

Proton-Pump Inhibitor Use and the Risk for Community-Acquired Pneumonia

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Background: Recent studies suggest that proton-pump inhibitors (PPIs) may increase the risk for community-acquired pneumonia (CAP).

Objective: To examine the association between PPI use and CAP in adults followed in general practices in the United Kingdom.

Design: Nested case-control study.

Setting: The General Practice Research Database (1987 to 2002) in the United Kingdom.

Participants: Patients age 18 years or older with at least 6 months of initial pneumonia-free follow-up in the database. Case patients ($n = 80\,066$) were defined as those who received an incident diagnosis of CAP. Control participants ($n = 799\,881$) were selected by using incidence density sampling, matching on practice site, calendar period, and follow-up duration.

Measurements: Use of PPIs within 30 days before the index date. Adjusted odds ratios (ORs) were estimated by using conditional logistic regression, adjusting for potential confounders.

Results: Overall, current PPI use was not associated with an increased risk for CAP (adjusted OR, 1.02 [95% CI, 0.97 to 1.08]) or

risk for CAP that required hospitalization (adjusted OR, 1.01 [CI, 0.91 to 1.12]). There was a strong increase in risk for CAP associated with current use of PPI therapy that was started within the previous 2 days (adjusted OR, 6.53 [CI, 3.95 to 10.80]), 7 days (adjusted OR, 3.79 [CI, 2.66 to 5.42]), and 14 days (adjusted OR, 3.21 [CI, 2.46 to 4.18]), but there was no statistically significant association for longer-term current PPI therapy. A separate matched case-control analysis, which included the 3 strongest confounders as additional matching factors, yielded similar results as the primary analysis (adjusted OR, 0.96 [CI, 0.91 to 1.02]).

Limitations: Adherence to PPI prescription was assumed to be 100%. No radiographic evidence was available to corroborate a diagnosis of CAP.

Conclusion: Proton-pump inhibitor therapy started within the past 30 days was associated with an increased risk for CAP, whereas longer-term current use was not.

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Proton-pump inhibitors (PPIs) are potent gastric acid suppressants. With its excellent efficacy for acid-related diseases and increasing availability of both over-the-counter and generic formulations, PPI use continues to escalate (1). Antiulcer drugs, primarily PPIs, ranked second in overall U.S. retail sales at \$10.8 billion in 2001 (2).

Two studies recently suggested that PPI use may increase the risk for community-acquired pneumonia (CAP) (3, 4). A proposed mechanism is increased bacterial colonization in the upper gastrointestinal tract due to gastric acid suppression (3, 4). However, other noncausal mechanisms may also be responsible for the association between PPIs and CAP. Residual confounding may have contributed to the relatively modest increased risk seen in these studies. Furthermore, both studies found that the association was weakest among current recipients who had been taking PPIs for the longest duration, which is contrary to what one would expect if PPIs increase the risk for CAP.

Community-acquired pneumonia leads to significant morbidity and mortality and dramatic costs to the health care system. In the United States, more than 1.1 million persons are hospitalized each year because of CAP (5). In the Medicare program alone, more than \$3.5 billion are spent on pneumonia-related admissions annually (5). Given the widespread use of PPIs, clarifying the potential association between PPI therapy and risk for CAP is of great importance to public health. A recent systematic re-

view on management strategies for gastroesophageal reflux disease, commissioned by the U.S. Agency for Healthcare Research and Quality, called for further studies to elucidate the role of acid suppression on the development of CAP (6). Thus, we sought to more definitively examine the effect of current PPI exposure on CAP development in a large, population-based cohort.

METHODS

Data Source

We conducted a nested case-control study by using the General Practice Research Database (GPRD). The GPRD comprises prospectively collected, computerized medical records from a sample of general practices throughout the United Kingdom that represents the U.K. population in terms of age, sex, and geographic distribu-

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Conversion of graphics into slides

Context

Some studies suggest that proton-pump inhibitors (PPIs) may increase risk for community-acquired pneumonia (CAP).

Contribution

This large, nested case-control study involving adults in general practices in the United Kingdom found that current, long-term PPI use was not associated with increased risk for CAP. Recently started PPI therapy was associated with increased risk: Adjusted odds ratios for PPI use started within 2, 7, and 14 days of CAP diagnosis were 6.5, 3.8, and 3.2, respectively.

Implication

Long-term PPI use is not associated with increased risk for CAP. The association between recently started PPIs and CAP risk is not clear but is not necessarily causal.

