**Indications, appropriateness and drug interactions of proton pump inhibitors prescribed at hospital discharge in older medical patients**

# Indications, appropriateness and drug interactions of proton pump inhibitors prescribed at hospital discharge in older medical patients

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Dear Editor,

Proton pump inhibitors (PPI) are among the most commonly used drugs worldwide, representing a cornerstone in the treatment of acid peptic disease.[1]

Although PPI have an excellent safety profile, long-term suppression of gastric acid raises a number of problems, including gastroduodenal bacterial overgrowth and infections such as *Clostridium difficile* enteritis.[2] Furthermore, chronic PPI use has been associated with increased risk of hip fractures,1 nutritional deficiencies[3] and overall mortality.[4]

PPI have also potentially adverse drug–drug interactions (DDI), such as the possible reduction of clopidogrel efficacy in coronary heart disease[5] and thyroxine malabsorption.[6] Finally, PPI have been linked to hyponatremia, especially in association with selective serotonin reuptake inhibitors.[7] Older patients are at greater risk of DDI because of polytherapy, and, consequently, of adverse drug reactions.

We carried out a retrospective study to evaluate clinical indications for PPI, prevalence, and predictors of inappropriate prescription and DDI involving PPI among older inpatients. The study was carried out at Città della Salute e della Scienza, a university teaching hospital in Turin, Italy. Patients aged ≥65 years discharged from a geriatric ward and an internal medicine ward with a PPI prescription between January and December 2014 were enrolled. Medical history, primary and secondary diagnosis, and therapy at discharge were collected. A prescription was defined appropriate when it was in keeping with the Italian Medicines Agency notes 1 or 48, which regulate the prescription of these drugs in Italy. Note 48 indicates PPI for the treatment of gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication and other acid hypersecretory conditions (e.g. Zollinger–Ellison syndrome). Note 1 allows PPI prescription for preventing gastrointestinal bleeding during chronic non-steroidal anti-inflammatory drugs or acetylsalicylic acid (ASA) treatment in patients with at least one of the following: age ≥65 years, gastrointestinal bleeding or peptic ulcer history, or concomitant therapy with corticosteroids or

anticoagulants. Potential DDI were assessed through the Micromedex database (Micromedex; Truven Health Analytics, see Supporting Information Reference S1 for database link), and defined as major (might be life-threatening and/or require medical intervention to prevent serious adverse effects) or moderate (might exacerbate the patient's condition and/or require a change in therapy).

Among 1786 patients discharged in the study period, 974 received a PPI prescription. The mean age was 80.0 ± 8 years, and 52.7% were women. The median length of stay was 9 days, and the mean number of drugs was 8 ± 3. The commonest indication for PPI (64.3%) was gastric protection during non-steroidal anti-inflammatory drugs or ASA treatment, almost all (97.5%) patients were receiving the latter. In patients receiving ASA, 19% of prescriptions occurred in patients aged ≥80 years without a history of cardiovascular events. Less common indications for PPI included gastric ulcer (14.2%), gastroesophageal reflux disease (8.2%), duodenal ulcer (6.7%), reflux esophagitis (3.8%), eradication of *Helicobacter pylori* (2.2%) and other acid hypersecretory conditions (0.6%). Inappropriate PPI prescription was documented in 43.4% of patients.

At least one potential major DDI was observed in 9% of patients, almost all involving citalopram and clopidogrel (48% and 46% of cases, respectively). At least one potential moderate DDI was found in 36% of patients; double or triple moderate DDI were found in 6.3% and 1.1% of patients, respectively. The most common drug involved was warfarin (31%), followed by digoxin (20%), levothyroxine (19%), alprazolam (11%) and iron (10%; for further details see Supporting Information Table S1).

