novel mechanisms of action that favor chlorthalidone over hydrochlorothiazide in reducing BP in hypertensive persons. Similarly, observational cohort studies and network meta-analyses have provided assessments of the comparative effectiveness of chlorthalidone and hydrochlorothiazide in everyday practice, as well as indirect comparisons of the effects of chlorthalidone and other low-dose thiazide-type diuretics, including hydrochlorothiazide, on CVD outcomes. In this context, a large observational study recently reported head-to-head comparative data on the effects of newly prescribed chlorthalidone versus hydrochlorothiazide on CVD and safety outcomes in elderly patients.

**WHAT DOES THIS IMPORTANT STUDY SHOW?**

A recent population-based retrospective observational study of older adults in Ontario compared the effects of starting treatment with chlorthalidone (10,384 patients) versus hydrochlorothiazide (propensity-matched sample of 19,489 patients) with a mean follow-up of about 1 year. Patients treated with chlorthalidone received higher doses despite its greater potency and were less likely to also be treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (drugs that increase potassium levels). Chlorthalidone was associated with a small nonsignificant reduction in the composite CVD outcome, from 3.4 to 3.2 per 100 patient-years (adjusted hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.81-1.06). However, chlorthalidone treatment also was associated with significantly more hospitalizations with (but not necessarily for) hypokalemia (0.69 vs 0.27 events/100 patient-years; adjusted HR, 3.06; 95% CI, 2.04-4.58) and hyponatremia (0.69 vs 0.49 events/100 patient-years; adjusted HR, 1.68; 95% CI, 1.24-2.28). The authors included hospitalizations that listed electrolyte abnormalities as secondary outcomes during hospitalizations for other indications. Hypokalemia and hyponatremia were each recorded as a secondary outcome noted during hospitalization less than once per 100 patient-years. In response to a letter suggesting that the analysis should be restricted to hospitalizations for hypokalemia, the authors responded that doing so would result in so few hospitalizations that “such an analysis would be severely underpowered.”

Thus, although it is not known whether chlorthalidone caused more hospitalizations for hypokalemia, it is clear that such hospitalizations were rare.

The Ontario study had the major advantages of large size and direct comparison of the 2 drugs in a single population. The principal disadvantages were the observational design and very small (and therefore potentially quite different) proportion of participants taking chlorthalidone. Only 11,389 (1.7%) of the 654,918 patients eligible for matching were treated with chlorthalidone. Incomplete adjustment for known confounders (eg, dose and cotreatment) or unrecognized confounders in the treated populations could have influenced the findings, as noted in a letter by the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) investigators. For example, chlorthalidone likely is used more often by hypertension specialists who might have been more attentive to recording electrolyte abnormalities on discharge summaries. A review of the US data indicates that chlorthalidone is used more often than hydrochlorothiazide in patients with
more severe hypertension and associated comorbid conditions. The Ontario study nevertheless raises questions regarding the possible superiority of chlorthalidone. In the correspondence following its publication, both the ALLHAT investigators and the Ontario authors stressed the need for a randomized trial to resolve this issue.

**HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?**

Prior studies have directly compared the pharmacokinetic and pharmacodynamic (BP-lowering) effects of chlorthalidone and hydrochlorothiazide in hypertensive persons. Chlorthalidone has a longer half-life (45-60 hours) than hydrochlorothiazide (16-24 hours), as well as a larger volume of distribution. Furthermore, chlorthalidone is 1.5-2.0 times as potent as hydrochlorothiazide, resulting in greater reductions in systolic BP (SBP), particularly during the night-time hours. Chlorthalidone also has non-hemodynamic pleomorphic effects that are not shared by hydrochlorothiazide, including reduction in vascular permeability and inhibition of carbonic anhydrase, which results in reduced epinephrine-mediated platelet aggregation. These effects may result in vasoprotection that is independent of BP lowering.

In the absence of randomized controlled trials directly comparing chlorthalidone with hydrochlorothiazide head to head, network meta-analytic techniques have provided indirect comparisons of their effects on CVD outcomes. An early network meta-analysis of placebo-controlled trials examined health outcomes associated with various first-line antihypertensive therapies, including chlorthalidone (2 studies) and other low-dose thiazide-type diuretics (3 studies). Fixed-effects techniques first were used to compare the relative risks of chlorthalidone and other thiazide-type diuretics versus placebo on CVD outcomes; the ratios of the relative risks then were used to obtain an indirect estimate of the effect of chlorthalidone versus other thiazide-type diuretics on health outcomes. The risk estimates for chlorthalidone versus other diuretics were similar; these findings suggested that large differences between chlorthalidone and the other diuretics were unlikely. As noted in a letter by Roush et al., this meta-analysis did not include more recent studies, such as ALLHAT, that favor chlorthalidone over hydrochlorothiazide in network analysis.