—The Editors

tion (7). Under the National Health Service, a general practitioner coordinates the health care of 98% of U.K. residents. The GPRD differs fundamentally from claims databases because it comprises the actual medical record, which contains complete and comprehensive clinical data. The information collected in the database includes demographic characteristics, prescription use, clinical diagnoses, subspecialty consultation notes, and hospital discharge diagnoses. Prescriptions for most medications are written for 1 month in U.K. general practices. Details of every prescription issued include date, dosage, quantity dispensed, duration of therapy, and indication. The Read clinical classification and the Oxford Medical Information System codes are used to classify medical diagnoses (8, 9). The Read clinical classification was adopted in the United Kingdom in 1990 as an electronic medical coding system. These codes incorporate information on medical history, physical examination, procedures, symptoms, medication use, and social history. These codes are cross-referenced with other major systems of medical coding, including but not limited to the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10), and Current Procedural Terminology-4. The Oxford Medical Information System codes are related to the ICD-9 codes, with the first 3 numbers typically corresponding to the first 3 digits of the ICD-9 codes. The GPRD uses a practice-based quality marker known as “up-to-standard” to indicate when data recording by the practice adhered to specific quality measures according to GPRD Recording Guidelines, with respect to completeness, continuity, and plausibility (7). We used only data that were collected after the up-to-standard date in each practice to maximize the validity of the study. Previous validation studies have shown that the GPRD captures 90% to 95% of the diag-

noses from specialty referral visits and greater than 90% of the principal hospital discharge diagnoses (10–12).

The institutional review board at the University of Pennsylvania and the GPRD Independent Scientific Advisory Committee approved this study. The University of Pennsylvania’s institutional review board granted a waiver of informed consent because we used existing data that contained no patient identifiers.

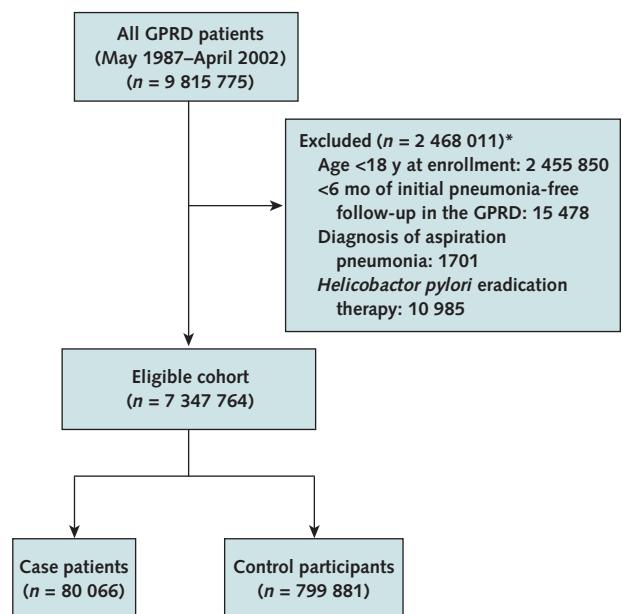
Study Cohort

Study participants were drawn from a cohort of approximately 9 million patients who started follow-up in the GPRD from May 1987 to April 2002. The Figure shows the cohort selection process and the exclusion criteria. A substantial proportion of patients met several exclusion criteria. We excluded patients who received a diagnosis of CAP within the initial 6 months of GPRD follow-up to avoid misclassification of prevalent CAP cases as incident cases (13). We excluded patients receiving *Helicobacter pylori* eradication therapy because their antibiotics concurrent with PPI therapy could potentially mask the effect of PPI use on the risk for CAP. We excluded patients who received a diagnosis of aspiration pneumonia because it differs from CAP in terms of pathophysiology and risk factors. Only 1% of case patients were excluded solely on the basis of this criterion.

Case Patients

Case patients consisted of all individuals in the eligible study cohort who received a diagnosis with their first epi-

Figure. Study flow diagram.



GPRD = General Practice Research Database.

* Some patients met multiple exclusion criteria.

sode of CAP within the GPRD follow-up period. The CAP diagnosis was determined on the basis of a list of relevant Read clinical classification or Oxford Medical Information System codes. The date of the first CAP diagnosis was designated as the index date for each case.

To improve the specificity of our CAP case patient definition, we did a secondary analysis in which we restricted our case-patient group to those who had a first episode of CAP in the GPRD that resulted in a hospital admission. A case of CAP was considered to have required hospitalization if the recorded diagnosis was linked with a hospitalization outcome code.

Control Participants

By using incidence density sampling, we randomly selected up to 10 control participants for each case patient from the eligible study cohort. Incidence density sampling of control participants yields odds ratios (ORs) that are unbiased estimates of the incidence rate ratios (14). Control participants were selected 1 case at a time with replacement (that is, a patient can be a control participant for several cases). For each CAP case, we first identified all patients in the study cohort who remained at risk for CAP on the index date of the case. We then selected, among patients at risk, those who were followed at the same general practice site as the case. From those at-risk patients in the same practice site, we then selected patients who started GPRD follow-up on a date that is within 1 month before or after the GPRD start date of the case. Patients who fulfilled all criteria were eligible matched control participants and were assigned an index date that was the same as the case index date. By definition, all eligible control participants were matched to their respective case patients on index date, general practice site, and both calendar period and duration (± 1 month) of follow-up before the index date. In the event that 10 or fewer eligible matched control participants were available for a particular case, all control participants were included. If more than 10 eligible matched control participants were available for a case, we randomly selected 10 for our analysis. We then repeated the process for all case patients. We were able to identify 10 control participants for greater than 99% of the cases and at least 1 eligible matched control participant for all cases.

