

# PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

## Major CVD outcomes with chlorthalidone vs hydrochlorothiazide: the VA Diuretic Comparison Project (DCP)



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The U.S. Department of Veterans Affairs (VA) Diuretic Comparison Project (DCP) primary results were recently published.<sup>1,2</sup> It has been believed by many for decades that the thiazide-like diuretic chlorthalidone (CTD) is superior to the thiazide diuretic hydrochlorothiazide (HCTZ) in lowering CVD events. In fact, several recent hypertension guidelines have recommended chlorthalidone and/or indapamide over HCTZ when diuretics are chosen in the management of hypertension. This preference was based mostly on observational assessment of the MRFIT trial experience, other major trials, such as HDFP, SHEP, and ALLHAT, showing benefit with CTD, compared with fewer trials showing definitive CVD benefits with HCTZ, and a meta-analysis suggesting a 21% lower CVD event rate with CTD vs HCTZ. In addition, CTD lowers BP more at typically used doses of each, especially over 24 hours, and has a much longer duration of action (2-3 days vs <24 hrs). It also has several theoretical advantages in terms of in vitro pleotropic effects. Despite these potential advantages, for many decades HCTZ has been much more commonly prescribed than CTD, especially in the U.S. However, there had never been a randomized controlled CVD outcome trial directly comparing CDT with HCTZ, since such a

trial using traditional clinical trial methodology was prohibitively costly.

The VA started a program using the usually less expensive pragmatic or point-of-care methodology, and DCP was the first large pragmatic trial in this program. In DCP, we randomly assigned 13,523 adults age  $\geq 65$  years (mean 72 years) who were patients in the VA health system and had been receiving HCTZ at a dose of 25 or 50 mg/d to continue therapy with HCTZ or to switch to CTD at equipotent doses of 12.5 or 25 mg/d, respectively. The primary composite outcome included nonfatal MI, stroke, HF resulting in hospitalization, urgent coronary revascularization for unstable angina, and non-cancer-related death. At baseline, 95% of patients recruited were on HCTZ 25 mg/d, so only 5% were randomized to the higher doses of CTD (25 mg/d) or stayed on HCTZ 50 mg/d. Baseline and follow-up systolic BP in each group was 139 mm Hg. At a median follow-up of 2.4 years, there was little difference in the primary outcome (CTD 10.4%, HCTZ 10.0%; HR, 1.04, 95% CI 0.94-1.16;  $p=0.45$ ). There were no between-group differences in the occurrence of any of the components of the primary outcome, nor in any prespecified subgroups, except in those who had a history of

MI or stroke: patients in the CTD group had a lower incidence of the primary outcome than patients in the HCTZ group (14.3% vs 19.4%; HR, 0.73; 95% CI 0.57-0.94). The incidence of hypokalemia was slightly higher in the CTD group (6.0% vs. 4.4%).

Since DCP was a pragmatic trial with no local coordinators or investigators, we focused on patients whose doses of HCTZ could be changed to equipotent doses of CTD. Overwhelmingly, when HCTZ was chosen in practice, PCPs used/use 12.5 or 25 mg of HCTZ to treat hypertension. Thus, we included those on 25 or 50 mg of HCTZ in order to convert to somewhat comparable doses of chlorthalidone (12.5 or 25 mg). Therefore, DCP is primarily a comparison of the 95% of participants on HCTZ 25 mg/d vs CTD 12.5 mg/d. These are lower doses than the target doses of these drugs used in the best outcome trials with these agents. For example, 70-80% of participants in SHEP and ALLHAT were on CTD 25 mg/d. Therefore, DCP essentially shows 25 mg of HCTZ has similar outcomes to 12.5 mg of CTD, but I believe the results should not be extrapolated to 12.5 mg of HCTZ (a lower dose than was studied in DCP, but frequently prescribed in practice), or higher doses of each. We plan to look at the 5% subgroup who were on 50 mg of HCTZ vs 25 mg of CTD, but this is too small a subgroup to provide much information and it was not prespecified.

DCP gives us confidence that HCTZ and CTD have similar CVD outcomes over several years at the HCTZ 25 mg and CTD 12.5 mg doses, but we can't extrapolate to other doses. In my own practice, when using HCTZ, I try to use a minimum dose of 25 mg. However, if more BP-lowering is needed, especially if the patient is on multidrug therapy, I will often change the HCTZ 25 mg/d to CTD 25 mg/d, primarily for greater BP-lowering efficacy. One limitation is the few single-pill combination medications available with CTD. HCTZ 50 mg/d is another option, but it has been difficult to get physicians and other providers to keep patients on 50 mg/d, since they have often been taught to limit HCTZ to 25 mg/d, despite guidelines recommending a maximum dose of 50 mg/d.

The better outcomes in the MI/stroke subgroup might lead me to especially use CTD preferentially in such patients, but we must admit that the results must be considered hypothesis-generating and need to be confirmed to be given a strong recommendation.

In conclusion, DCP demonstrates both the considerable strengths, but also the limitations, of conducting pragmatic clinical trials. There is no question many more trials can be conducted less expensively with this methodology than depending on traditional research site-based randomized trials. However, there are many trial questions for which pragmatic trials are not likely to be appropriate. DCP addressed an important question that likely would not have been funded otherwise, and at least strongly suggests these two diuretics in these lower doses have similar CVD outcomes.

## References

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**Disclosure:** The opinions expressed in this article are those of the author and do not necessarily reflect the position of the U.S. federal government, the Department of Veterans Affairs, or the DCP Study Group.