# Acid reflux drug may cause heart disease

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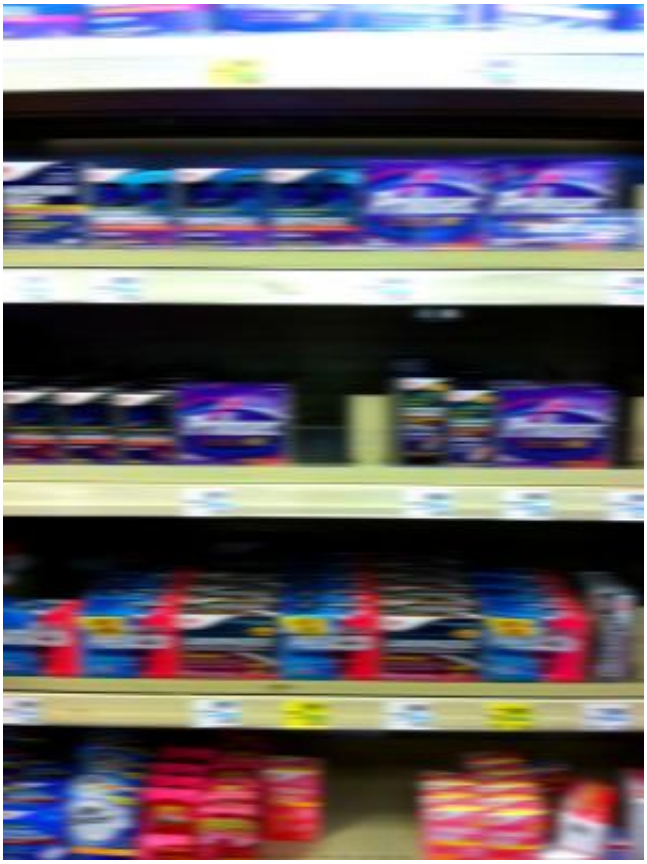

Proton pump inhibitors are the third-most used drug in the U.S.

(Medical Xpress)—Drugs that help millions of people cope with acid reflux may also cause cardiovascular disease, report scientists from Houston Methodist Hospital and two other institutions in an upcoming issue of *Circulation*. It is the first time researchers have shown how proton pump inhibitors, or PPIs, might cause cardiovascular problems.

In human tissue and mouse models, the researchers found PPIs caused the constriction of blood vessels. If taken regularly, PPIs could lead to a variety of cardiovascular problems over time, including hypertension and a weakened heart. In the paper, the scientists call for a broad, large-scale study to determine whether PPIs are dangerous.

"The surprising effect that PPIs may impair vascular health needs further investigation," said John Cooke, M.D., Ph.D., the study's principal investigator. "Our work is consistent with previous reports that PPIs may increase the risk of a second heart attack in people that have been hospitalized with an acute coronary syndrome. Patients taking PPIs may wish to speak to their doctors about switching to another drug to protect their stomachs, if they are at risk for a heart attack."

Commonly used proton pump inhibitors in the United States are lansoprazole and omeprazole, and these drugs are purchasable over the counter as brands or generics. The FDA estimates about 1 in 14 Americans has used them. In 2009, PPIs were the third-most taken type of drug in the U.S., accounting for $13 billion in sales. PPIs are used to treat a wide range of disorders, including gastroesophageal reflux disease, or GERD, infection by the ulcer-causing Helicobacter pylori, Zollinger-Ellison syndrome, and Barrett's esophagus.

Recent studies of proton pump inhibitors use by people who've already experienced severe cardiovascular events have raised concern about the anti-reflux drugs, at least for this subgroup of patients, said Cooke, chair of the Department of Cardiovascular Sciences and director of the Center for Cardiovascular Regeneration at Houston Methodist DeBakey Heart & Vascular Center.

PPIs are initially inert. After oral consumption, they are activated by specialized cells in the stomach. Once active, the molecules suppress the movement of protons into the intestine, which reduces the amount of

acid present there and in the stomach.

In mouse models and cultures of human endothelial cells, Cooke and lead author Yohannes Ghebremariam, Ph.D., found that PPIs suppressed the enzyme DDAH, dimethylarginine dimethylaminohydrolase. That caused an increase in the blood levels of ADMA (asymmetric dimethylarginine), an important chemical messenger. They found ADMA in turn suppressed the production of another chemical messenger, nitric oxide, or NO, proven by 1998 Nobel Prize winners Furchgott, Ignarro, and Murad to impact cardiovascular function. Quantitative studies in mouse models showed animals fed PPIs were more likely than controls to have tense vascular tissue.

"We found that PPIs interfere with the ability of blood vessels to relax," said Ghebremariam, a Houston Methodist molecular biologist. "PPIs have this adverse effect by reducing the ability of human blood vessels to generate nitric oxide. Nitric oxide generated by the lining of the vessel is known to relax, and to protect, arteries and veins."

The researchers found PPIs led to an approximately 25 percent increase in ADMA in mouse and tissue cultures, and reduced the ability of mouse blood vessels to relax by over 30 percent on average.

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