The reason for choosing 10 control participants was based on considerations for statistical power and efficiency of analysis. Generally, significant statistical power can be gained by going from a 1-to-1 to a 1-to-10 case-control ratio. There would be little further gain in statistical power, yet the computational time would increase significantly by increasing the control-case ratio above 10.

Measure of Exposure

The primary exposure of interest was current PPI therapy: use of any PPI (esomeprazole, omeprazole, rabeprazole, pantoprazole, or lansoprazole) within 30 days before

the index date. Patients were considered to be exposed if they had a PPI prescription that would have lasted beyond 30 days before the index date. Among current PPI recipients, we examined the effect of daily dose (≤ 1.5 defined daily dose/d vs. > 1.5 defined daily dose/d) (15) and duration of use before index date (that is, < 30 days, 30 to 180 days, or > 180 days) as a secondary analysis. We also did a sensitivity analysis by varying the current exposure window to 15, 60, 90, and 120 days. Past recipients were those who were exposed to PPI therapy that ended more than 30 days before the index date in the primary analysis.

Statistical Analysis

We used conditional logistic regression to calculate the ORs and the 95% CIs. In addition to age, sex, and the matching factors, we examined a comprehensive list of potential confounders with known associations with PPI therapy, pneumonia risk, and/or comorbid conditions. These included current smoking, total number of general practice visits during the past year, total number of hospitalizations during the past year, chronic obstructive pulmonary disease or asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, history of CAP before GPRD enrollment, cancer other than basal-cell carcinoma, dementia, and alcoholism. We also considered exposure to histamine-2-receptor antagonists, anxiolytics, antidepressants, antipsychotics, antibiotics, antiparkinson drugs, barbiturates, opiates, corticosteroids, and long-term nonsteroidal anti-inflammatory drugs. We included antibiotics for their association with infection in general; histamine-2-receptor antagonists for their effect on gastric acid; and antiparkinson drugs, barbiturates, anxiolytics, antipsychotics, antidepressants, and opiates for a possible association with airway compromise and therefore risk for pneumonia. We included corticosteroids because of immunosuppressive effects. We intended to capture long-term current use of nonsteroidal anti-inflammatory drugs or aspirin (that is, > 1 year of cumulative use and last use within 1 year before index date) as a marker of comorbid disease and a predisposing factor for PPI use. A previously published validation study found that data on prescription nonsteroidal anti-inflammatory drugs or aspirin recorded in GPRD correctly classified status of long-term nonsteroidal anti-inflammatory drugs or aspirin in greater than 98% of the GPRD participants (16). Others have found similar reliability of GPRD data in capturing long-term nonsteroidal anti-inflammatory drugs or aspirin recipients (17–21). We defined corticosteroid use as at least 2 weeks of treatment with the last use no more than 30 days before the index date, presuming that this exposure could compromise immune status. Exposure to the remaining medications was any use within 30 days before the index date. We did not adjust for antibiotic treatment that started within 7 days of the index date because it was probably intended for CAP treatment among the case patients. We found that risk for CAP among pa-

Table 1. Characteristics of Case Patients and Control Participants with Community-Acquired Pneumonia

Characteristic	Case Patients (n = 80 066)	Control Participants (n = 799 872)
Mean age (SD), y	73.5 (17.6)	49.5 (18.3)
Men, %	47.4	52.6
Alcoholism, %	2.3	1.5
Dysphasia, %	1.8	0.9
Dementia, %	14.4	1.5
Stroke, %	19.2	3.5
Diabetes, %	4.9	2.6
Cirrhosis, %	0.3	0.1
Renal failure, %	0.5	0.1
Congestive heart failure, %	10.5	1.8
Myocardial infarction, %	9.3	3.3
Chronic obstructive pulmonary disease or asthma, %	22.4	10.3
Cancer, %	7.3	4.2
Previous community-acquired pneumonia, %	3.2	0.9
Mean hospitalizations in year before index date (SD), n	0.8 (1.4)	0.1 (0.5)
Mean office visits in year before index date (SD), n	4.2 (5.2)	0.8 (1.8)
Current smoker, %	14.5	15.9
Nonsteroidal anti-inflammatory drugs, %	7.5	3.0
Corticosteroids, %	9.7	1.2
Histamine-2-receptor antagonists, %	5.5	1.6
Antibiotics, %	19.8	6.5
Antiparkinson drugs, %	2.9	0.4
Antidepressants, %	10.5	3.6
Anxiolytics, %	17.8	3.6
Opiates, %	8.0	0.8
Barbiturates, %	0.1	0.0
Antipsychotics, %	9.0	0.9

tients with such antibiotic exposure was 10-fold higher than for those without this exposure. Adjustment for such antibiotic exposure would have biased the results toward the null. Effect modification was examined for those age 60 years or older versus those younger than age 60 years. The reason for this cutoff is based on a dramatic increase in CAP incidence after age 60 years (22) and previously reported effect modification between these age groups (3).

We did not conduct a formal power calculation. However, our source population was at least 10 times larger than either of the 2 previous studies that reported a modest association. Therefore, we should have been able to detect even a modestly increased risk if it was present.

