Chlorthalidone Versus Hydrochlorothiazide as the Preferred Diuretic

Is There a Verdict Yet?

John M. Flack, Domenic A. Sica, Shawna Nesbitt

See related article, pp 689–694

In this issue of *Hypertension,* the retrospective observational cohort analysis of the Multiple Risk Factor Intervention Trial by Dorsch et al[1] adds to the growing body of evidence supporting the superiority of chlorthalidone over hydrochlorothiazide (HCTZ) as the preferred diuretic in the treatment of hypertension. In the absence of a randomized, controlled clinical end point trial directly comparing chlorthalidone and HCTZ, the data from observational cohort analysis of Dorsch et al[1] is another important and convincing piece of the available data repository; this report is the first analysis of the relative impact of chlorthalidone and HCTZ on pressure-related cardiovascular disease (CVD) end points available in the published literature. Importantly, they reported a highly significant 21% lower risk of CVD among those taking chlorthalidone compared with those taking HCTZ over a median follow-up of 6 years.

Although not a randomized trial, these investigators made a very credible effort to delineate the unbiased relative effect of these 2 diuretics on pressure-related CVD end points. They also examined the relative effects of chlorthalidone and HCTZ on several secondary end points, total and low-density lipoprotein cholesterol, potassium, uric acid, and glucose, with proven links to CVD. The chlorthalidone group had lower blood pressure (BP) throughout most of the study, as well as lower total and low-density lipoprotein cholesterol; however, potassium levels were lower and uric acid levels were higher in those taking chlorthalidone. Thus, some of these trends in secondary end points would favor lower CVD risk, whereas some would be more consistent with higher CVD risk in the chlorthalidone group.

Most of the available data regarding the relative merits of chlorthalidone versus HCTZ as the preferred diuretic in the treatment of hypertension comes from much smaller data sets that have reported the short-term relative effects of these diuretics on BP.[2–4] Accordingly, Ernst et al[2] report that 12.5 to 25.0 mg/d of chlorthalidone lowered ambulatory systolic BP >25 to 50 mg/d of HCTZ (−12.4 versus −7.4 mm Hg; $P=0.054$) over 8 weeks; the lowering of systolic BP in favor of chlorthalidone was especially prominent at night (−13.5 versus −6.4 mm Hg; $P=0.009$). It has also been established that the pharmacokinetic profiles of these 2 diuretics are different. Chlorthalidone has a much longer half-life than HCTZ (45 to 60 versus 8 to 15 hours), as well as a much longer duration of action, and, on a per-milligram basis, chlorthalidone is 1.5 to 2.0 times more potent than HCTZ.[5] These 2 observations alone make chlorthalidone putatively a more desirable diuretic than HCTZ for hypertension treatment.

Most of the National Institutes of Health–sponsored hypertension clinical outcome trials, Hypertension Detection and Follow-Up Program, the Systolic Hypertension in the Elderly Program, the Treatment of Mild Hypertension Study, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, have used the diuretic chlorthalidone rather than HCTZ. None of them, however, have directly compared chlorthalidone with HCTZ. Accordingly, the body of outcome evidence with hard clinical end points is stronger in support of the use of chlorthalidone rather than HCTZ. Adding to the controversy over the preferred diuretic in hypertension treatment was the recently reported Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Study.[6] In this study of the relative effect of combination therapy (HCTZ+benazepril versus amlodipine+benazepril) the calcium antagonist+angiotensin-converting enzyme inhibitor reduced the risk of the primary composite CVD end point 20% more than the diuretic+angiotensin-converting enzyme combination in high-risk hypertensives after early termination of the trial (mean follow-up: 36 months); over the course of the study, systolic BP was ≈1 mm Hg lower in the amlodipine+benazepril group. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Study has been criticized for the use of HCTZ, rather than chlorthalidone, at doses of HCTZ lower than what has been shown to provide CVD protection; the median HCTZ dose was 22.1 mg/d.

There are caveats, as always, with the interpretation of the retrospective observational cohort analysis of the Multiple Risk Factor Intervention Trial by Dorsch et al.[1] The majority of the chlorthalidone-treated patients were in the special intervention group that also received smoking cessation and

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Divisions of Translational Research and Clinical Epidemiology and Endocrinology, Metabolism, and Hypertension (J.M.F.), Departments of Medicine and Physiology, Wayne State University, Detroit, MI; Division of Nephrology and Hypertension (D.A.S.), Department of Medicine, Virginia Commonwealth University Medical Center, Richmond, VA; Division of Hypertension (S.N.), Department of Medicine, University of Texas Southwestern, Dallas, TX.

