Some heartburn drugs may boost risk of heart attack, study finds

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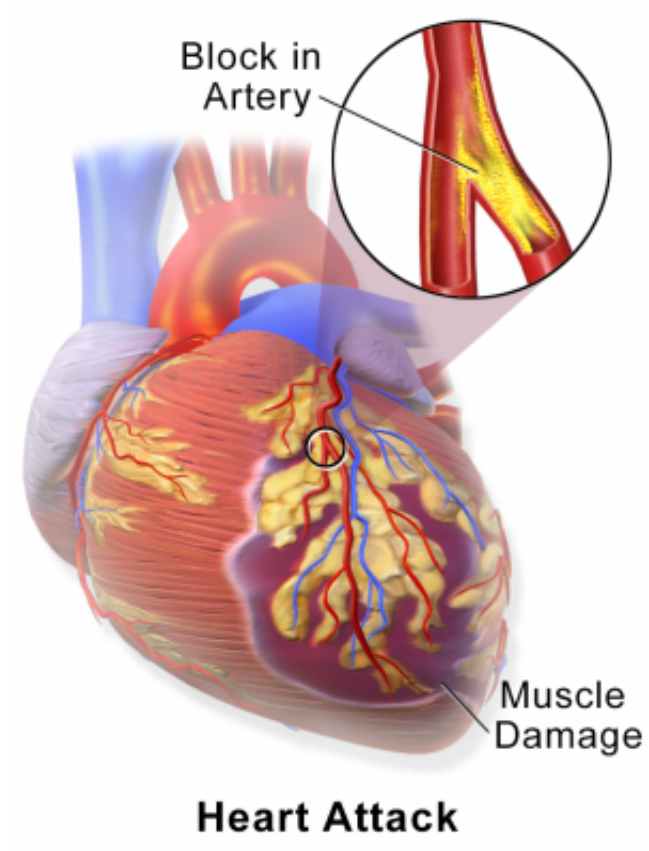


Myocardial Infarction or Heart Attack. Credit: Blausen Medical Communications/Wikipedia/CC-A 3.0

A large data-mining study carried out by investigators at the Stanford University School of Medicine has linked a popular class of heartburn drugs to an elevated risk of heart attack.

Proton-pump inhibitors, or PPIs, are among the world's most widely prescribed drugs, with $14 billion in annual sales. They are effective at lowering the acidity of the stomach, in turn preventing heartburn, a burning sensation in the chest that occurs when stomach acid rises up into the esophagus. In any given year, more than 20 million Americans—about one in every 14—use PPIs such as omeprazole (trade name Prilosec) for heartburn, also known as acid reflux or gastroesophageal reflux disease.

'The association we found with PPI use and increased chances of a subsequent heart attack doesn't in and of itself prove causation,' said the study's lead author, Nigam Shah, Ph.D., MBBS, an assistant professor of biomedical informatics and assistant director of the Stanford Center for Biomedical Informatics Research. But, he said, the study combed through electronic health records of nearly three million people and crunched trillions of pieces of medical data, raising concerns that should be taken seriously, especially now that PPIs are available over the counter.

More than 100 million prescriptions are filled every year in the United States for PPIs, a class of drugs long considered benign except for people concurrently taking the blood thinner clopidogrel (Plavix). However, the new study upends this view: it indicates that PPI use was associated with a roughly 20 percent increase in the rate of subsequent heart-attack risk among all adult PPI users, even when excluding those also taking clopidogrel.

A paper describing the findings will be published June 10 in *PLOS ONE*.

'These drugs may not be as safe as we think,' said Nicholas Leeper, M.D., the study's senior author and an assistant professor of vascular surgery and of cardiovascular medicine.