All analyses were done with Stata software, version 8.2 (Stata, College Station, Texas). A 2-tailed *P* value less than 0.05 was considered statistically significant.

Role of Funding Source

This study was funded by an Academic Development Fund provided to Dr. Yang by the Department of Medicine at the University of Pennsylvania. The funding source played no role in defining study objectives, data collection, analysis, interpretation, or the decision to submit the manuscript for publication.

RESULTS

We identified 80 066 case patients with CAP and 799 881 control participants. About 25% (*n* = 20 192) of the case patients required hospitalization. **Table 1** lists the characteristics of the case patients and control participants. The former group was much more likely to have chronic disease and to be receiving medications that could compromise airway protection.

After we adjusted for sex and age, the OR for CAP associated with current PPI use within 30 days of the index date was 2.05 (95% CI, 1.96 to 2.15; *P* < 0.001). After adjustment for all additional covariates, current exposure to PPIs was not associated with an increased risk for CAP (**Table 2**). The results were similar when we varied the exposure window to 15, 60, 90, or 120 days (**Appendix Table 1**, available at www.annals.org). Furthermore, the adjusted OR for CAP associated with current histamine-2-receptor antagonist use was 0.99 (CI, 0.95 to 1.04; *P* = 0.78). When we restricted the case group to patients with CAP who required hospital admission, current PPI use still had no association with risk for CAP (adjusted OR, 1.01 [CI, 0.91 to 1.12]; *P* = 0.82).

When we stratified the current PPI recipient group on the basis of duration of exposure before the index date, PPI use for fewer than 30 days was associated with moderately increased risk for CAP (**Table 2**). Among current PPI recipients with longer periods of PPI exposure, risk for CAP did not increase (**Table 2**). A close examination of the group with current PPI use for fewer than 30 days revealed that new PPI therapy started within the 30 days before the index date accounted for all of the increased risk for CAP in this group (**Table 2**). In addition, increases in risk for CAP were progressively larger among recipients who started PPI or histamine-2-receptor antagonist therapy within 14, 7, or even 2 days before the index date (**Table 3**).

We found a modest increase in risk for CAP associated with high daily PPI dosing among current PPI recipients (**Table 2**). However, this positive effect was attenuated substantially and was no longer statistically significant after new recipients of PPI therapy were excluded (adjusted OR, 1.13 [CI, 0.95 to 1.35]; *P* = 0.15). At a daily dose of less than 1.5 times the defined daily dose, current PPI exposure was not associated with an increased risk for CAP (**Table 2**).

The risk for CAP in PPI recipients younger than age 60 years modestly increased (adjusted OR, 1.16 [CI, 1.02 to 1.32]; *P* = 0.02). However, this weakly positive effect diminished further after new recipients of PPI therapy were excluded (adjusted OR, 1.08 [CI, 0.94 to 1.23]; *P* = 0.29). Furthermore, current PPI use was not associated with CAP in persons age 60 years or older (adjusted OR, 0.99 [CI, 0.93 to 1.04]; *P* = 0.67).

We did a separate case-control analysis after including the aspiration pneumonia case patients and reselected con-

trol participants by using incidence density sampling. We found virtually no change in our primary effect estimate for current PPI use with the adjusted OR increasing from 1.02 to 1.03 (CI, 0.97 to 1.09; $P = 0.27$).

We also conducted a separate, matched case-control analysis after adding the 3 most influential confounders in our primary analysis (that is, total number of general practice visits during the past year, total number of hospitalizations during the past year, and current opiate use) to the original list of matching factors (Appendix Table 2, available at www.annals.org). Approximately 78% ($n = 62\,032$) of the original case patients were matched with at least 1 eligible control participant in this separate analysis. We adjusted for age and sex in this matched case-control data set and calculated an OR of 1.00 (CI, 0.95 to 1.05; $P = 0.9$) for the risk for CAP associated with current PPI exposure. Adjustment for the remaining potential confounders included in the primary analysis led to a slight decrease in the OR (0.96 [CI, 0.91 to 1.02]; $P = 0.2$). The adjusted OR for the risk for CAP associated with past PPI use was 0.86 (CI, 0.82 to 0.90; $P < 0.001$).

DISCUSSION

In this large, population-based study, current PPI use overall was not associated with an increased risk for CAP. However, we saw a markedly increased risk for CAP associated with PPI use started within a few days before the index date, whereas longer periods of current PPI use were not associated with an increased risk.

We did a MEDLINE search from 1995 to January 2008 to identify studies in English that have examined the association between PPIs and pneumonia. We found 2 previous population-based, nested case-control studies, both of which reported a positive association between current PPI use and risk for CAP (3, 4). The study, which was conducted in a Dutch cohort, reported an 80% to 90% increase in the risk for CAP associated with current PPI exposure compared with past PPI exposure (4). Another study, conducted in a Danish cohort, found a 50% increase in the risk for hospitalization for CAP associated with current PPI use (3). However, both studies saw an inverse relationship between the magnitude of the association and the duration of PPI exposure, with the weakest association among current recipients who received the drug for the longest duration.