Demographic and clinical variables of patients and results of univariate analysis are reported in Table 1. After multivariate analysis, internal medicine ward discharge (OR 1.35, 95% CI 1.03–1.76), longer length of stay (OR 1.02, 95% CI 1.01–1.04) and the presence of moderate DDI (OR 1.75, 95% CI 1.33–2.30) were associated with a greater risk of inappropriate prescription, whereas older age (OR 0.98, 95% CI 0.97–0.99) and prescription of esomeprazole (OR 0.33, 95% CI 0.15–0.71) were associated with increased appropriateness.

**Table 1.** Demographic and clinical characteristics of the 974 patients discharged with proton pump inhibitors according to appropriate versus inappropriate prescription (univariate analysis)

| Demographic and clinical variables | All ($n$ = 974) | Appropriate prescriptions ($n$ = 551) | Inappropriate prescriptions ($n$ = 423) | Test | *P* |
|---|---|---|---|---|---|
| Ward, *n* (%)† | | | | | |
| Geriatric | 504 (51.7%) | 311 (61.7%) | 193 (38.3%) | 10.98 | 0.0009 |
| Internal medicine | 470 (48.3%) | 240 (51.1%) | 230 (48.9%) | | |
| Female, *n* (%)† | 513 (52.7%) | 289 (56.3%) | 224 (43.7%) | 0.09 | NS |
| Drug, *n* (%)† | | | | | |
| Omeprazole | 612 (62.8%) | 327 (53.5%) | 285 (46.5%) | 6.47 | 0.01 |
| Lansoprazole | 103 (10.6%) | 63 (61.2%) | 40 (38.8%) | 0.96 | NS |
| Pantoprazole | 213 (21.9%) | 128 (60.1%) | 85 (39.9%) | 1.33 | NS |
| Esomeprazole | 40 (4.1%) | 30 (75.0%) | 10 (25.0%) | 5.73 | 0.02 |
| Rabeprazole | 6 (0.6%) | 3 (50.0%) | 3 (50.0%) | 0.11 | NS |
| Major DDI, *n* (%)† | 88 (9.0%) | 49 (55.7%) | 39 (44.3%) | 0.04 | NS |
| Moderate DDI, *n* (%)† | 350 (35.9%) | 169 (48.3%) | 181 (51.7%) | 15.81 | 0.00007 |
| Age, median (25th–75th percentile)‡ | 80 (75–85) | 81 (75–86) | 79 (74–85) | −2.91 | 0.0036 |
| Length of stay, days, median (25th–75th percentile)‡ | 9 (6–14) | 8 (6–13) | 9 (6–15.5) | −2.77 | 0.0057 |
| No. medications (mean ± SD)§ | 8.33 ± 3.06 | 8.40 ± 3.17 | 8.24 ± 2.91 | 0.70 | NS |

†χ2-test; ‡Mann–Whitney U-test; §ANOVA. DDI, drug–drug interactions; NS, not significant

The present results, in keeping with other studies, confirm a high prevalence of inappropriate PPI prescription in the setting of a university teaching hospital.[8] Gastric bleeding prevention in ASA-treated patients accounts for the great burden of PPI prescription in older patients. Although Italian Medicines Agency indications allow PPI prescription in all older patients in treatment with ASA, the risk of ASA-induced gastric lesions might be highly dependent on the patient's general health and feeding conditions.[9] Noteworthy, 19% of PPI prescriptions for patients receiving ASA occurred in patients aged >80 years without previous cardiovascular events, where there is still scant evidence of net clinical benefit of low-dose ASA, according to the Beers criteria.[10] In these patients, a prescription of questionable benefit led to further potentially inappropriate long-term use of PPI, generating a typical “prescribing cascade”.

Older age and geriatric ward discharge were associated with increased appropriateness of PPI prescription, possibly suggesting a greater attention to age-specific therapeutic recommendations in this setting. Potential moderate DDI, which were associated with inappropriate prescription, were also observed in one-third of patients.

The present results suggest the need to harmonize discharge prescriptions with current regulations, not only for economic reasons, but also to prevent iatrogenic harm in vulnerable older patients.

### Disclosure statement

The authors declare no conflict of interest.

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