Acid Suppressants Reduce Risk of Gastrointestinal Bleeding in Patients on Antithrombotic or Anti-Inflammatory Therapy

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BACKGROUND & AIMS: We investigated the effect of different prevention strategies against upper gastrointestinal bleeding (UGIB) in the general population and in patients on antithrombotic or anti-inflammatory treatments. **METHODS:** We performed a population-based, nested, case-control study using The Health Improvement Network UK primary care database. From 2000 to 2007, we identified 2049 cases of UGIB and 20,000 controls. The relative risk (RR) of UGIB associated with various gastroprotective agents was estimated by comparing current use (defined as use within 30 days of the index date) with nonuse in the previous year, using multivariate logistic regression. **RESULTS:** The adjusted RR of UGIB associated with current use of proton pump inhibitors (PPIs) for more than 1 month was 0.58 (95% confidence interval [CI], 0.42–0.79) among patients who received low-dose acetylsalicylic acid (ASA), 0.18 (95% CI, 0.04–0.79) for clopidogrel, 0.17 (95% CI, 0.04–0.76) for dual antiplatelet therapy, 0.48 (95% CI, 0.22–1.04) for warfarin, and 0.51 (95% CI, 0.34–0.78) for nonsteroidal anti-inflammatory drugs. The corresponding estimates for therapy with histamine-2–receptor antagonists (H_2RAs) were more unstable, but tended to be of a smaller magnitude. In the general population, PPI use was associated with a reduced risk of UGIB compared with nonuse (RR, 0.80; 95% CI, 0.68–0.94); no such reduction was observed for H_2RAs or nitrates. **CONCLUSIONS: PPI use was associated with a lower risk of UGIB in the general population and in patients on antithrombotic or anti-inflammatory therapy compared with nonuse of PPIs. The reduction in risks of UGIB was smaller in H_2RA than in PPI users.**

Keywords: Gastrointestinal Hemorrhage; Aspirin; Antiplatelet Agents; Side Effects.

Several randomized controlled trials (RCTs) and observational studies have suggested that proton pump inhibitors (PPIs) can reduce the risk of upper gastrointestinal bleeding (UGIB) in patients taking antiplatelet drugs and nonsteroidal anti-inflammatory drugs (NSAIDs).[1–4] However, large-scale studies of the association between PPIs, antiplatelet agents, and UGIB in real-life clinical practice are needed for 2 key reasons.

First, although well-conducted RCTs avoid confounding, they frequently evaluate intermediary end points and use selected populations. The generalizability of these results is therefore unclear. Second, it has been suggested that PPIs may be associated with adverse cardiac outcomes in patients taking clopidogrel owing to a potential pharmacologic interaction between the 2 agents. However, the evidence for adverse cardiac events in observational studies is inconsistent[5–7] and the results of a recent prospective randomized trial suggest that any pharmacologic interaction does not translate into a major negative cardiovascular effect.[8] Nevertheless, it is essential to accurately estimate the various components of the risk-benefit ratio when prescribing PPIs to patients taking antithrombotic agents such as clopidogrel. The value of other gastroprotective drugs also should be assessed as alternative preventive measures against gastrointestinal adverse events in these populations. Few large population-based studies have examined the effects of PPIs, histamine-2 receptor antagonist (H_2RAs), and nitrates on the risk of UGIB among users of specific gastrotoxic agents. Specifically, although dual antiplatelet therapy (DAT) with low-dose acetylsalicylic acid (ASA) and clopidogrel has been prescribed increasingly,[9,10] little is known about the effect of gastroprotective agents in DAT users.

Herein, we conduct a population-based cohort study with a nested case–control analysis to estimate the effect of PPIs, H_2RAs, and nitrates on the risk of UGIB in the general population as well as in users of specific antithrombotic and anti-inflammatory drugs.

Materials and Methods

Source Population

A cohort study with a nested case-control analysis was performed using data extracted from The Health Improvement Network (THIN) UK primary care database. Anonymized data on more than 3 million patients are prospectively and systematically recorded by participating primary care practitioners (PCPs) as part of their routine patient care and sent to THIN for use in research projects.

Abbreviations used in this paper: ASA, acetylsalicylic acid; CI, confidence interval; DAT, dual antiplatelet therapy; H_2RA, histamine type 2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care practitioner; PPI, proton pump inhibitor; PUD, peptic ulcer disease; RCT, randomized controlled trial; RR, relative risk; THIN, The Health Improvement Network; UGIB, upper gastrointestinal bleeding.