Our study elucidates the association between acid suppressive therapy and risk for CAP in several respects. First, residual confounding may be responsible for much of the previously seen associations. In particular, patients with comorbid conditions or poor health status were more likely to be prescribed PPIs and have a higher risk for CAP (23). In our crude analysis, when we controlled only for sex, age, and the matching variables, PPI use was strongly associated with risk for CAP. However, this effect vanished after adjustment for additional variables, suggesting a substantial

influence of confounding effect in this association. In particular, the most significant attenuation in the sex- and age-adjusted OR was seen after we controlled individually for the numbers of hospitalizations and general practice visits during the year before the index date (Table 2). The Danish study did not include either of these measures, and the Dutch study only adjusted for general practice visits. Furthermore, current use of opiates was the third most influential covariate, leading to a 30% reduction in the sex- and age-adjusted OR in our study, and neither previous study accounted for this variable. Other important confounders not considered in at least 1 of the previous studies included current use of anxiolytics or antidepressants and previous stroke. A similar drastic attenuation of the positive effect was in the Danish study (3). The Dutch study reported a much smaller decrease from the crude to the adjusted ORs, but its nested case-control analysis was done in a PPI recipient subcohort, and it accounted for a much shorter list of potential confounders (4). Furthermore, simple adjustment of covariates may not adequately exclude potential confounding if overlapping covariate distributions between the comparison groups are lacking. Therefore, we conducted a separate case-control analysis in which we matched case patients with control participants by the most influential confounders in our primary analysis along with the original matching factors. This analysis yielded results similar to those of our primary analysis. Thus, our OR estimates may be less influenced by residual confounding than those in the previous studies.

Similar to the Dutch study, we excluded patients with aspiration pneumonia, who made up only 1% of the total case patients. Therefore, it is unlikely that we missed a positive association because of this exclusion. Our separate analysis, including those with aspiration pneumonia, also yielded nearly identical results as our primary analysis.

Second, we saw a marked increase in risk for CAP associated with being issued a new PPI prescription in the past 48 hours. Notably, this positive effect diminished or disappeared for PPI therapy started in the more distant past. Such an inverse temporal relationship was also demonstrated in the Danish study (3). In the Dutch study, current PPI recipients who received short-duration PPI therapy (that is, <30 days) before the index date had a much stronger risk for CAP than did current PPI recipients who had used PPIs for longer periods (4). These observations counter those that one would expect from a true causal association because the acid suppressive effect of PPIs takes at least 7 days to reach maximum effect (24). If such a dramatic risk increase in new recipients of PPI therapy had a biological basis, it should have been more pronounced, or at least persistent, among current PPI recipients who had been receiving the medication for much longer periods.

We also saw a similar inverse temporal trend and an even more pronounced increase in the risk for CAP among new recipients of histamine-2-receptor antagonists (Table

Table 2. Odds Ratios for Community-Acquired Pneumonia Associated with Proton-Pump Inhibitor Exposure

Proton-Pump Inhibitor Exposure	Case Patients, n (%)	Control Participants, n (%)	Odds Ratio (95% CI); P Value		
			Adjusted for Sex and Age*	Adjusted for Sex, Age, and Hospitalizations	Adjusted for Sex, Age, Hospitalizations, and Office Visits
Nonrecipient	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Current recipient	3455 (4.3)	10 031 (1.3)	2.05 (1.96–2.15); <0.001	1.51 (1.43–1.59); <0.001	1.21 (1.14–1.27); <0.001
Daily dose					
≤1.5 DDD	3056 (3.8)	9126 (1.1)	1.92 (1.83–2.02); <0.001	1.46 (1.39–1.55); <0.001	1.17 (1.11–1.24); <0.001
>1.5 DDD	399 (0.5)	905 (0.1)	2.89 (2.52–3.31); <0.001	1.94 (1.67–2.25); <0.001	1.56 (1.33–1.83); <0.001
Duration of use					
<30 d	469 (0.6)	1100 (0.1)	3.16 (2.79–3.59); <0.001	2.37 (2.07–2.73); <0.001	1.96 (1.69–2.29); <0.001
New recipients†	361 (0.5)	595 (0.1)	4.31 (3.69–5.04); <0.001	3.27 (2.77–3.87); <0.001	2.78 (2.33–3.33); <0.001
Others‡	108 (0.1)	505 (0.1)	1.71 (1.35–2.16); <0.001	1.23 (0.95–1.59); 0.11	0.99 (0.76–1.30); 0.94
30–180 d	940 (1.2)	2447 (0.3)	2.53 (2.32–2.76); <0.001	1.62 (1.47–1.79); <0.001	1.25 (1.12–1.38); <0.001
>180 d	2046 (2.6)	6484 (0.8)	1.68 (1.59–1.78); <0.001	1.33 (1.25–1.41); <0.001	1.09 (1.02–1.16); 0.01
Past recipient	3424 (4.3)	19 215 (2.4)	1.50 (1.44–1.56); <0.001	1.20 (1.14–1.25); <0.001	1.01 (0.97–1.09); 0.58

DDD = defined daily dose.

