## Assessing the Need for Proton Pump Inhibitors for Patients Using Long-Term Nonsteroidal Anti-inflammatory Drugs without a History of Ulcers

Nonsteroidal anti-inflammatory drugs (NSAIDs) are toxic to the stomach. One proposed mechanism of this toxicity is a prostaglandin-mediated increase in gastric acid secretion.[1] If so, it would follow that increasing stomach pH, perhaps by means of an agent such as a proton pump inhibitor (PPI), would help to prevent ulcer complications secondary to NSAID use, such as bleeding and perforation. Clinical practice guidelines have recommended that patients at moderate risk (i.e., having at least one of the following factors: > 65 years old; receiving high-dose NSAID therapy; previous history of uncomplicated ulcers; or concurrent use of low-dose acetylsalicylic acid [ASA], corticosteroids, or anticoagulants) be given either cyclooxygenase-2 (COX-2) inhibitors alone or traditional nonselective NSAIDs plus misoprostol or a PPI.[2] The UpToDate clinical decision resource recommends PPIs as an option for reducing the risk of gastroduodenal toxicity and suggests that they may prevent ulcers in those who require NSAIDs.[3] We characterized the current evidence and determined the characteristics of patients to whom this evidence would apply.

We conducted a scoping search of the literature to identify a recently published systematic review of randomized controlled trials (RCTs) on this topic, and found 2 potentially suitable reviews.[4,5] The most recent systematic review, by Scally and others,[5] was unsuitable for our purposes because the authors did not report raw data for the trials included in their analysis. Instead, we examined the slightly older review, by Yang and others.[4] We did not look beyond the published data included within the systematic review. We focused specifically on RCTs that compared PPIs with placebo for patients receiving long-term NSAID therapy for pain; we did not consider trials of low-dose ASA. We collected information deemed relevant to our study question, specifically the types of outcomes and adverse events reported and the characteristics of included patients.

Yang and others[4] performed a meta-analysis of 15 RCTs to evaluate the "effectiveness and safety of PPIs" for "prevention of NSAID-associated serious ulcer complications". Six of the trials involved low-dose ASA, and 9 used NSAIDs for pain. We determined that the 9 NSAID trials, all of which were placebo-controlled, were relevant to our question. In terms of their study populations, 5 of the 9 included a mix of patients with and without a history of ulcers, and 3 included patients with previous ulcers; for 1 study, the population was unclear. Across the 9 trials, *Helicobacter pylori* status was highly variable: for 3 of the 9 trials, 100% of the patients tested negative; for 1 trial, 100% of the patients tested positive; for 4 trials, *H. pylori* status was mixed; and for 1 trial, *H. pylori* status was not reported. The following efficacy outcomes were reported: endoscopic ulcers ($n$ = 7 trials), recurrent ulcer bleeding ($n$ = 1 trial), and ulcer complications such as bleeding, perforation, or obstruction ($n$ = 1 trial). In terms of safety outcomes, 3 of the 9 trials reported serious adverse events, 2 reported gastrointestinal (GI) bleeding, and 3 reported deaths. The authors concluded that "PPIs were significantly more effective than placebo in reducing ulcer complications (relative risk [RR] = 0.29; 95% confidence interval [CI], 0.20 to 0.42)".

An interesting finding was that the majority of trials reported on endoscopic ulcers as opposed to clinically important outcomes such as ulcer complications. The question of whether endoscopic ulcers lead to clinical ulcers is a point of contention, and there are opposing views on this issue in the current literature.[6,7] Because most of the identified evidence supporting PPIs in long-term NSAID use is based on their apparent influence on endoscopic ulcers,[8] it is important to determine whether a decrease in endoscopic ulcers is truly associated with a clinical reduction in ulcers or their subsequent complications.

Other independent risk factors besides long-term NSAID use may contribute to ulcer development. For example, it is believed that *H. pylori* infection plays a role in the occurrence of ulcers.[9] Several articles included in the review by Yang and others[4] involved patients who tested positive for *H. pylori* or had recently healed from the infection. It is unclear at this point whether PPIs are exerting their protective effects on NSAIDs or on other disease processes (e.g., *H. pylori* positivity).

We recognize that there is evidence showing an association between GI complications and NSAID use.[10,11] Patients should be made aware of these risks before starting short-term or long-term therapy. Our goal with this investigation was to ascertain whether PPIs are effective in mitigating the risk of GI complications. Overall, we found little evidence showing that PPI prophylaxis leads to fewer clinically important adverse outcomes in long-term NSAID users, especially those without a history of ulcer complications and those with no risk factors. Instead, we found that the trials included in the review by Yang and others[4] had the following common features: included patient populations with either a mixed or positive history of ulcers; mostly considered low-dose ASA to confer a GI risk similar to that of long-term NSAID use, which may not be true; and reported

on endoscopic outcomes as opposed to clinical ulcer complications. We realize that this evidence has some limitations, including the fact that the trials were of short duration and the fact that the risk of NSAID complications is cumulative over time. Some might suggest that there is a role for PPIs in preventing complications in long-term NSAID users who are at high risk of bleeding (e.g., those who test positive for *H. pylori*, have a history of ulcers, or are taking other GI-toxic medications), but we could not find any evidence to support this claim. We suggest that it may be appropriate to share this information with patients, specifically to address the uncertainties discussed here and especially with the knowledge that long-term PPI use may increase the risks of bone disease, infection, and other harms.[12,13]

**References**

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