Medical Xpress

# Digoxin increases the risk of death in patients with heart problems

May 4 2015

There is conflicting evidence about whether digoxin, a drug that has been used worldwide for centuries to treat heart disease, might contribute to an increase in deaths in patients with atrial fibrillation (AF) or congestive heart failure (CHF). Now, the largest review of all the evidence to date shows that it is associated with an increased risk of death in these patients, particularly in those being treated for AF.

In a study published online today (Tuesday) in the *European Heart Journal*, researchers from the J.W. Goethe University in Frankfurt, Germany, conducted a systematic review and meta-analysis of all studies published in peer-reviewed journals between 1993-2014 that looked at the effects of digoxin on death from any cause in AF and CHF patients.

They identified 19 relevant studies that included a total of 326,426 patients (235,047 AF and 91,379 CHF patients). They found that among patients who were treated with digoxin, there was an overall 21% increased risk of death from any cause compared to patients who were not receiving this treatment. When they looked at the group of AF patients and the group of CHF patients separately, digoxin was associated with a 29% and 14% increased risk of death from any cause respectively, when compared to patients not receiving the drug.

Digoxin is extracted from the foxglove plant (digitalis) and it helps the heart beat more strongly and with a more regular rhythm. It is commonly used in patients with atrial fibrillation (an irregular heartbeat) and also in patients with heart failure (congestive heart failure is when the heart's

function as a pump is impaired). However, it can be difficult to use successfully as there is a narrow dose range at which it is effective and beyond which it can be dangerous. Regular blood tests are required to test the levels of digoxin in the blood and high levels have been correlated with an increased death rate in patients.

Currently, its use is recommended in guidelines from the USA and from the European Society of Cardiology for patients with heart failure and problems with control of the heart's rhythm. However, the authors of this study write: "These recommendations reflect the highly unsatisfactory data basis on which to judge the supposed benefits of digoxin." They call for randomised controlled trials of digoxin and write that "until such proper randomized controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF".

Stefan Hohnloser, Professor of Cardiology at the university, who led the study, said: "Definite evidence can only come from results of randomised controlled trials. However, next to these, carefully performed meta-analyses provide the best clinical guidance and serve to generate hypotheses that need to be tested prospectively. Our analysis, together with evidence from other studies, all point in the same direction: there is harm associated with the use of digoxin."

Prof Hohnloser said that there has only been one prospective randomised controlled trial of digoxin, which was carried out in 6,800 CHF patients, and none in AF patients. "We need randomised controlled trials to examine the use of digoxin for both conditions and that test the drug versus a placebo or another, active treatment.

"Digoxin has been used for decades and even now it is used in approximately one in three AF patients, yet we have been able to do this meta-analysis only now. My personal feeling is that the time of digoxin -

particularly as a heart rate-controlling drug in AF - is over. But this needs to be tested in appropriately designed studies."

Digoxin's effect on the heart's rhythm and pumping ability may be implicated in the mechanisms that also can lead to death, particularly if levels of the drug in the blood go above the recognised safe limits. The researchers say that this can be made worse by interactions with other drugs, and they point to a recent trial of dronedarone in AF patients that had to be stopped prematurely because of an excess number of deaths among patients receiving dronedarone. Analysis of the results showed that 11 out of 13 deaths among patients in the dronedarone arm of the trial occurred in those who had received digoxin at the same time. "The most likely explanation for this is the drug-drug interaction between dronedarone and digoxin at the level of the P-glycoprotein transport system, which resulted in significantly elevated serum digoxin levels in patients who died," they write in their EHJ paper.

**More information:** "Digoxin-associated mortality: a systematic review and meta-analysis of the literature", by Mate Vamos, Julia Erath, and Stefan H. Hohnloser et al. *European Heart Journal*. DOI: 10.1093/eurheartj/ehv143

Provided by European Society of Cardiology