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THIN contains patient information such as demographic factors, consultation rates, referrals, hospitalizations, laboratory test results, and prescriptions written by PCPs, including the doses and duration of treatment. Diagnoses and test procedures are recorded using Read codes.[11,12] Prescriptions written by PCPs are generated and recorded automatically in the database using a coded drug dictionary (Multilex).[13] That the data in THIN are accurate and representative of the UK population is supported by their similarity to UK national statistics.[14,15]

The source population for this study comprised all individuals recorded in THIN who were ages 40–84 years from January 1, 2000, to December 31, 2007, and who were enrolled permanently with a PCP. Individuals entered the source population on the date they had been enrolled with their PCP for at least 2 years and had a computerized prescription history of at least 1 year (start date). Patients with a recorded diagnosis of cancer, esophageal varices, Mallory–Weiss disease, alcohol abuse, liver disease, or coagulopathy before the start date were excluded from the source population. Individuals who were age 65 years or older at the start date and who had a follow-up period of more than 1 year but no recorded data during the follow-up period were excluded as a proxy for incomplete data recording. All members of the source population were followed up from the start date until the earliest of the following end points: recorded diagnosis of UGIB (case detection), recorded diagnosis of an exclusion factor, reaching the age of 85 years, death, or the end of the study period.

Case Definition and Ascertainment

The computerized patient profiles of all potential cases (including free-text comments) were reviewed manually. Individuals were defined as UGIB cases if their bleed was located in the stomach or duodenum, they had met no exclusion criteria in the 2 months after the recorded UGIB, and they had not been discharged from the hospital in the previous month. Patients with bleeding in the esophagus or lower gastrointestinal tract were not considered UGIB cases.

The present study is an extension of an earlier study in which the effects of ASA, traditional NSAIDs, and selective inhibitors of cyclooxygenase 2, alone and in combination, on the risk of UGIB were investigated in patients recorded in THIN during 2000–2005.[16] The validity of the procedure used for ascertaining UGIB events was shown in this earlier study, in which a positive predictive value of greater than 95% was estimated for the UGIB definition compared with PCP records in a random sample.[16,17] Therefore, no further validation was performed as part of the current study.

After the manual review of computerized records, the final number of confirmed cases of UGIB was 2049. A control group of 20,000 individuals, frequency-matched by age, sex, and calendar year to the cases, randomly was sampled from the same source population.

Exposure Definition

Computerized prescription records were used to assess the use of PPIs, H_2RAs, and nitrates before the index date (for cases this was the date of the UGIB diagnosis and for controls it was a random date during the follow-up period). To control for potential confounding by concomitant use of gastrotoxic drugs, we also assessed use of low-dose ASA (75–300 mg/day), clopidogrel, oral anticoagulants, NSAIDs (cyclooxygenase 2 inhibitors and traditional NSAIDs), selective serotonin reuptake inhibitors, and oral corticosteroids.

Drug exposure was classified into 2 categories based on the expected pharmacologic effects: current use was defined as use lasting until the index date or ending in the 30 days before the index date, and past use was defined as use ending 31–365 days before the index date. However, in a previous study[18] we found that the risk of UGIB among NSAID users starts to decrease quite markedly around 7 days after treatment cessation, reflecting the reversible nature of the inhibition of cyclooxygenase by NSAIDs. Therefore, for NSAID use, current use was defined as lasting until the index date or ending in the 7 days before the index date, recent use was defined as ending 8–90 days before the index date, and past use was defined as ending 91–365 days before the index date. For all studied medications, the reference group (nonuse) was defined as no exposure to the respective drug treatment in the year before the index date.

The risk of UGIB is expected to be increased during the first few weeks after PPI initiation for several reasons. First, clinical trials have shown that the gastrointestinal protection conferred by PPIs is most apparent after a few weeks of continuous use.[1,2] Second, in nonrandomized settings, acid-suppressing drugs may be used to treat early symptoms of UGIB, which results in initiation of drug regimens immediately before the clinical onset of the index UGIB event.[19,20] The lack of an immediate protective effect combined with the strong confounding by indication after treatment initiation in the general population results in estimates of association that evaluate the risk of UGIB after the initial onset of gastrointestinal symptoms rather than evaluating the protective effect against UGIB. Therefore, our primary exposure of interest for acid-suppressing drugs was current use of a PPI or H_2RA that was initiated more than 1 month before the index date.

Analysis

Nested case-control analysis was performed to estimate the relative risk (RR) of UGIB associated with the use of PPIs, H_2RAs, and nitrates. Adjusted RRs and 95% confidence intervals (CIs) were calculated using unconditional logistic regression. These estimates were adjusted by age, sex, calendar year, number of PCP visits, and hospitalizations in the year before the index date, history of peptic ulcer disease (PUD), smoking status, alcohol consumption, and use of oral corticosteroids, selective

serotonin reuptake inhibitors, oral anticoagulants, NSAIDs, low-dose ASA, nitrates, H_2RAs, and PPIs in the year before the index date. The final estimates were not adjusted by a history of cardiovascular disease because this factor was not associated with UGIB after adjusting for the use of antithrombotic agents. Including it in the model did not affect the results appreciably. All statistical tests performed were 2-sided. Analyses were conducted using SAS software (version 9.2; SAS Institute, Inc, Cary, NC).

