

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

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In this issue of *Hypertension*, the retrospective observational cohort analysis of the Multiple Risk Factor Intervention Trial by Dorsch et al<sup>1</sup> 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<sup>1</sup> 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.<sup>2–4</sup> Accordingly, Ernst et al<sup>2</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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  $\approx 1$  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.<sup>1</sup> The majority of the chlorthalidone-treated patients were in the special intervention group that also received smoking cessation and

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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.<sup>7</sup>

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.<sup>8</sup> The recently published consensus statement<sup>9</sup> 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 hyper-

tension treatment. The study by Dorsch et al<sup>1</sup> has further strengthened this position.

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