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Editorial

# The benefits and risks of proton pump inhibitor therapy

Proton pump inhibitors (PPIs) have become one of the most commonly used types of medications worldwide. They can be effective in treating peptic ulcer disease (PUD), peptic ulcer bleeding (PUB), as well as nonerosive and erosive esophagitis via gastric acid inhibition. PPIs are also a fundamental element of combination therapy for *Helicobacter pylori* eradication. For prophylaxis, PPIs effectively protect against aspirin and nonsteroidal anti-inflammatory drug (NSAID)-induced PUD and PUB.[1,2] However, no medication is completely devoid of adverse effects, and three major concerns with PPI therapy have been raised, including the risks of pneumonia, enteric infections, and bone fracture.

Mechanistically, whether PPI use has any effect on the risk of pneumonia in patients remains unclear. PPIs enable the proliferation of microorganisms in the stomach that could reflux back and be aspirated, which could increase the risk of pneumonia.[3] Two meta-analysis studies evaluated the association between PPI therapy and the occurrence of hospital- and community-acquired pneumonia in case-control and observational studies.[4,5] They found a positive association between PPI therapy and pneumonia (odds ratio [OR] ~1.27−1.36). However, the studies were heterogeneous, and also indicated that the association with pneumonia was much stronger if a PPI was prescribed within the past 7 days than if the drugs were prescribed within the past 30−180 days.[6,7] It seems that protopathic bias remains the most likely explanation for this finding. In observational studies, the modest associations between a risk factor and a disease are usually attributable to bias or confounding and are rarely the result of a causal effect. The association between PPI therapy and pneumonia might also be an example of this phenomenon. Two systematic reviews investigating the association between PPI therapy and pneumonia in randomized control trials (RCTs) did not find any statistically significant effects.[6,7]

One of the main roles of gastric acid is to kill bacteria in food that could be potential pathogens while we eat. A systematic review of observational studies from 10,430 subjects found a significant association between PPI therapy and the risk of enteric infection cause by *Salmonella* and *Campylobacter* species (OR: 3.33).[8] The potential association between *Clostridium difficile*-associated diarrhea (CDAD) and PPI therapy is complex. A systematic review without each paper's adjusting for potential confounding factors found an association between CDAD and PPI therapy, but the OR (2.05) was lower than for other enteric infections.[8] It is possible that PPI therapy alters the composition of the gut bacterial flora, which would provide an environment enabling toxigenic strains of CD to flourish. Regarding gut micropathogen-associated disease while taking PPIs, a population-based case-control study showed that PPI therapy significantly increased the risk of cryptogenic liver abscess.[9] A meta-analysis study revealed that PPI therapy was associated with a greater risk of spontaneous bacterial peritonitis (SBP) in hospitalized patients with cirrhosis.[10] Otherwise, Ho's[11] study did not find that PPI therapy increased the risk of colonic diverticulitis.

Systematic reviews and meta-analyses including five cohort and six case-control studies concluded that patients on PPI therapy had a significantly increased risk of hip fractures (OR: 1.25) and vertebral fractures (OR: 1.50).[12] No evidence supported an association between PPI therapy and the risk of wrist or forearm fracture. However, the observed statistically significant association cannot be interpreted as proof of causality, because the association could have resulted from residual or unmeasured confounding, as was described for the association between pneumonia and PPI therapy. The most commonly proposed mechanism is that PPI therapy, by decreasing the absorption of ingested calcium, leads to a negative calcium balance and eventually to bone loss and osteoporosis.[13] Two RCTs that utilized more reliable methods (dual stable isotope method) than the previous studies showed no evidence of an effect of PPI use on the absorption of calcium under customary physiological conditions in healthy young volunteers and postmenopausal women, respectively.[14,15] In brief, there is no persuasive evidence that the association is causal, although this can never be excluded as a possibility.[16]

In conclusion, although the possibility of adverse events attributable to PPI therapy cannot be excluded, including pneumonia, enteric infections, CDAD, SBP, and bone fracture, it is important that PPIs are only prescribed to patients who may benefit from them such as patients with reflux esophagitis, PUD, PUB post endoscopic therapy, and patients with a high risk of PUB when taking antiplatelets or NSAIDs.

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## Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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