Results

Risk Factors for UGIB

The risk of UGIB was increased significantly in patients with a previous diagnosis of complicated PUD, uncomplicated PUD, or dyspepsia/gastritis compared with those with no antecedents of upper gastrointestinal disease (Table 1). The risk of UGIB was also significantly higher in current smokers than nonsmokers and in individuals who consumed 25 or more units of alcohol per week than those who consumed fewer than 2 units of alcohol per week. In addition, patients with a greater frequency of health care use, including number of PCP visits or prior hospitalizations, had a higher risk of UGIB. As expected, NSAID, oral corticosteroid, low-dose ASA, clopidogrel, and oral anticoagulant treatment all were associated with an increased risk of UGIB.

The Effect of Acid-Suppressing Agents in Users of Gastrotoxic Drugs

PPIs. PPI use was associated with a significant reduction in the risk of UGIB among users of clopidogrel, low-dose ASA, DAT, and traditional NSAIDs. PPI use was associated with a nonsignificant decrease in the risk of UGIB among users of oral anticoagulants, cyclooxygenase 2 inhibitors, and oral corticosteroids (Figure 1). In patients taking at least one of the gastrotoxic drugs, current use of PPIs for more than 1 month was associated with a reduced risk of UGIB (RR, 0.59; 95% CI, 0.47–0.74), but neither past use nor current use of PPIs for less than a month was associated with a reduced risk. In users of the gastrotoxic drugs, we found no clear dose effect of PPIs on the risk of UGIB, but long-term use of a PPI appeared to have a more pronounced inverse association with UGIB compared with short-term use (Table 2).

H_2RAs. We found that, in users of gastrotoxic agents, the reductions in the risk of UGIB associated with H_2RA use were in general smaller than that with PPI use. Among NSAID users, current use of H_2RAs for more than 1 month was associated with a reduced risk of UGIB (RR, 0.55; 95% CI, 0.31–0.97) (Figure 1*A*). Although the corresponding estimates for clopidogrel monotherapy and DAT users were unstable, combining all current users of clopidogrel, H_2RA use was associated with a reduced risk of UGIB (RR, 0.14; 95% CI, 0.03–0.69). In patients taking at least one of the gastrotoxic drugs, current use of H2RAs for more than 1 month has a nonsignificant inverse association with the risk of UGIB (RR, 0.89; 95% CI, 0.64–1.22). In the same population, we found no clear dose effect of H_2RAs on the risk of UGIB; estimates stratified by treatment duration appear to be unstable and inconclusive (Table 3).

The Effect of Acid-Suppressing Agents in the General Population

Patients who had been using PPIs for more than 1 month had a significantly lower risk of UGIB than nonusers (RR, 0.80; 95% CI, 0.68–0.94) in the general population. The corresponding RR for H_2RA use was 1.17 (95% CI, 0.92–1.50) (Table 4).

Comparative Effectiveness of PPIs and H_2RAs in Various Populations

The RR of UGIB associated with PPI use (in individuals not using H_2RAs) compared with H_2RA use (in individuals not using PPIs) was 0.70 (95% CI, 0.53–0.95) in the general population, 0.57 (95% CI, 0.34–0.95) in users of low-dose ASA monotherapy, and 0.94 (95% CI, 0.46–1.90) in users of NSAIDs.

The Effect of Nitrates on UGIB

We found no significant association between current use of nitrates and the risk of UGIB in the general population (RR, 0.98; 95% CI, 0.81–1.19). The estimates for nitrates were more unstable among users of gastrotoxic agents, but were compatible with there being no association (Figure 1).

Discussion

We found that PPI treatment was associated with a 20% lower risk of UGIB in the general population and that this reduction ranges from 50% to 80% in users of gastrotoxic agents. The corresponding estimates for H_2RA treatment were more unstable, but tended to be of a smaller magnitude. We found no association between nitrate use and UGIB either in the general population or in users of gastrotoxic agents.

