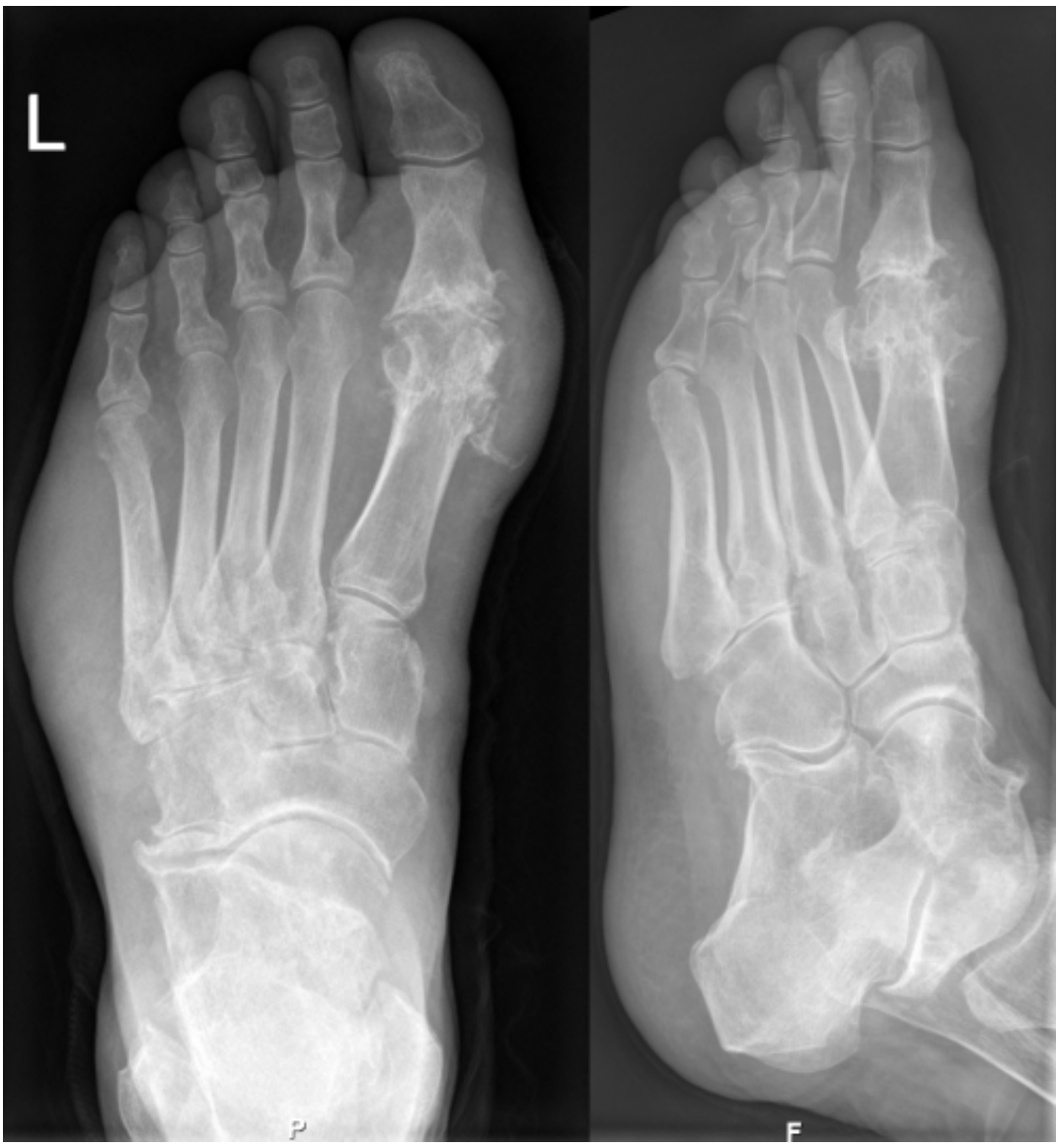
FAST study finds no increased risk of cardiovascular events with febuxostat as compared with allopurinol for gout

November 10 2020



Gout in X-ray of left foot. Credit: Hellerhoff/Wikipedia.

