Patient-centered Outcomes with Concomitant Use of Proton Pump Inhibitors and Other Drugs

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ABSTRACT

Purpose: We performed a systematic review of patient-centered outcomes after the concomitant use of proton pump inhibitors (PPIs) and other drugs.

Methods: We searched 4 databases in July 2016 to find studies that reported mortality and morbidity after the concomitant use of PPIs and other drugs. We conducted direct meta-analyses using a random-effects model and graded the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group approach.

Findings: We included data from 17 systematic reviews and meta-analyses, 16 randomized controlled trials, and 16 observational studies that examined the concomitant use of PPIs with medications from 10 drug classes. Low-quality evidence suggests that the use of PPIs is associated with greater morbidity when administered with antiplatelet drugs, bisphosphonates, antibiotics, anticoagulants, metformin, mycophenolate mofetil, or nelfinavir. Concomitant PPIs reduce drug-induced gastrointestinal bleeding and are associated with greater docetaxel and cisplatin response rates in patients with metastatic breast cancer. For demonstrated statistically significant relative risks and benefits from concomitant PPIs, the magnitudes of the effects are small, with <100 attributable events per 1000 patients treated, and the effects are inconsistent among specific drugs. Among individual PPIs, the concomitant use of pantoprazole or esomeprazole, but not omeprazole or lansoprazole, is associated with an increased risk for all-cause mortality, nonfatal myocardial infarction, or stroke. Clopidogrel is associated with a greater risk for myocardial infarction compared with prasugrel. Conflicting results between randomized controlled trials and observational studies and high risk for bias in the body of evidence lessened our confidence in the results.

Implications: Available evidence suggests a greater risk for adverse patient outcomes after the concomitant use of PPIs and medications from 9 drug classes and warns against inappropriate drug combinations. (*Clin Ther*. 2017;39:404–427) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: anticoagulants, antiplatelets, cardiovascular disease, combination therapy, drug–drug interactions, hypertension, outcomes, PPIs, proton pump inhibitors.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the medications most commonly prescribed for primary gastroduodenal ulcers and for preventing drug-induced gastrointestinal adverse events and bleeding, especially in elderly patients, in the inpatient and outpatient settings.[1–3] The concomitant use of PPIs in combination with other drug classes is common and increases over time.[4,5] Pharmacokinetic and pharmacodynamic interactions between PPIs and other drug classes involve changes in drug absorption secondary to gastric acid suppression, a decrease in oral drug absorption, changes in drug metabolism after the induction or inhibition of cytochrome P450 (CYP), and/or impaired drug distribution after the inhibition of P-glycoprotein or breast cancer resistance protein–mediated drug transport (data on file, Bristol-Myers Squibb, New York, New York).[6–51]

Much more controversial is the evidence regarding changes in mortality and morbidity in patients with

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long-term the concomitant use of PPIs and other commonly recommended medications, including antiplatelet and anticoagulant drugs and NSAIDs.[4,5] For instance, dual antiplatelet therapy is recommended for the majority of patients with coronary artery or cerebrovascular disease.[52,53] However, there is conflicting evidence about an increased risk for cardiovascular adverse events in patients concurrently taking PPIs.[54–60] The concomitant use of PPIs is believed to prevent the gastrointestinal toxicity common with NSAIDs use but has been associated with increased risks for cardiovascular adverse events, pneumonia, and *Clostridium difficile*-associated diarrhea.[54–57,59–63] Bisphosphonates are commonly used in patients with osteoporosis and low bone density for the prevention of bone fractures, but there are questions regarding their effectiveness in patients taking PPIs.[64] To examine patient-centered benefits and risks with long-term concomitant use of PPIs and other drugs in patients with various diseases, we conducted a systematic literature review.

MATERIALS AND METHODS

We developed a protocol (see **Supplemental Appendix A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.011) for a systematic literature review following recommendations from the Cochrane Collaboration and the Agency for Healthcare Research and Quality.[65,66] Our objective was to examine patient-centered outcomes, including mortality and morbidity, after the concomitant use of PPIs with any other drug class. We tested the null hypotheses of no differences in patient mortality and morbidity with versus without PPIs administered concurrently with other drug classes, including antiplatelets, anticoagulants, NSAIDs, bisphosphonates, antibiotics, statins, biguanides, immunosuppressants, protease inhibitors, or taxanes. We also tested a null hypothesis of no differences in patient mortality and morbidity after the concomitant use of different PPIs compared with each other.

We refined the clinical questions and defined the target population as adults treated concomitantly with PPIs and other drugs. We defined *exposure* as the effect of the concomitant use of the PPI esomeprazole, omeprazole, lansoprazole, pantoprazole, or rabeprazole sodium with any other drug class. Eligible comparators included the same drugs administered without the PPI. We defined *morbidity* as reported in the studies to avoid bias in outcome selection.[67] We excluded studies that focused on the intermediate outcomes of drug interactions and that did not report patient-centered outcomes.

We conducted a comprehensive search of PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov to find published and unpublished (up to July 2016) meta-analyses, randomized controlled trials (RCTs), and nationally representative controlled observational studies that reported adjusted effect estimates (for strings, see **Supplemental Appendix B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.011).[68] All of the authors and the medical librarians determined the studies' eligibility. All citations found during the searches are stored in a reference database.

An external contractor used DOC Data Software Platform version 2.0 (Doctor Evidence LLC, Santa Monica, California) to perform dual abstraction and quality control of the data (see **Supplemental Appendix C** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.011). We performed meta-analyses when definitions of the active and control interventions and patient outcomes were deemed sufficiently similar and were assessed at similar follow-up times.[69]

We used the Agency for Healthcare Research and Quality–recommended methodologic approach in the integration of existing systematic reviews into our comprehensive synthesis of evidence.[70] Our goal was the integration of previously published high-quality reviews and consistent ranking of the quality of evidence using Grading of Recommendations Assessment, Development and Evaluation methodology. When analyzing the evidence from RCTs, we conducted de novo meta-analyses using random-effect models for relative risk and absolute risk differences.[65] To avoid redundancy in our analyses, we did not combine in the models pooled estimates from published meta-analyses with the data from primary studies. When analyzing the evidence from observational studies, we used pooled estimates from published systematic reviews and adjusted estimates from individual studies.[70]

We calculated absolute risk difference, number needed to treat, and number of attributable events based on data from the published RCTs, using Stata software version 11 (StataCorp LP, College Station, Texas). Statistical significance was evaluated at a 95% confidence level.

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