* Case patients and control participants were matched on practice site, calendar year, and duration of follow-up before index date.

† Adjusted for sex, age at index date, current smoking status, alcoholism, total number of general practice visits during the past year, total number of hospitalizations during the past year, community-acquired pneumonia before General Practice Research Database enrollment, chronic obstructive pulmonary disease or asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, any cancer other than basal-cell carcinoma, and dementia. We also considered use of histamine-2-receptor antagonists, anxiolytics, antidepressants, antiparkinson drugs, antipsychotics, barbiturates, opiates, corticosteroids, antibiotics, and nonsteroidal anti-inflammatory drugs.

‡ Current recipients who began proton-pump inhibitor therapy <30 days before the index date.

§ Patients whose first prescription was >30 days before the index date but whose use extended into the 30-day window before the index date.

3). Because histamine-2-receptor antagonists are weaker acid suppressants than PPIs, these results provided further evidence that the increased risk for CAP seen among new PPI recipients is unlikely to result from the acid suppressive or immunosuppressive effect of the PPIs.

A possible contributing factor for the elevated ORs associated with newly started PPI therapy is protopathic bias (that is, drugs given to treat early symptoms that may seem temporally associated with the subsequent illness) (25). For example, nonspecific, early symptoms related to the ensuing CAP, such as coughing, might be mistaken as acid-related symptoms and be treated empirically with PPIs shortly before the eventual diagnosis of CAP. However, empirical PPI therapy is generally indicated only for subacute or chronic cough, which is uncommon for CAP (26, 27). A potentially more likely scenario is that PPIs could have been initiated for symptoms caused by nonsteroidal anti-inflammatory drug therapy started for early symptoms of CAP. However, we could not adequately assess this hypothesis because recipients of short-term nonsteroidal anti-inflammatory drugs probably obtained them over the counter, which would not have been captured by the GPRD.

A modest protective effect was associated with current PPI use for longer than a total duration of 6 months in our primary analysis. A similarly modest inverse association between past PPI use and risk for CAP was seen in our secondary analysis with expanded case-control matching criteria. We do not have a compelling explanation for these findings. For the former, perhaps factors leading to PPI adherence may be protective. Alternatively, these results

could be chance findings or could be due to residual confounding.

Our study has several potential limitations. First, PPI prescription is an imperfect surrogate for PPI use. Such misclassification of PPI use, if nondifferential, would bias the results toward the null. This is less likely among current long-term PPI recipients compared with short-term recipients because it is unlikely that recipients receiving long-term PPI therapy would continue monthly visits to their general practitioner for PPI prescriptions if they were not receiving the medication. However, we saw no increased risk for CAP among current recipients receiving long-term PPI therapy. If PPI therapy was truly associated with risk for CAP, to the extent that misclassification among longer-term recipients was less than that among short-term recipients, one would expect to see a gradual increase in the OR associated with current PPI use as the duration of use increases. However, we saw the opposite temporal trend, and thus it seems unlikely that relying on prescription information to define PPI use was responsible for the null effect in our study. The previous 2 studies that reported a positive association also used prescriptions as a marker for PPI use (3, 4). Both reported a much weaker effect among the long-term current PPI recipients than among all current PPI recipients, arguing against a significant effect of nondifferential misclassification as a result of using prescriptions as a surrogate of use in populations receiving universal health care.

Second, the GPRD does not contain adequate radiographic data to corroborate diagnoses of CAP. Misclassification of the cases, if nondifferential, would bias the results

Table 2—Continued

Adjusted for Sex, Age, Hospitalizations, Office Visits, and Opiate Use	Fully Adjusted†
1.0 (reference) 1.13 (1.08–1.20); <0.001	1.0 (reference) 1.02 (0.97–1.08); 0.48
1.11 (1.05– 1.17); <0.001 1.42 (1.22– 1.67); <0.001	1.00 (0.95–1.06); 0.94 1.23 (1.05–1.45); 0.01
1.85 (1.60–2.15); <0.001 2.61 (2.18–3.13); <0.001	1.74 (1.49–2.03); <0.001 2.45 (2.04–2.95); <0.001
0.96 (0.73–1.26); 0.75 1.18 (1.06–1.31); 0.003	0.91 (0.69–1.19); 0.48 1.09 (0.98–1.22); 0.11
1.02 (0.96–1.09); 0.49 0.99 (0.94–1.04); 0.65	0.91 (0.84–0.97); 0.01 0.95 (0.90–1.0); 0.05

toward the null. To address this concern, we did a separate analysis that included only patients who required hospitalization. Generally, case patients hospitalized for CAP have more severe CAP—and more thorough documentation of the clinical information is expected—than do patients who are not hospitalized for CAP. Furthermore, in the Danish study, the effect estimates for radiography-confirmed and non-radiography-confirmed case patients hospitalized for

CAP were virtually identical, suggesting that radiographic confirmation may not be essential in the analysis involving case patients hospitalized for CAP in this context. Thus, although there may be residual misclassification associated with the definition of patients hospitalized for CAP, it should have an improved specificity for a true CAP event. To the extent that hospitalization for CAP is a more specific definition than any CAP in our study, if current PPI use was truly associated with risk for CAP, one would expect the effect estimate in the hospitalized CAP analysis to move in the positive direction away from that seen in the analysis for any CAP. However, the point estimates were virtually identical in these 2 analyses, suggesting that misclassification of case patients probably did not have a significant influence on our results.