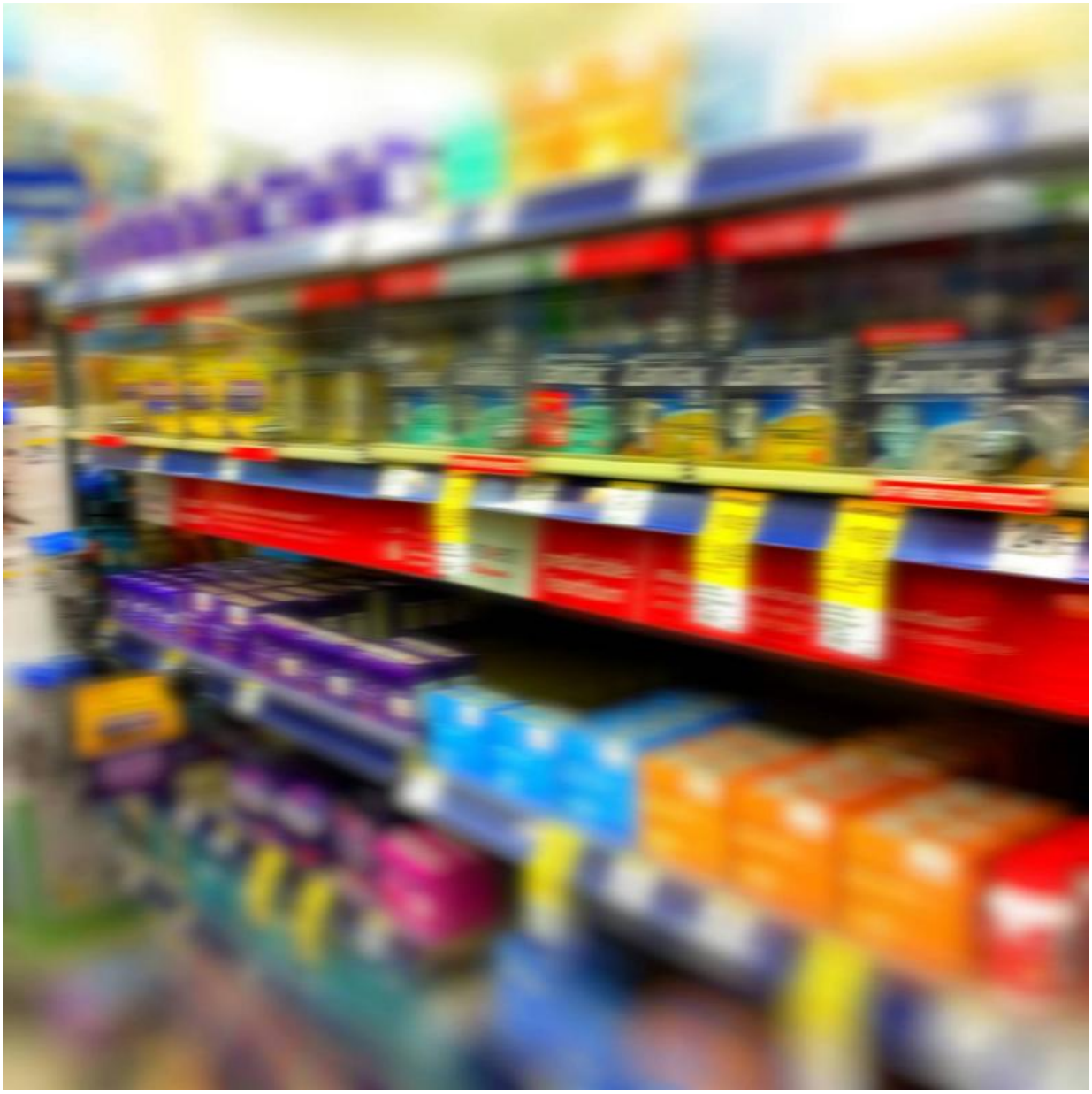
No elevated risk linked to H2 blockers

Interestingly, another commonly prescribed heartburn drug class called H2 blockers showed no association with elevated heart-attack risk. H2 blockers, which have been around longer than PPIs, are reasonably effective against heartburn and are the second-largest-selling class of drugs used to treat it.

The study's findings lend support to an explanation for an untoward effect of PPIs on heart-disease risk proposed by Stanford scientists a few years ago. Research done then showed that PPIs impede the production of an important substance, nitric oxide, in the endothelial cells that line all of the nearly 100,000 miles of blood vessels in an average adult's body.

