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Major cardiovascular study of gout patients has unexpected finding

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A large study of cardiovascular events in gout patients taking one of two medications to prevent excess build-up of uric acid has found that one of the drugs, febuxostat, increased the risk of death for those with heart disease, compared to study participants taking allopurinol.

Yet the two drugs were comparable with respect to a combination of non-fatal heart attack, non-fatal stroke, urgent surgery to treat angina, and death due to cardiovascular causes.

The findings of the CARES trial were first released at the American College of Cardiology's 67th Annual Scientific Session on March 12, and published in the *New England Journal of Medicine* by UConn School of Medicine's Dr. William B. White, principal investigator of the trial and the study's lead author.

The mortality findings with regard to febuxostat were "entirely unexpected," says White, professor of medicine at the Calhoun Cardiology Center of UConn School of Medicine, who in addition to helping with the design of the trial has served as chair of the cardiovascular events committee for the past seven years. "The results were consistent across many subgroups; there was no evidence of a relationship with age, gender, race or ethnicity, history of cardiovascular disease, or duration or severity of the gout."

Previously, no cardiovascular clinical trial has ever demonstrated an increased risk of cardiovascular death without also showing a heightened

risk of other cardiovascular outcomes such as non-fatal heart attack and stroke.

"A very extensive pre-clinical evaluation of febuxostat showed no explanation for the excess in sudden cardiac deaths," he says, adding that there was no difference between patients taking either febuxostat or allopurinol with regard to any of the non-fatal events, including hospitalizations for heart failure, arrhythmias, pulmonary embolism, myocardial infarction, or stroke.

More than 8 million Americans suffer from gout, a complex form of arthritis that occurs when uric acid crystals form and cause intense joint pain in the big toe or other joints. Elevated uric acid levels have been associated with cardiovascular problems, including high blood pressure, angina, and heart attack.

The key to preventing gout attacks is a healthy diet and lifestyle modifications, but many patients with gout also need a type of medication known as xanthine oxidase inhibitors to prevent the excess build-up of uric acid in the body that leads to gout. The two medications approved for the treatment of elevated uric acid levels in patients with gout are allopurinol, approved in 1966, and febuxostat, approved in 2009.

Febuxostat was developed in an effort to offer a safer alternative to the mainstay therapy of allopurinol, which can cause kidney problems and is associated with rare but severe allergic reactions in some – particularly African-American – gout patients.

While febuxostat was in development, however, it showed a modest increase in non-fatal cardiovascular events compared to allopurinol, leading the FDA to require a major long-term cardiovascular event study to be conducted as a condition of approving the drug.

The seven-year CARES trial, which began in 2010, enrolled more than 6,000 gout patients at 320 centers in North America. All study participants had gout as well as established cardiovascular disease, such as a previous heart attack, stroke, hospitalization for chest pain (unstable angina), peripheral arterial disease, or both diabetes and small vessel disease. Half of the patients were randomly assigned to receive febuxostat and half received allopurinol; neither the patients nor their doctors knew which drug they had received.

Participants continued taking their assigned medication as researchers tracked their health outcomes for more than 2.5 years on average, and as long as 6.5 years in some patients.

A high proportion of patients (45 percent) stopped participating in the trial. In those who stopped taking febuxostat, the elevated risk of death decreased. However, little else is known about these patients, including whether they resumed taking allopurinol or febuxostat by prescription.

The research team will continue to explore the clinical trial's database for insights on the optimal treatment for gout, especially for those who have both cardiovascular disease and chronic kidney disease. In the approximately 50 percent of study patients patients with a history of chronic kidney disease, mortality was not significantly different among those taking febuxostat and those taking allopurinol.

More information: William B. White et al, Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout, *New England Journal of Medicine* (2018). DOI: 10.1056/NEJMoa1710895 , dx.doi.org/10.1056/NEJMoa1710895

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