Third, although we had comprehensive prescription information for the relevant medications, it is not clear how these variables should be defined to fully capture their potential confounding effects. However, adjustment for these covariates led to a marked decrease in the OR, suggesting that we did in fact account for a substantial amount of confounding effect. Among the covariates examined, only antibiotic use may be protective against CAP. An analysis excluding antibiotic recipients yielded results identical to our primary analysis. Furthermore, incomplete adjustment for other potential confounders would probably have increased the OR for PPI use. That we saw an overall null association would argue against the possibility that we missed a positive association between PPI use and CAP as a result of misclassification of confounders.

In conclusion, after accounting for potential confounders, we found that current PPI use is not associated

Table 3. Odds Ratios for Community-Acquired Pneumonia Associated with Exposure to Proton-Pump Inhibitors and Histamine-2-Receptor Antagonists among New Recipients of Each Drug*

Exposure	Case Patients, n (%)	Control Participants, n (%)	Sex- and Age-Adjusted Odds Ratio (95% CI)†	P Value	Fully Adjusted Odds Ratio (95% CI)‡	P Value
Nonrecipients	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	–	1.0 (reference)	–
New proton-pump inhibitor recipients (before index date)						
≤14 d	204 (0.25)	288 (0.04)	4.99 (4.03–6.17)	<0.001	3.16 (2.45–4.08)	<0.001
≤7 d	124 (0.15)	148 (0.02)	5.85 (4.39–7.79)	<0.001	3.80 (2.70–5.41)	<0.001
≤2 d	64 (0.08)	54 (0.01)	8.40 (5.43–12.99)	<0.001	6.53 (3.95–10.80)	<0.001
New histamine-2-receptor antagonist recipients (before index date)						
≤14 d	327 (0.41)	424 (0.05)	6.39 (5.36–7.61)	<0.001	3.90 (3.18–4.78)	<0.001
≤7 d	210 (0.26)	228 (0.03)	7.98 (6.33–10.06)	<0.001	5.21 (4.00–6.80)	<0.001
≤2 d	105 (0.13)	90 (0.01)	10.95 (7.69–15.59)	<0.001	7.66 (5.19–11.31)	<0.001

* All new recipients had their first proton-pump inhibitor or histamine-2-receptor antagonist prescription in the General Practice Research Database within 14, 7, or 2 days before index date.

† Case patients and control participants were matched on practice site, calendar year, and duration of follow-up before index date.

‡ Adjusted for sex, age at index date, current smoking status, alcoholism, total number of general practice visits during the past year, total number of hospitalizations during the past year, community-acquired pneumonia before General Practice Research Database enrollment, chronic obstructive pulmonary disease or asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, any cancer other than basal-cell carcinoma, and dementia. We also considered use of histamine-2-receptor antagonists, anxiolytics, antidepressants, antiparkinson drugs, antipsychotics, barbiturates, opiates, corticosteroids, antibiotics, and nonsteroidal anti-inflammatory drugs.

with a clinically significant increase in the risk for CAP or the risk for CAP that requires hospitalization. Although marked increases in risk for CAP were seen within days of starting PPI therapy, no increased risk was seen among current recipients who were prescribed these drugs for longer periods. Such a pattern of association has no obvious biological explanation, and a causal relationship cannot be established given the observational nature of our study.

This topic would benefit from a randomized, controlled trial. Ethical considerations would arise in designing such a trial, especially among patients with conditions for which PPIs have proven benefit. Perhaps future trials addressing this topic could target patients using PPIs for gastric protection, for which less definitive evidence establishing a benefit is available. Our findings significantly advance the current understanding of the association between PPI therapy and risk for CAP beyond the existing literature and may help physicians and policymakers achieve more accurate risk–benefit assessment in the management of acid-related disorders.

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Appendix Table 2. Odds Ratios for Community-Acquired Pneumonia Associated with Proton-Pump Inhibitor Exposure with Expanded Case–Control Matching Criteria*

Proton-Pump Inhibitor Exposure	Case Patients, n (%)	Control Participants, n (%)	Sex- and Age-Adjusted Odds Ratio (95% CI)*	P Value	Adjusted Odds Ratio (95% CI)†	P Value
Nonrecipient	57 630 (92.9)	486 144 (93.8)	1.0 (reference)	–	1.0 (reference)	–
Current recipient	2093 (3.4)	12 333 (2.4)	1.00 (0.95–1.05)	0.90	0.96 (0.91–1.02)	0.20
Past recipient	2309 (3.7)	19 593 (3.8)	0.86 (0.82–0.90)	<0.001	0.86 (0.82–0.90)	<0.001

* Case patients and control participants were matched on practice site, calendar year, duration of follow-up before index date, total number of general practice visits during the past year, total number of hospitalizations during the past year, and current opiate use.