Shah has pioneered the use of data-mining techniques to capture sometimes elusive but medically important phenomena. His methodology makes it possible, for example, to scour huge numbers of electronic health records—not only their structured portions, but also free-form notes entered by attending clinicians—for hints of an association between use of a drug or drug combination and unanticipated health outcomes, whether good or bad.

The work is an example of Stanford Medicine's Biomedical Data Science Initiative, which strives to make powerful transformations in human health and scientific discovery by fostering innovative collaborations among medical researchers, computer scientists, statisticians and physicians.



Recent studies show increased risk of heart attack for people who use proton pump inhibitors to control GERD and other excess-acid issues. Credit: Houston Methodist Hospital

At Stanford, all clinical notes dating back to 1994 have been entered into a database known by its acronym, STRIDE. Shah, Leeper, and their

colleagues sifted through data on 19 million encounters between Stanford physicians and 1.8 million patients and identified more than 70,000 who were age 18 or older and had been diagnosed with heartburn. To this number, the scientists added more than 227,000 adult heartburn patients culled from another privately held health-record database containing data on 1.1 million patients. They compared subsequent heart-attack frequencies of those who either had been prescribed PPIs, or said they were using them, with those of heartburn sufferers who were not using PPIs. The researchers saw a 16-21 percent increase in the rate of heart attacks, depending on which statistical approach they used, among members of the PPI group. This higher heart-attack frequency could be seen even in otherwise healthy PPI users under age 45.

Other bad outcomes

To further validate the association, they turned to an ongoing prospective, longitudinal study of 1,500 patients with chest pain, shortness of breath or abnormal stress-test results, conducted by Stanford in collaboration with Mount Sinai Medical Center in New York City. As a routine part of this study, patients are asked whether they are using PPIs.

To ensure that they would spot adverse drug effects if there were any, Shah, Leeper and their colleagues looked for not only heart attacks but cardiac arrest, stroke and other bad outcomes. They found that in this study population, PPI use more than doubled the risk of a patient's suffering a subsequent major adverse cardiovascular event.

Several hypotheses have been advanced to explain the increased cardiovascular risk attributable to PPI use among clopidogrel users, who in the past were often placed on PPIs because clopidogrel can increase gastric distress. But those hypotheses haven't held up well under scrutiny.

A new hypothesis was born in 2013, when a study in Circulation by John Cooke, M.D., Ph.D., then a professor of cardiovascular medicine at Stanford, and his colleagues, including Yohannes Ghebremariam, Ph.D., implicated PPIs in igniting a cascade of biochemical reactions that led to diminished nitric oxide levels in endothelial tissue. (Cooke and Ghebremariam, both now at Houston Methodist Research Center, are co-authors of the new study.)

'That study implied that PPIs' cardiovascular-risk effect had nothing to do with clopidogrel but was, instead, a direct effect on blood vessels themselves,' Leeper said. 'That could mean everybody on PPIs, not just people with coronary disease, is at increased risk from these drugs.'

Those findings inspired Shah and Leeper to undertake the new study. 'We looked at cardiovascular risk for different PPI drugs,' said Shah. 'And we found that the degree to which the use of any particular PPI was associated with a subsequent heart attack mirrors the degree to which the drug inhibits nitric oxide in the vasculature.'

A small pilot trial led by Leeper and recently published in *Vascular Medicine* showed a trend between PPI use and increases in a chemical known to impair the function of an enzyme that produces nitric oxide. But the study population of 21 subjects was too small to show a conclusive link.

'This association needs to be tested in a large, prospective, randomized trial,' said Leeper. 'The truth will come out when we randomize several hundred people, give half of them PPIs and put the other half on H2 blockers, and see what happens.'

Neither Shah nor Leeper recommends that people now on PPIs simply stop taking them without first talking to their doctors about alternatives.

Meanwhile, they both said, the study results should give clinicians and patients pause when deciding whether to take these medications—particularly because they're so often taken for far longer time periods than the label recommends.

More information: "Proton pump inhibitor usage and the risk of myocardial infarction in the general population," by Nigam H. Shah et al, *PLOS ONE*

Provided by Stanford University Medical Center