Recommended diuretic causes more side effects than similar hypertension drug

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Chlorthalidone, the guideline-recommended diuretic for lowering blood pressure, causes more serious side effects than hydrochlorothiazide, a similarly effective diuretic, according to a new study led by researchers at Columbia University Irving Medical Center. The findings, published in *JAMA Internal Medicine*, contrast with current treatment guidelines

recommending chlorthalidone over hydrochlorothiazide.

The researchers found that patients taking chlorthalidone had nearly three times the risk of developing dangerously low levels of potassium and a greater risk of other electrolyte imbalances and kidney problems compared with those taking hydrochlorothiazide. Information from the largest individual database studied by the team revealed that 6.3% of patients treated with chlorthalidone experienced hypokalemia (low blood potassium), compared with 1.9% of patients who were treated with hydrochlorothiazide.

Hypokalemia rates remained higher for patients taking chlorthalidone even when given at a lower dose than hydrochlorothiazide.

"Doctors prescribing chlorthalidone should monitor for certain side effects in their patients," says George Hripcsak, MD, MS, chair and Vivian Beaumont Allen Professor of Biomedical Informatics at Columbia University Vagelos College of Physicians and Surgeons and lead author of the study.

The study, which looked at 17 years of data on more than 730,000 individuals treated for hypertension, is the largest multisite analysis directly comparing the two antihypertensive drugs in the general patient population.

The results were generated by the Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND) Hypertension study, a method for analyzing data in millions of electronic health records around the world developed by the Observational Health Data Sciences and Informatics (OHDSI) network, which has a central coordinating center at Columbia University.

An earlier LEGEND Hypertension study, published in *The Lancet*, found

that thiazide diuretics were more effective and caused fewer side effects than ACE inhibitors when used as first-line antihypertensive drugs.

In the current paper, the researchers found that chlorthalidone and hydrochlorothiazide were similarly effective in preventing heart attack, hospitalization for heart failure, and stroke. However, patients treated with chlorthalidone had a significantly higher risk of side effects, including hypokalemia, which can lead to abnormal heart rhythms; hyponatremia (low sodium), which can cause confusion; kidney failure; and type 2 diabetes.

"The difference in the occurrence of side effects was striking," says Hripcsak. "Hypokalemia, hyponatremia, chronic and acute kidney problems, along with other electrolyte imbalances, are all potentially dangerous side effects."

The new study is not the first to find side effects associated with chlorthalidone. A previous observational study found that the drug was associated with more electrolyte imbalances than hydrochlorothiazide.

Nearly 95% of patients in the study were first treated with hydrochlorothiazide, which was the preferred diuretic for treating hypertension throughout most of the study period (2001-2018). However, in 2017, the American College of Cardiology and American Heart Association issued new guidelines favoring chorothalidone, based on the drug's longer half-life and indirect evidence that it may be more effective in reducing cardiovascular risk.

"Until we have more studies directly comparing the two diuretics, we don't really know whether the risk of the side effects seen in observational studies outweighs the potential cardiovascular benefits," says Hripcsak, who notes that the VA Office of Research and Development is now conducting a randomized clinical trial to help settle

the debate.

The research team performed several sensitivity analyses (time at risk, blood pressure, dose), as well as other best practices developed within the OHDSI network (including propensity scoring and the use of negative controls) to ensure a lack of bias in the results. These best practices are used throughout the LEGEND project, which OHDSI collaborators believe will continue to impact critical decisions in health care. These analyses ensure that the compared groups are similar in severity of illness, comorbidities, baseline blood pressures, age, sex, and all other measurable variables.

"LEGEND is a novel approach that could transform the way we use real-world evidence in healthcare," says co-author Patrick Ryan, Ph.D., adjunct assistant professor of biomedical informatics at Columbia. "Rather than inefficiently conducting bespoke analyses one-question-one-method-one-database-at-a-time, leaving us vulnerable to various threats to scientific validity, LEGEND provides a systematic framework that can reproducibly generate evidence by applying advanced analytics across a network of disparate databases for a wide array of exposures and outcomes."

"Not only does LEGEND offer a path to scale to the real needs of the health care community," Ryan added, "it also provides the complementary diagnostics to help us understand how much we can trust the evidence we've produced."

The paper is titled "Real-World Evidence on the Effectiveness and Safety of Chlorthalidone and Hydrochlorothiazide."

Provided by Columbia University Irving Medical Center