A major new study examining the relative safety of medicines for the treatment of gout will be presented at the American College of Rheumatology Convergence conference and will be published in *The Lancet.*

The FAST Study finds no increased risk of cardiovascular events with febuxostat as compared with allopurinol.

Led by investigators at the Universities of Dundee, Glasgow and Edinburgh in collaboration with others in Aberdeen, Highland, and Nottingham UK centers and researchers at the University of Southern Denmark and Sweden, the Febuxostat versus Allopurinol Streamlined Trial (FAST) has compared the cardiovascular safety of two gout medicines—allopurinol and febuxostat—in over 6,000 patients with gout between 2011 and 2019.

FAST found that cardiovascular events such as heart attacks strokes and particularly cardiovascular causes of death and all-cause deaths were not different between the older medicine called allopurinol and the newer medicine called febuxostat.

"FAST should allay any fears that doctors treating gout may have had about using febuxostat," said chief investigator Prof Tom MacDonald.

The FAST study followed gout patients aged 60 or over who all had some risks for cardiovascular disease for an average of 4 years.

"A strong feature of the FAST trial was the ability to track patient outcomes using national electronic records of hospitalizations and deaths" said the lead author Professor Isla Mackenzie.

This process, known as record-linkage, is possible in some European countries and greatly increases confidence that all events are captured.

Professor Ian Ford at the Robertson Centre for Biostatistics at Glasgow University, who pioneered the use of record-linkage in clinical trials said; "The good thing about record-linkage is that it captures things patients may have forgotten about. Also, patient who want to stop being contacted in trials are often very happy to be followed up by record-linkage so investigators can still find out what happened to them."

Emeritus professor George Nuki and professor Stuart Ralston, from the University of Edinburgh, who are rheumatologists and authorities in the management of gout said, "We hope that the FAST trial results will help to reassure patients with gout and doctors who treat them that febuxostat is as safe as allopurinol in patients with increased risks of cardiovascular disease. Febuxostat isn't currently recommended in patients with pre-existing cardiovascular disease because a previous study suggested that the risk of cardiovascular deaths may be increased. The FAST study has reassuringly shown that there was no difference in cardiovascular events or mortality between the two treatments in patients with cardiovascular risk factors or established cardiovascular disease. We hope that this new information will also be useful to regulatory agencies in re-evaluating the role of febuxostat in the management of gout'".

Allopurinol has been the mainstay treatment for gout patients since about 1966. Whilst it is generally well tolerated it does have some side effects and it is harder to use in patients with kidney disease.

Other trial experts in Glasgow, Aberdeen, Nottingham, Denmark and Sweden all contributed to the success of FAST.

The FAST trial was requested by the European Medicines Agency and the outcome has been keenly awaited by doctors who treat gout,

particularly following the puzzling results of a similar-sized trial done in the U.S., Canada and Mexico called The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial that reported in 2018.

Like FAST, CARES was a trial performed to check that the newer treatment, febuxostat, was not worse than the standard treatment, allopurinol, in terms of associations with serious cardiovascular events including heart attacks, strokes and cardiovascular deaths. When these events were added together in CARES, they found that febuxostat and allopurinol were similar, but they found more cardiovascular deaths with febuxostat when this was looked at alone. They then went on to do an unplanned analysis of all-cause deaths and found that these were also increased. Interestingly, there was no difference in cardiovascular or all deaths between the two medications whilst patients were taking the medication, but the differences got bigger after patients had stopped treatment.

One of the big problems with CARES was that 57% of patients stopped taking their allocated medication throughout the trial and 47% withdrew from the trial and could not thereafter be contacted. A private investigation company called Omnitrace was employed to find out how many of those who withdrew had died and when this was done the deaths on each medication was similar.

Nevertheless, medicines regulators issued warnings that febuxostat could cause more deaths than allopurinol.

The CARES result could have resulted in the FAST trial being stopped but an independent committee set up to monitor the safety of FAST reported confidentially to trial regulators who allowed FAST to continue.

This scene setting is important as the FAST study again found febuxostat

and allopurinol to be similar for heart attacks, strokes and cardiovascular deaths together but there was no hint of increased cardiovascular or all-cause death in FAST.

More information: Isla S Mackenzie et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial, *The Lancet* (2020). DOI: 10.1016/S0140-6736(20)32234-0

Provided by University of Glasgow