New study finds digoxin safe despite recent reports

April 16 2013

A study published today in the *European Heart Journal* found no evidence that digoxin increases mortality in patients with atrial fibrillation (AF), the opposite of results just published by another group in the same journal analyzing the same data.

Older patients with AF also often have heart failure, and digoxin is approved to treat both conditions. AF is the most common kind of cardiac arrhythmia, an electrical malfunction that throws off the heart's rhythm and pumping rate. It may cause no symptoms or cause some patients to faint, but is seldom fatal. Heart failure, a gradual weakening of the heart's pumping strength, contributes to 280,000 U.S. deaths each year.

Both the earlier study that found digoxin increases mortality in AF and the study published today were re-analyses of data first collected as part of a clinical trial called Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) in 2002. The recent study that found digoxin increases mortality used an approach called "time-varying treatment," where patients who continued to receive digoxin over 3.4 years as part of the follow-up to AFFIRM were compared to those who did not.

According to current study, this "time-varying treatment" technique produced misleading results. By analyzing data from sicker patients who required continued digoxin treatment over the long term, it inadvertently introduced bias in its analysis of digoxin-related mortality.

"Digoxin is recommended by major national guidelines for use in heart failure and atrial fibrillation," said Mihai Gheorghiade, M.D., lead author of the study and professor of medicine and of surgery at Northwestern University Feinberg School of Medicine. "It is an inexpensive drug that is generally well tolerated at low doses, and there is no reason to question its usefulness or reassess its safety. We need to remember that although digoxin has been used for over two centuries, it was approved by the FDA in the late 1999s under its strict guidelines for new drug approval based on its safety and efficacy data from multiple randomized clinical trials. So, we are not talking about a new or unsafe drug when we talk about digoxin."

To test the safety of digoxin, the current authors used AFFIRM patient data to assemble a group found to be similar based on 59 characteristics, including age, sex, race, other conditions beside AF (including heart failure) and other medications. Researchers then divided this pool of similar patients into two groups, one that had received digoxin therapy and a second that had not.

The study team found that during the 3.4 years of follow-up, 14 percent of patients receiving digoxin and 13 percent of patients not getting it died. This difference is well within the study's margin of error and, in practical terms, represents no increase in mortality associated with digoxin (hazard ratio, 1.06; 95% confidence interval {CI}, 0.83.37; P=0.640). Among matched patients, digoxin was also not associated with all-cause hospitalization (hazard ratio, 0.96; 95% CI, 0.85.09; P=0.510) or arrhythmias (hazard ratio, 0.90; 95% CI, 0.37.23; P=0.827).

"Heart failure is the only other condition for which digoxin is used, so many of the patients who continued digoxin in the AF clinical trial also had heart failure," said Ali Ahmed, M.D., professor in the divisions of Gerontology, Geriatrics, & Palliative Care and Cardiovascular Disease within the School of Medicine at the University of Alabama at

Birmingham (UAB), and the new study's senior author. "You cannot conclude that a drug kills more people without considering whether or not the drug is prescribed for a deadly condition."

The authors conducted the study out of concern that older patients might be deprived of digoxin, which can be helpful in treating AF. They worried that the perception that digoxin increases mortality in AF might gain traction and extend to the treatment of heart failure.

Ahmed recently demonstrated that digoxin could reduce by 34 percent the chances that heart failure patients will be admitted to the hospital within 30 days of first taking it. Preventing frequent admissions is national priority, as the Centers for Medicare and Medicaid Services (CMS) penalized thousands of hospitals in 2012 for above average 30-day readmission rates in patients with pneumonia, heart attack or heart failure.

One in five Medicare recipients is readmitted within 30 days at an annual national cost of $17 billion. Heart failure is the most common culprit. Digoxin is known to reduce acute heart failure symptoms like shortness of breath, which can send people racing back to emergency rooms.

The current debate over the digoxin comes at the end of a decline in use since it failed to lower mortality in an original clinical trial. Research in recent years, however, has shown that digoxin is the only drug in its class (positive inotropes) that does not increase mortality at the traditional dose, and that it may block neurohormone systems like beta blockers or ACE inhibitors. This may explain study results suggesting that low-dose digoxin not only reduces the risk of hospitalization, but may also reduce the risk of death.

In a final note, the current study authors said the scientific community

has for years been urging sponsors of large clinical trials for more transparency and data sharing. The National Heart, Lung and Blood Institute (NHLBI) has been a leader in this regard, establishing the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), which has made available the public-use copy of the AFFIRM data that enabled the study authors to challenge the conclusions of the previous study.

Provided by Northwestern University