

# 'Burden-free' study method finds two blood pressure drugs equally effective

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A large Veterans Affairs (VA) clinical trial found that the blood pressure drug chlorthalidone (CTD) was not superior to hydrochlorothiazide (HCTZ) for the prevention of cardiovascular disease or non-cancer

death.

Both drugs are in a class of medications called thiazide diuretics, commonly known as water pills. They are used to help the body rid itself of excess fluid, which can lower blood pressure.

The study was a first-of-its-kind pragmatic trial that was embedded in usual clinical care. As part of VA's clinical trials enterprise, it allowed participation from across the country with no additional staff. Also, all study procedures were done as part of routine clinical care. There was no additional burden placed on Veterans who participated in the study—including no extra visits.

"Because of the number of Veterans VA cares for and our systemwide electronic medical record, we were able to embed this massive clinical trial within day-to-day care without any additional burden to the thousands of Veterans who volunteered for this study," said Rachel Ramoni, VA's chief research and development officer. "The result is important evidence of how these widely-used medications work in the real world."

Current clinical guidelines say that CTD may be more effective than HCTZ to [lower blood pressure](#), but this recommendation is unsupported by direct evidence. Both medications have been used for more than 50 years and each is considered a first-line treatment for hypertension.

"In 2020, Medicare reported that approximately 1.5 million people were prescribed CTD compared to 11.5 million prescribed HCTZ, despite guideline recommendations," said principal investigator Dr. Areef Ishani, director of the Minneapolis VA Health Care System's Primary Care and Specialty Care Integrated Care Community. "This discrepancy between clinical guidelines and [real-world](#) usage is possibly related to the belief that CTD has a greater risk of adverse effects without clear

evidence for differences in cardiovascular outcomes."

The Diuretic Comparison Project (CSP 597) is a large pragmatic clinical trial that was conducted at 537 VA medical centers and community clinics in the U.S. The trial enrolled more than 4,000 providers and 13,500 Veterans with high blood pressure who were taking HCTZ at baseline. Study participants were randomized to stay on their current dose of HCTZ or take an equivalent dose of CTD. Ninety-five percent of study participants were taking a lower dose of HCTZ, so the main study comparison was 12.5 mg CTD to 25 mg HCTZ.

The team found no difference between the two drugs, at these lower doses, for the prevention of cardiovascular disease or non-cancer death, which included [heart attack](#), stroke, heart failure, or lack of blood flow requiring medical intervention. There was a slight increase in the risk for low potassium in the CTD group, which quickly resolved with potassium supplements.

"We were able to compare two commonly prescribed [generic drugs](#) using a low-cost methodology," said Ishani. "This trial has shown that large, embedded trials are operationally feasible. They can be incorporated into the clinical workflow of providers by leveraging the electronic health record and other existing infrastructure."

The findings are published in the *New England Journal of Medicine*.

**More information:** Areef Ishani et al, Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events, *New England Journal of Medicine* (2022). [DOI: 10.1056/NEJMoa2212270](https://doi.org/10.1056/NEJMoa2212270)

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