# The Verdict: Proton Pump Inhibitors have been found guilty of causing death. Any objections?

*Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017; 7: e015735.*

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Proton pump inhibitors (PPIs) have changed the clinical practice in gastroenterology in many ways for more than 25 years without any proven serious adverse effects (AEs). PPIs have lowered mortality of upper gastrointestinal system bleeding, decreased gastrointestinal complications of nonsteroidal anti-inflammatory drugs, improved symptoms of gastroesophageal reflux disease, been needed to eradicate Helicobacter pylori and been used for Barrett's esophagus since the late 1980s (1). PPIs are very useful and lifesaving, strong gastric acid inhibitors, which can be easily reached by people even over-the-counter without prescription. However, health statistics from many countries show that PPIs are one of the most commonly prescribed medicines. Recently, some observational retrospective studies reported that there are many life threatening AEs associated with PPI use including acute myocardial infarction, dementia, chronic liver disease, acute interstitial nephritis, hip fracture, osteoporosis, and vitamin and mineral deficiencies (2-5). The news about the AEs of PPIs has been reported in TV news, newspapers, and even social media. These concerns which have been mainly coming from retrospective observational studies might make physicians unwilling to prescribe PPIs and lead patients to stop their treatment.

Recently, Xie and colleagues from USA completed a longitudinal observational cohort study using the US Departments of Veterans Affair database to investigate if PPI use was associated with excess risk of death (6). They also tried to determine if there was a correlation between the all-cause mortality rate and the duration of PPI use. They compared outcomes of acid suppression therapies including PPI and histamine H2 receptor antagonists (H2 blockers) for all-cause mortality rates. They built cohorts of new users of PPI or H2 blockers (n=349 312), PPI versus no PPI (n=3 288 092), and PPI versus no acid suppression medicine (n=2 887 030). They used "risk of death" as a main outcome measure of the study. Median follow up was 5.7 years. A strong association was found between PPI use and increased risk of death. Among the new PPI users, the association between the duration of exposure and the risk of death was correlated positively. The all-cause mortality was much more pronounced in PPI using patients with no documented medical indication for acid suppression treatment.

The authors could not explain the biological mechanisms underlying this increased mortality among PPI users. They mentioned, however, in the discussion part of the paper about some findings from other small studies; and they claimed that PPI may cause decreased regenerative capacity of liver, increased activity of heme oxygenase-1 enzyme, impaired lysosomal acidification, increased oxidative stress, telomere shortening, and endothelial cell aging. Any of these hypothesis could not been proven in any experimental or in vivo study yet.

The study is important and adding a very new and important information to what is already known in the literature. This study has the potential to affect the daily practice of physicians. Although the study was completed with a nationwide-large-scale cohort, it has some important limitations. It is an observational study and not a randomized prospective trial. The authors used many strategies to lessen the possibility of confounding, but, as the authors suggest, they could not completely eliminate all biases. Furthermore, the cohort primarily included older white males, which may limit the generalizability of the findings. We think the most important limitation is the lack of any information about the cause of death. The question of "why did they die?" is unanswered.

A paper "special report" by Katz and colleagues, which appeared in Gastroenterology and Endoscopy News at the end of last year, is very useful for clinicians evaluating retrospective observational studies about the AEs of PPIs (7). The report was released as an expert consensus

about the benefit-to-risk ratio of PPIs. The experts accept that these observational studies revealed some degree of association between some AEs and long-term use of PPIs. Population based cohort studies may be very useful tool to find out certain AEs of a drug which could not be observed during the phase trials. Sometimes, however, data from these large population based studies may exaggerate the findings, may hide the real causal association, and may lead to misunderstanding and misinterpretation. For example, an observational study of more than 73,000 elderly dementia patients had a 1.44 hazard ratio, which is very weak (5). These elderly patients were not analyzed for other possible causes of dementia including vitamin deficiencies, medications, and other systemic or nervous system diseases. Another study used a data-mining process to investigate the link between PPI therapy and myocardial infarction (4). The adjusted odd ratio (OR) was very low, just 1.16. Additionally, the authors of this study stressed that, although data-mining is a valid method for this kind of study, it may cause false positivity. Nevertheless, their article's title was "Proton pump inhibitor usage and the risk of myocardial infarction in the general population" which was a tempting title to become the focus of attention. The competition to find important AEs of PPIs started with a study from the United Kingdom that concluded that increased duration of PPI therapy was linked to increased risk of hip fracture compared to H2 receptor antagonists (OR 1.82) (8). This study gained a lot of attention from the media and the community. However, patients with more severe systemic diseases are more likely to be on PPI therapy, especially if the patient is elderly. So, this elderly sick patient may have a hip fracture risk much higher than another same age person because of comorbidities, poor nutrition, less mobility, and decreased weight. The mechanisms of action between PPIs and AEs should be assessed before an AE is claimed to be associated with PPI therapy, including inhibition of bone metabolism and impaired calcium absorption. Efforts to prove the presence of underlying mechanisms associated with myocardial infarction, dementia, osteoporosis, increased cancer rate, and chronic kidney disease have all failed (7). Acute interstitial nephritis, which is an idiosyncratic cell-mediated immunologic reaction with many unknown triggers, is claimed to be another very rare AE associated with PPI use. It is very difficult to confirm that a case of acute interstitial nephritis is caused by PPIs and not nonsteroidal anti-inflammatory drugs, antibiotics, or common infectious diseases. Recently, the news about a 96% increased risk of renal failure in PPI users appeared on visual media in Turkey. The study and findings were misinterpreted by some "health journalists." The news was denied and corrected by a press declaration from the Turkish Gastroenterology Association.

Proton pump inhibitors also have some well-established AEs as acceptable as other commonly used medications such as mild increases in small intestinal bacterial overgrowth, clostrium difficile infection, pneumonia, and some mineral and vitamin deficiencies. A very rare but serious side effect is hypomagnesemia. Even though the mechanism of hypomagnesemia caused by PPIs is not clear yet, a safety alert about hypomagnesemia was issued by the FDA in 2011, following another safety alert for a possible increased risk of osteoporosis-related fractures in 2010.

In daily life many family physicians and patients hear about the AEs of PPIs from the media and they stop prescribing or using PPIs even in appropriate indication, which may cause serious morbidity and mortality. This artificial and unrealistic fear, without any confirming knowledge, is against the science and our patient's wellbeing.

Many studies and our clinical experience over the last 30 years suggest that PPIs are safe and very effective for treating many troublesome conditions and diseases of the gastrointestinal system. Physicians should be careful about the indications of PPI, and they should prescribe the lowest dose and duration needed for symptom control and treatment achievement. Physicians should also be aware of the signs and symptoms of the AEs associated with PPIs so that they are able to recognize them early and manage them appropriately. For patients who benefit from long-term courses of PPI treatment, periodically reconsidering and recalculating the benefit to risk ratio is appropriate.

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