Results from RCTs have suggested that PPI use can reduce the recurrence of ulcer bleeding in patients taking antiplatelet and anti-inflammatory drugs.[1,2] Lai et al[1] found that, in ASA users, lansoprazole therapy was associated with a reduced recurrence of ulcer complications compared with placebo (1.6% vs 14.8%). Chan et al[2] reported that in users of NSAIDs other than ASA, omeprazole therapy was associated with a reduced rate of recurrent bleeding compared with *Helicobacter pylori* eradication therapy (4.4% vs 18.8%). A large case-control study also revealed that the risk of UGIB was reduced substantially by PPI (RR, 0.18; 95% CI, 0.14–0.24), H_2RA (RR, 0.39; 95% CI, 0.26–0.57), or nitrate (RR, 0.51; 95% CI, 0.35–0.74) therapy in users of low-dose ASA or NSAIDs but less so in nonusers.[3] Their estimates, however, should be compared with our findings with caution because they included only hospitalized cases whereas we investigated UGIB cases treated on both an inpatient and an outpatient basis. It

Table 1. The Relative Risk of UGIB Associated With Baseline Characteristics

Variable	Cases (N = 2049), n (%)	Controls (N = 20,000), n (%)	RR[a] (95% CI)
Number of PCP visits			
0–3	349 (17.0)	6157 (30.8)	1.00 (–)
4–7	440 (21.5)	4895 (24.5)	1.80 (1.55–2.09)
8–13	537 (26.2)	4752 (23.8)	2.46 (2.13–2.85)
>13	723 (35.3)	4196 (21.0)	4.04 (3.50–4.66)
Number of hospitalizations			
0	1686 (82.3)	18,172 (90.9)	1.00 (–)
1	286 (14.0)	1594 (8.0)	2.00 (1.74–2.29)
≥2	77 (3.8)	234 (1.2)	3.73 (2.86–4.86)
History of gastrointestinal disease			
No history of peptic ulcer/dyspepsia	1133 (55.3)	15092 (75.5)	1.00 (–)
History of ulcer complications	146 (7.1)	391 (2.0)	4.94 (4.04–6.05)
History of PUD	213 (10.4)	714 (3.6)	3.97 (3.36–4.69)
Dyspepsia/gastritis	557 (27.2)	3803 (19.0)	2.00 (1.79–2.23)
Smoking status			
Nonsmoker	884 (43.1)	9892 (49.5)	1.00 (–)
Current smoker	412 (20.1)	2981 (14.9)	1.58 (1.39–1.79)
Former smoker	631 (30.8)	5554 (27.8)	1.41 (1.26–1.58)
Alcohol consumption, *U/wk*[b]			
<2	968 (47.2)	8991 (45.0)	1.00 (–)
2–24	691 (33.7)	7115 (35.6)	0.90 (0.81–1.00)
≥25	106 (5.2)	642 (3.2)	1.53 (1.22–1.91)
Cardiac history			
No history of ischemic heart disease	1566 (76.4)	17,018 (85.1)	1.00 (–)
Prior myocardial infarction	192 (9.4)	1071 (5.4)	1.94 (1.64–2.29)
Prior coronary artery disease	291 (14.2)	1911 (9.6)	1.64 (1.43–1.88)
NSAID use			
Nonuse	1347 (65.7)	15,860 (79.3)	1.00 (–)
Current use (0–7 days)	370 (18.1)	1338 (6.7)	3.17 (2.78–3.60)
Recent use (8–90 days)	148(7.2)	999 (5.0)	1.72 (1.43–2.06)
Past use (91–365 days)	184 (9.0)	1803 (9.0)	1.19 (1.02–1.40)
Oral steroid use			
Nonuse	1890 (92.2)	19,007 (95.0)	1.00 (–)
Current use (0–30 days)	87 (4.2)	435 (2.2)	1.98 (1.56–2.51)
Past use (31–365 days)	72 (3.5)	558 (2.8)	1.29 (1.00–1.66)
SSRI use			
Nonuse	1854 (90.5)	18,874 (94.4)	1.00 (–)
Current use (0–30 days)	123 (6.0)	717 (3.6)	1.86 (1.53–2.28)
Past use (31–365 days)	72 (3.5)	409 (2.0)	1.84 (1.42–2.37)
Oral anticoagulant use			
Nonuse	1912 (93.3)	19,245 (96.2)	1.00 (–)
Current use (0–30 days)	113 (5.5)	636 (3.2)	1.79 (1.46–2.21)
Past use (31–365 days)	24 (1.2)	119 (0.6)	1.95 (1.25–3.05)
Clopidogrel use			
Nonuse	1960 (95.7)	19,615 (98.1)	1.00 (–)
Current use (0–30 days)	68 (3.3)	295 (1.5)	2.57 (1.96–3.38)
Past use (31–365 days)	21 (1.0)	90 (0.5)	2.74 (1.70–4.44)
Low-dose ASA use			
Nonuse	1319 (64.4)	15,584 (77.9)	1.00 (–)
Current use (0–30 days)	631 (30.8)	3778 (18.9)	2.13 (1.91–2.38)
Past use (31–365 days)	99 (4.8)	638 (3.2)	1.94 (1.55–2.43)