Correspondence to John M. Flack, Wayne State University, Department of Medicine, University Health Center, 4201 St Antoine, 2E, Detroit, MI 48201. E-mail jflack@med.wayne.edu

(*Hypertension*. 2011;57:665-666.)

***Hypertension* is available at http://hyper.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.110.164566

dietary counseling; statistical adjustment will not likely fully eliminate this imbalance in favor of chlorthalidone-lowering CVD risk. The doses of chlorthalidone and HCTZ used in these analyses were higher than contemporary doses used of either agent. Thus, the outcomes in this analysis have to be extrapolated back into a lower dose range to have any current clinical relevance. The Multiple Risk Factor Intervention Trial cohort was entirely composed of men, so there should be at least a modicum of caution in extrapolating these outcomes to women. The Multiple Risk Factor Intervention Trial cohort was also at high risk for coronary heart disease, and, thus, the outcomes may not directly apply to lower-risk hypertensive patients. On the other hand, the authors took a very credible approach for preventing the effect of undue bias on the reported results.

The importance of this study is 2-fold: it provides hard outcomes data, albeit not from a randomized trial, as a measure of the relative efficacy of these 2 diuretic treatments; and this study adds to the totality of evidence already suggesting that chlorthalidone is superior to HCTZ as an antihypertensive agent. Nevertheless, there will obviously be those who remain unconvinced and, therefore, unwilling to favor chlorthalidone over HCTZ without a prospective, randomized, double-blind trial. The pharmaceutical industry has largely shunned chlorthalidone in favor of HCTZ for their single-pill, fixed-dose combination drugs. Moreover, practitioners overwhelmingly use HCTZ over chlorthalidone, although there is some uptick in the use of the latter, albeit from a very low baseline level of use.[7]

The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure hypertension guidelines published in 2003 did not specify which thiazide or thiazide-like diuretic to use.[8] The recently published consensus statement[9] on the management of hypertension in blacks from the International Society on Hypertension in Blacks did, however, express the clear preference for chlorthalidone over HCTZ based on the totality of the currently available evidence. A direct comparison of chlorthalidone and HCTZ in a prospective, randomized outcomes clinical trial would more definitively answer the important question of which diuretic was superior for the treatment of hypertension. However, until such data become available, the totality of the evidence favors the use of chlorthalidone over HCTZ as the preferred diuretic in hypertension treatment. The study by Dorsch et al[1] has further strengthened this position.

Sources of Funding

J.M.F. received funding from NIH-Cardiovascular Outcomes in Renal Atherosclerotic Lesions, ASPREE, WSU CUAAH Admin Core, WSU Center for Urban and African American Health – Obesity, Nitric Oxide, Salt Sensitivity Study, and Chronic Renal Insufficiency Cohort Study (amount greater than $25 000) and Daiichi Sankyo-3 Combo Tx in HTN (amount greater than $25 000). D.S. received funding for the use of baroreceptor stimulation therapy for resistant hypertension (amount greater than $10 000).

Disclosures

D.A.S. is a member of the speakers bureau at Takeda (amount less than $10 000), has received honoraria from Takeda (amount less than $10 000), and is on the consultant/advisory board for Takeda (amount less than $10 000).

References

1. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension.* 2011;57:689–694.
2. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effectsd of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47:352–358.
3. Bowlus WE, Langford HG. A comparaison of the antihypertensive effect of chlorthalidone and hydrochlorothiazide. *Clin Pharmacol Ther*. 1964;5:708–711.
4. Finnerty FA Jr. A double-blind study of chlorthalidone and hydrochlorothiazide in an outpatient population of moderate hypertensives. *Angiology*. 1976;27:738–744.
5. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension*. 2004;43:4–9.
6. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
7. Ernst ME, Lund BC. Renewed interest in chlorthalidone: evidence from the Veterans Health Administration. *J Clin Hypertens*. 2010;12:927–934.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252.
9. Flack JM, Sica D, Bakris G, Brown AL, Ferdinand KC, Grimm RH Jr, Hall WD, Jones WE, Kountz DS, Lea JP, Nasser, Nesbitt SD, Saunders E, Scisney-Matlock M, Jamerson KA, on behalf of the International Society on Hypertension in Blacks. Management of high blood pressure in blacks: an update on the International Society on Hypertension in Blacks Consensus Statement. *Hypertension.* 2010;56:780–800.

Hypertension
Journal of the American Heart Association

Chlorthalidone Versus Hydrochlorothiazide as the Preferred Diuretic: Is There a Verdict Yet?

John M. Flack, Domenic A. Sica and Shawna Nesbitt

Hypertension. published online March 7, 2011;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563