

EDITORIALS



Thiazide-like versus Thiazide Diuretics — Finally, an Answer?

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The treatment of hypertension has extended millions of lives since the mid-20th century, when hypotensive medications were few. Since then, therapeutic options have expanded to include multiple classes and scores of individual antihypertensive agents — diuretics, beta-blockers, renin–angiotensin system blockers (angiotensin-converting–enzyme inhibitors and angiotensin II receptor blockers, foremost), calcium-channel blockers, alpha-blockers, α^2 -receptor agonists, combined alpha- and beta-blockers, vasodilators, and centrally acting compounds. Some of the antihypertensives that were approved first remain in use, including chlorthalidone, a thiazide-like sulfonamide-derived diuretic, which was first approved by the Food and Drug Administration (FDA) in 1960.¹ Chlorthalidone was used heavily over the ensuing 20 years, but hydrochlorothiazide, which was FDA-approved in 1977,² is currently prescribed more often than chlorthalidone for hypertension than chlorthalidone. The question of which agent is better remains unresolved.³

There are clinically important differences between these two drugs.³ Chlorthalidone has a longer half-life (40 to 60 hours) and is 1.5 to 2 times as potent as hydrochlorothiazide (half-life, 6 to 12 hours) and is associated with more potassium loss. Chlorthalidone acts by inhibiting the sodium–chloride symporter in the distal convoluted tubule and also inhibits carbonic anhydrase. Hydrochlorothiazide acts similarly and promotes diuresis and lowers plasma volume, but long-term use is also associated with vasodilation.

Currently, initiating blood-pressure control

with either a thiazide-like or thiazide diuretic is not as common as in previous eras. Yet, seemingly straightforward questions regarding the use of diuretics remain unanswered — among them, whether chlorthalidone, long recommended in guidance documents, is equivalent to thiazide diuretics, especially hydrochlorothiazide. Indeed, trials to answer the question have been limited for various reasons.^{4–6}

This week, results of the Diuretic Comparison Project (DCP),⁷ which was carried out within the Veterans Affairs Healthcare System, appear in the *Journal*.⁸ This comparative-effectiveness, open-label, point-of-care, pragmatic trial pitted chlorthalidone against hydrochlorothiazide with a primary composite end point of nonfatal myocardial infarction, stroke, hospitalization for heart failure, urgent coronary revascularization for unstable angina, and non–cancer-related death.^{7,8}

In this trial, 13,523 patients (mean age, 72.5 years) with hypertension who were receiving hydrochlorothiazide at baseline (25 or 50 mg per day) were randomly assigned to continue hydrochlorothiazide at their baseline dose or to switch to chlorthalidone (12.5 or 25 mg per day). The mean baseline systolic blood pressure was 139 mm Hg in both trial groups (and did not change substantially during the trial). Over a median follow-up of 2.4 years, there was no difference in the primary outcome between the chlorthalidone group (702 patients [10.4%]) and the hydrochlorothiazide group (675 patients [10.0%]) (hazard ratio, 1.04; 95% confidence interval, 0.94 to 1.16). In addition, there were no treatment differences between the two groups in any primary outcome component. Hypokalemia and potassium supple-

ment use were more common in the chlorthalidone group than in the hydrochlorothiazide group.

These results are not surprising and may not change clinical practice. Instead, the importance of the trial lies in its design — a large number of participants and a design that shows that a high-quality pragmatic comparative effectiveness trial can be accomplished in a cost-effective manner within a health-care system with little disruption in patient care.

The limitations of this trial are substantial. For example, the primary outcome event was anticipated to occur in 13.5% of the patients, yet the actual percentage was only 10.4%, which probably affected interpretation. In addition, patients were eligible to participate only if they continued to have hypertension while receiving hydrochlorothiazide (95% of the participants were receiving 25 mg of hydrochlorothiazide and only 5% were receiving 50 mg, which limited comparisons of the dose generally used in practice). Finally, only approximately 13% of the patients were receiving hydrochlorothiazide alone for the treatment of hypertension at baseline.

Given the pragmatic nature of the trial, the trial-dose levels of chlorthalidone were determined by the preenrollment hydrochlorothiazide dose of 25 or 50 mg. Thus, the chlorthalidone doses were chosen to be half those of hydrochlorothiazide on the basis of the potencies of the drugs (i.e., the dose of chlorthalidone was 25 mg if the dose of hydrochlorothiazide at baseline was 50 mg). With the longer half-life of chlorthalidone, once-daily dosing may have favored that agent. Previous trials, such as ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),⁹ which showed benefits on cardiovascular outcomes, used higher target doses (≥ 50 mg of hydrochlorothiazide or ≥ 25 mg of chlorthalidone). Furthermore, 15% of the participants who had been randomly assigned to receive chlorthalidone reverted to hydrochlorothiazide therapy, but only 3.8% of those who had been assigned to continue receiving hydrochlorothiazide switched to chlorthalidone.

All told, will this trial change clinical care? Uniquely, the DCP is the first head-to-head comparison of hydrochlorothiazide and chlorthalidone in a randomized, prospective outcome trial. Without an apparent difference in the hazard ratios for the primary outcome in the two

groups over the median follow-up of 2.4 years, results suggest that chlorthalidone therapy remains a good choice for hypertension despite the secondary observation that hypokalemia was more common with chlorthalidone than with hydrochlorothiazide. Although a subgroup analysis suggested that chlorthalidone was better than hydrochlorothiazide for participants with a history of myocardial infarction or stroke, that result may have been by chance. Currently, clinicians generally prefer using hydrochlorothiazide in their patients; these DCP results suggest similar benefits for the primary outcome with both agents but without any likely impetus for change. Furthermore, combined therapy and polypills may alter therapy beyond the results of this well-done, highly anticipated trial. Thus, its major effect may be as a model for other pragmatic study programs, which are greatly needed.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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