NOTE. RRs for use of a medicine were compared with those not exposed in the year before the index date.
ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care practitioner; PUD, peptic ulcer disease; RR, relative risk; SSRI, selective serotonin reuptake inhibitors.
[a]Estimates adjusted for matching factors (age, sex, and calendar year).
[b]A unit of alcohol consumption = 8 g of alcohol (eg, a half pint of 3.5% beer or lager, or one 25-mL measure of spirits.) A small (125-mL) glass of average-strength (12%) wine contains 1.5 U.

has been reported that low-risk patients with UGIB (Rockall score, ≤ 2) can be managed as outpatients[21,22] and that this population comprises up to 30% of all UGIB cases.[23] Another large cohort study estimated the RR of hospitalization caused by a peptic ulcer to be 0.46 (95% CI, 0.28–0.73) associated with PPI use and 0.84 (95% CI, 0.50–1.40) associated with use of double-dose H_2RA among users of traditional NSAIDs, which are consistent with our findings.[24] The same group of investigators later reported that, in users of clopidogrel, PPI use was associ-

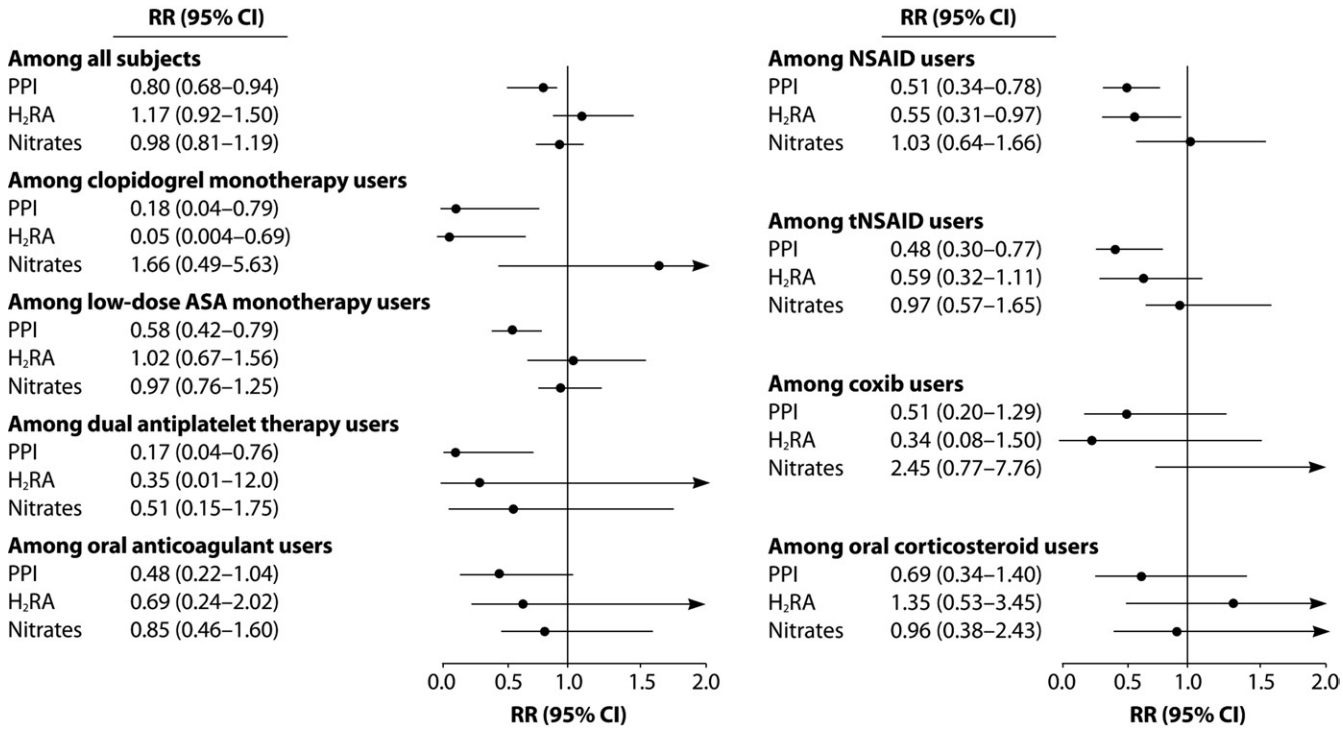

Figure 1. Effect of acid-suppressing drugs and nitrates in patients on antithrombotic and anti-inflammatory treatments. RRs were estimated by comparing current use (exposed within 30 days) of gastroprotective agents with nonuse (not exposed in the prior year) of the same treatment. RRs were adjusted for age, sex, calendar year, PCP visits, prior hospitalizations, prior history of PUD, smoking status, alcohol consumption, and use of oral corticosteroids, selective serotonin reuptake inhibitors, oral anticoagulants, NSAIDs, ASA, nitrates, H_2RA, and PPI use in an unconditional logistic regression model. RR, relative risk; PCP, primary care practitioner; PUD, peptic ulcer disease; ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drug; coxib, cyclooxygenase 2 inhibitor; tNSAID, traditional NSAID; H_2RA, histamine type 2 receptor antagonist; PPI, proton pump inhibitor.