A more recent comparison of chlorthalidone versus hydrochlorothiazide on CVD outcomes included a systematic review of randomized controlled trials with either diuretic as the step 1 agent, followed by 2 types of network meta-analyses, adjusted for drug or for office SBP. The percentage of risk reduction for all CVD events was significantly greater for chlorthalidone in both the drug-adjusted and office SBP-adjusted analyses. The investigators concluded that chlorthalidone is better than hydrochlorothiazide in preventing CVD events. Further, the authors posit that these results are not entirely because hydrochlorothiazide has a lesser effect on office SBP than chlorthalidone, but rather could be related to chlorthalidone’s pleomorphic effects or to hydrochlorothiazide’s shorter duration of action, which may leave night-time BP inadequately controlled.

A recent retrospective observational cohort analysis from the MRFIT (Multiple Risk Factor Intervention Trial) data set compared the effects of chlorthalidone versus hydrochlorothiazide on CVD event rates. MRFIT tested whether a multifaceted intervention program (hypertension treatment beginning with chlorthalidone or hydrochlorothiazide, 50 or 100 mg daily; smoking cessation; and dietary counseling) could reduce coronary heart disease (CHD) mortality compared to usual care. Chlorthalidone treatment was associated with significantly fewer CVD events; lower SBP, potassium, and total and low-density lipoprotein cholesterol levels; and significantly higher uric acid levels compared with hydrochlorothiazide. However, the findings of this nonrandomized comparison are confounded by large differences in dosage, randomized group, and lipid lowering, and both diuretics reduced CVD events compared with neither drug (usual care). Importantly, the CHD mortality benefit of chlorthalidone was recognized during the course of the trial, leading to a protocol change mandating chlorthalidone as the thiazide-type diuretic of choice. CHD mortality rates in clinics that switched from hydrochlorothiazide to chlorthalidone decreased by 28%, suggesting that chlorthalidone may be the preferred thiazide-type diuretic for hypertension in patients at high risk of CVD events.

**WHAT SHOULD CLINICIANS AND RESEARCHERS DO?**

Because hospital “admission with” hyponatremia or hypokalemia has unclear clinical relevance, was a relatively rare event, apparently was not associated with overall higher major CVD outcomes, and was based on observational analyses, the report by Dhalla et al should be considered hypothesis generating. In addition, observational studies of the relationships of drug use and various outcomes often result in misleading results that are not borne out in randomized controlled trials, primarily because of confounding by indication or severity of disease. In a randomized controlled trial, these potential confounders, both measured and unmeasured, are likely to be distributed evenly between the randomized groups. This confounding may be more likely in the
report by Dhalla et al11 because BP levels and other indications of severity of hypertension (eg, number and doses of other antihypertensive medications) were not accounted for. Therefore, because both drugs have effectively reduced CVD events in randomized placebo-controlled trials and have been unsurpassed (or are superior for some outcomes) in trials compared with other antihypertensive agents when used in appropriate doses, this study should not affect clinical practice. However, it should be a reminder that chlorthalidone, 12.5-25 mg, and hydrochlorothiazide, 25-50 mg, are the lowest daily doses of these drugs proved in clinical trials to reduce major CVD events. Investigators should keep this in mind when designing hypertension trials using either of these agents. Most importantly, this report highlights the urgent need for a comparative efficacy outcome trial comparing these 2 diuretics.

Suzanne Oparil, MD
The University of Alabama at Birmingham
Birmingham, Alabama

William C. Cushman, MD
University of Tennessee
Memphis, Tennessee

Frank A. Lederle, MD
VA Medical Center
Minneapolis, Minnesota

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: In the previous 36 months, Dr Oparil has received research support and consultancies from AstraZeneca AB; Backbeat; Bayer; Boehringer-Ingelheim; Daiichi Sankyo Inc; Duke University; Eli Lilly; Medtronic; Merck and Co; National Heart, Lung, and Blood Institute; Novartis; Pfizer; and Takeda Global Research & Development Inc. Dr Cushman has received consultancies from Takeda, the manufacturer of azilsartan-medoxomil/chlorthalidone. Dr Lederle declares that he has no relevant financial interests.

REFERENCES