ated with a reduced risk of gastroduodenal bleeding (RR, 0.50; 95% CI, 0.39–0.65).[25]

To date, very few studies have directly estimated the effect of gastroprotective agents in patients receiving DAT with low-dose ASA and clopidogrel. A prematurely terminated RCT of omeprazole vs placebo in patients receiving DAT showed a significant decrease in the risk of UGIB in patients taking omeprazole (Hazard ratio, 0.13; 95% CI,

Table 2. The Effect of PPIs on the Risk of UGIB in Patients Taking Gastrotoxic Agents

	Cases (N =1021), n (%)	Controls (N = 5793), n (%)	Adjusted RR[a] (95% CI)
Recency			
Nonuse (in 1 year)	785 (76.9)	4523 (78.1)	1.00 (–)
Current user (within 30 days), duration > 1 month	118 (11.6)	886 (15.3)	0.59 (0.47–0.74)
Current user (within 30 days), duration ≤ 1 month	38 (3.7)	100 (1.7)	1.67 (1.12–2.50)
Past user (31–365 days)	80 (7.8)	284 (4.9)	1.25 (0.94–1.65)
Dose effect (among current user with duration > 1 month)[b]			
Nonuse (in 1 year)	785 (76.9)	4523 (78.1)	1.00 (–)
Low dose	42 (4.1)	393 (6.8)	0.52 (0.37–0.73)
Medium dose	67 (6.6)	396 (6.8)	0.71 (0.53–0.96)
High dose	9 (0.9)	95 (1.6)	0.41 (0.20–0.83)
Duration effect (among current user with duration > 1 month)			
Nonuse (in 1 year)	785 (76.9)	4523 (78.1)	1.00 (–)
31–90 days	17 (1.7)	82 (1.4)	0.89 (0.51–1.55)
91–365 days	35 (3.4)	187 (3.2)	0.80 (0.54–1.19)
>365 days	66 (6.5)	617 (10.7)	0.48 (0.36–0.64)

[a]RRs adjusted for age, sex, calendar year, PCP visits, prior hospitalizations, history of PUD, smoking status, alcohol consumption, and use of oral corticosteroids, selective serotonin reuptake inhibitors, oral anticoagulants, NSAIDs, low-dose ASA, nitrates, H_2RAs, and PPIs in an unconditional logistic regression model.

[b]Specific cut-off values for PPI dose: omeprazole 20 mg, esomeprazole 40 mg, lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg. Doses less than the cut-off value were classified as low doses, doses equal to the cut-off value were classified as medium doses, and doses greater than the cut-off value were classified as high doses.

Table 3. The Effect of H_2RA on the Risk of UGIB in Patients Taking Gastrotoxic Agents

	Cases (N = 1021), n (%)	Controls (N = 5793), n (%)	Adjusted RR[a] (95% CI)
Recency			
Nonuse (in 1 year)	922 (90.3)	5406 (93.3)	1.00 (–)
Current user (within 30 days), duration > 1 month	57 (5.6)	243 (4.2)	0.89 (0.64–1.22)
Current user (within 30 days), duration ≤ 1 month	9 (0.9)	29 (0.5)	1.14 (0.51–2.56)
Past user (31–365 days)	33 (3.2)	115 (2.0)	1.11 (0.73–1.69)
Dose (among current users with duration > 1 month)[b]			
Nonuse (in 1 year)	922 (90.3)	5406 (93.3)	1.00 (–)
Low/medium dose	6 (0.6)	26 (0.4)	0.79 (0.31–2.01)
High dose	51 (5.0)	217 (3.7)	0.90 (0.64–1.26)
Duration (among current users with duration > 1 month)			
Nonuse (in 1 year)	922 (90.3)	5406 (93.3)	1.00 (–)
31–90 days	8 (0.8)	16 (0.3)	1.32 (0.53–3.32)
91–365 days	7 (0.7)	49 (0.8)	0.47 (0.21–1.09)
>365 days	42 (4.1)	178 (3.1)	0.96 (0.67–1.39)

[a]RRs adjusted for age, sex, calendar year, PCP visits, prior hospitalizations, prior history of PUD, smoking status, alcohol consumption, and use of steroids, selective serotonin reuptake inhibitors, oral anticoagulants, NSAIDS, low-dose ASA, nitrates, H_2RAs, and PPIs in an unconditional logistic regression model.

[b]Specific cut-off values for H_2RA dose: cimetidine 800 mg, famotidine 40 mg, nizatidine 300 mg, and ranitidine 300 mg. Doses less than the cut-off value were classified as low doses, doses equal to the cut-off value were classified as medium doses, and doses greater than the cut-off value were classified as high doses.

0.03–0.56).[8] Another observational study, based on only one case exposed to a PPI, found a RR of UGIB of 0.04 (95% CI, 0.002–0.21) for PPI use and a corresponding estimate of 0.43 (95% CI, 0.18–0.91) for H_2RA use in DAT users.[26] Our data confirm that PPI use has a strong inverse association with UGIB (RR, 0.17; 95% CI, 0.04–0.76) in patients on DAT. However, we did not have a sufficient number of exposed individuals to assess the corresponding effect of H_2RAs.

Our results revealed that PPIs may have a stronger inverse association with UGIB than that conferred by H_2RAs in the general population. This trend also was observed in users of low-dose ASA but not in users of NSAIDs. Unfortunately, the sample sizes were not large enough to directly compare the effect of PPIs and H_2RAs in users of clopidogrel. Lanas et al[3] reported that PPI use was associated with more profound protective effects against UGIB than H_2RA use in the general population as well as in users of low-dose ASA or NSAIDs.

It is important to note that PPIs and H_2RAs were prescribed commonly to treat existing PUD or to prevent PUD with or without complications in patient at high risk of UGIB,[4,27,28] which may lead to confounding by indication if the protective effects of acid-suppressing agents were attenuated by the high baseline risk of UGIB. Although we adjusted for an extensive list of confounders for UGIB, there still may be residual confounding. To further address this issue, we reviewed manually the electronic medical records with free-text comments to determine the indication of PPI and H_2RA use. Among these indications, PPIs or H_2RAs prescribed for PUD or UGI symptoms, such as dyspepsia or abdominal pain, might have been used to treat existing conditions that could later progress to a UGIB event, and they were indeed associated with an increased risk of UGIB in our analysis. This association reflects that acid suppressants often are used to treat PUD rather than that they increase the risk of UGIB. In contrast, for other indications for which these

Table 4. The Effect of Acid-Suppressing Agents on the Risk of UGIB in the General Population

	Cases (N = 2049), n (%)	Controls (N = 20,000), n (%)	Adjusted RR[a] (95% CI)
PPI			
Nonuse (in 1 year)	1554 (75.8)	17,183 (85.9)	1.00 (–)
Current user (within 30 days), duration ≤ 1 month	88 (4.3)	212 (1.1)	2.87 (2.18–3.78)
Current user (within 30 days), duration > 1 month	231 (11.3)	1788 (8.9)	0.80 (0.68–0.94)
Past user (31–365 days)	176 (8.6)	817 (4.1)	1.48 (1.23–1.79)
H_2RA			
Nonuse (in 1 year)	1834 (89.5)	19,147 (95.7)	1.00 (–)
Current use (within 30 days), duration ≤ 1 month	27 (1.3)	71 (0.4)	2.43 (1.51–3.92)
Current use (within 30 days), duration > 1 month	98 (4.8)	450 (2.3)	1.17 (0.92–1.50)
Past use (31–365 days)	90 (4.4)	332 (1.7)	1.68 (1.30–2.18)

[a]RRs adjusted for age, sex, calendar year, PCP visits, prior hospitalizations, prior history of PUD, smoking status, alcohol consumption, and use of steroids, selective serotonin reuptake inhibitors, oral anticoagulants, NSAIDS, low-dose ASA, nitrates, H_2RAs, and PPIs in an unconditional logistic regression model.

agents were used as preventive measures, we observed 30%–40% reductions in the risk of UGIB associated with PPI use and a 10% reduction associated with H_2RA use in the general population (data not shown).

Our analysis did not show different effects on UGIB associated with PPIs or H_2RAs of different doses. Ray et al[25] reported essentially the same effect of high-dose vs low-dose PPIs for reducing NSAID-associated gastroduodenal bleeding. We observed that long-term use of PPIs appears to have a more pronounced inverse association with UGIB compared with short-term use, but 95% CIs of the estimates overlap substantially. The estimates of H_2RA use of different duration were more unstable and inconclusive.

We found no significant association between use of nitrates and the risk of UGIB. Although 2 prior observational studies using similar design and populations have reported that the use of nitrates is associated with a reduced risk of UGIB,[3,29] no clinical trial to date has investigated this association.

We need to acknowledge several limitations in this study. First, we did not have a uniform recording of *H pylori* testing, and quite a few subjects were missing this information, which makes it difficult for us to assess the role of *H pylori* eradication in the associations we studied. Theoretically, patients with *H pylori* infection could get more PPI prescriptions (eg, for eradication). Because these patients are also at a higher risk of UGIB, lack of adjustment for it would attenuate the protective effect of PPIs on UGIB. Therefore, the actual magnitude of the effect may be greater than what we have reported. Also, without assessing the interaction between PPIs and *H pylori* infection, our results may not be directly generalizable to a population with a different prevalence of *H pylori* infection.

In addition, THIN only captures recorded prescription medications, and we were unable to take into account the use of over-the-counter ASAs, NSAIDs, or acid-suppressing drugs. It is likely that some patients were using over-the-counter PPIs or H_2RAs and therefore may have been misclassified as nonusers in this study. Nondifferential misclassification of a drug would bias the effect toward the null. However, comparing patients being treated with omeprazole, which is available over the counter in the United Kingdom, with those using other prescription-only PPIs, we found very similar RRs of UGIB. A similar pattern was observed for H_2RAs. Also, given that prescriptions are free for patients older than the age of 60 years in the United Kingdom, elderly patients have a strong financial incentive to use prescribed medications.

A major strength of this study was its large sample size. Also, patients recorded within THIN have been proven to be representative of the UK general population.[14] Moreover, the outcome of this study has been validated: more than 95% of UGIB cases from a random sample were confirmed upon consultation with the PCPs in a previous study.[16,17]

It is important to quantify the absolute risk reduction of UGIB associated with PPIs or H_2RAs in a real clinical setting. Based on the baseline incidence rates of peptic ulcer bleeding and the RRs of UGIB associated with use of specific gastrotoxic drugs estimated in the UK population,[30,31] we estimated the incidence rates of UGIB in users of gastrotoxic drug to be 9.3–25.0 per 1000 person-years in the United Kingdom. The number needed to treat to prevent one UGIB over 6 months of treatment with a PPI was 382 in users of low-dose ASA, 230 in users of clopidogrel, 97 in users of DAT, and 265 in users of NSAIDs. The corresponding number needed to treat in DAT users estimated by the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial was 98.[8]

Although findings suggest that PPI use may be protective against the risk of UGIB among patients receiving antithrombotic or anti-inflammatory drugs, in clinical decision making, benefits should be balanced against potential risks. Prior studies have reported that PPI use may be associated with an increased risk of *Clostridium difficile* and other enteric infections, vitamin B_{12} deficiency, and osteoporotic fractures, mainly through suppression of acid secretion in the stomach.[32] There also have been concerns that concomitant use of PPIs may limit the reduction of coronary events among those requiring treatment of clopidogrel because of the potential pharmacologic interaction between the 2 agents, but data have been inconsistent and a recent RCT did not support this association.[6,8] Because our analysis has focused on UGIB, other outcomes potentially associated with PPIs cannot be addressed in the current study.

We identified several factors associated with a higher risk of UGIB, including history of complicated PUD, uncomplicated PUD, or dyspepsia/gastritis, smoking, and heavy alcohol consumption. Although some of these associations also have been reported by prior studies,[33–35] we included them as potential confounders and, therefore, these results should not be overinterpreted. The current study controlled age by matching cases to controls within 1 year of age difference, so we were unable to estimate the independent effect of age on the risk of UGIB. However, we had considered age as a risk factor in prior studies using similar populations and found the incidence of UGIB to steeply increase with age.[36] In the current analysis, PPI use appeared to be associated with a greater protective effect against UGIB in gastrotoxic drug users age 65 years and older (RR, 0.53; 95% CI, 0.41–0.69) than in those younger than age 65 (RR, 0.88; 95% CI, 0.54–1.44).

In conclusion, we found that PPIs may reduce the risk of UGIB in the general population and in users of antithrombotic drugs, oral corticosteroids, and NSAIDs. The reductions in the risk of UGIB associated with use of H_2RAs, even at high doses, tend to be smaller and have larger CIs than those associated with use of PPIs. We found no association between use of nitrates and the risk of UGIB.

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Conflicts of interest

These authors disclose the following: Sonia Hernández-Díaz has received research funding and consultancy fees from AstraZeneca R&D, and has participated in data safety monitoring boards for Novartis; Luis García Rodríguez works for the Spanish Centre for Pharmacoepidemiologic Research, which has received research funding and consultancy fees from AstraZeneca R&D (Mölndal, Sweden). The remaining authors disclose no conflicts.

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