† Adjusted for sex, age at index date, current smoking status, alcoholism, community-acquired pneumonia before General Practice Research Database enrollment, chronic obstructive pulmonary disease or asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, cancer other than basal-cell carcinoma, and dementia. We also considered use of histamine-2-receptor antagonists, anxiolytics, antidepressants, antiparkinson drugs, antipsychotics, barbiturates, opiates, corticosteroids, antibiotics, and nonsteroidal anti-inflammatory drugs.

Appendix Table 1. Odds Ratios for Community-Acquired Pneumonia Associated with Proton-Pump Inhibitor Exposure (15-, 60-, 90-, or 120-Day Exposure Window)

Proton-Pump Inhibitor Exposure	Case Patients, n (%)	Control Participants, n (%)	Sex- and Age-Adjusted Odds Ratio (95% CI)*	P Value	Fully Adjusted Odds Ratio (95% CI)†	P Value
15-d exposure window						
Nonrecipients	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	–	1.0 (reference)	–
Current recipients	3076 (3.8)	9147 (1.1)	1.98 (1.88–2.08)	<0.001	1.00 (0.93–1.04)	0.61
Daily dose						
≤1.5 DDD	2733 (3.4)	8349 (1.0)	1.85 (1.76–1.94)	<0.001	1.00 (0.91–1.03)	0.33
>1.5 DDD	343 (0.4)	798 (0.1)	2.72 (2.35–3.14)	<0.001	1.15 (0.96–1.37)	0.12
Duration of use before index date						
<30 d	417 (0.5)	877 (0.1)	3.43 (3.00–3.93)	<0.001	1.93 (1.64–2.28)	<0.001
New recipients‡	361 (0.5)	595 (0.1)	4.29 (3.68–5.01)	<0.001	2.44 (2.02–2.94)	<0.001
Others§	56 (0.1)	282 (0.0)	1.52 (1.10–2.09)	0.01	0.87 (0.60–1.26)	0.47
30–180 d	816 (1.0)	2144 (0.3)	2.48 (2.26–2.72)	<0.001	1.04 (0.93–1.17)	0.48
>180 d	1843 (2.3)	6126 (0.8)	1.58 (1.49–1.68)	<0.001	0.86 (0.80–0.93)	<0.001
Past recipients	3803 (4.8)	20 099 (2.5)	1.57 (1.51–1.64)	<0.001	0.98 (0.93–1.03)	0.36
60-d exposure window						
Nonrecipients	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	–	1.0 (reference)	–
Current recipients	3859 (4.8)	11 296 (1.4)	2.08 (1.99–2.17)	<0.001	1.04 (1.00–1.10)	0.11
Daily dose						
≤1.5 DDD	3418 (4.3)	10 251 (1.3)	1.97 (1.88–2.06)	<0.001	1.03 (0.98–1.09)	0.27
>1.5 DDD	441 (0.6)	1045 (0.1)	2.84 (2.49–3.22)	<0.001	1.23 (1.05–1.43)	0.01
Duration of use before index date						
<30 d	542 (0.7)	1501 (0.2)	2.73 (2.44–3.06)	<0.001	1.50 (1.31–1.72)	<0.001
New recipients‡	361 (0.5)	595 (0.1)	4.33 (3.71–5.05)	<0.001	2.45 (2.03–2.95)	<0.001
Others§	181 (0.2)	906 (0.1)	1.59 (1.33–1.91)	<0.001	0.85 (0.69–1.05)	0.13
30–180 d	1083 (1.4)	2930 (0.4)	2.53 (2.33–2.74)	<0.001	1.13 (1.02–1.25)	0.02
>80 d	2234 (2.8)	6865 (0.9)	1.75 (1.65–1.85)	<0.001	0.94 (0.88–1.00)	0.09
Past recipients	3020 (3.8)	17 950 (2.2)	1.43 (1.37–1.50)	<0.001	0.92 (0.90–0.97)	0.002
90-d exposure window						
Nonrecipients	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	–	1.0 (reference)	–
Current recipients	4094 (5.1)	12 278 (1.5)	2.07 (1.98–2.15)	<0.001	1.04 (0.99–1.09)	0.14
Daily dose						
≤1.5 DDD	3623 (4.5)	11 125 (1.4)	1.96 (1.87–2.04)	<0.001	1.03 (0.97–1.08)	0.36
>1.5 DDD	471 (0.6)	1153 (0.1)	2.80 (2.47–3.17)	<0.001	1.23 (1.06–1.43)	0.01
Duration of use before index date						
<30 d	607 (0.8)	1853 (0.2)	2.52 (2.27–2.81)	<0.001	1.38 (1.22–1.57)	<0.001
New recipients‡	361 (0.5)	595 (0.1)	4.33 (3.71–5.06)	<0.001	2.45 (2.03–2.95)	<0.001
Others§	246 (0.3)	1258 (0.2)	1.59 (1.36–1.85)	<0.001	0.84 (0.70–1.02)	0.08
30–180 d	1171 (1.5)	3361 (0.4)	2.42 (2.25–2.62)	<0.001	1.09 (0.99–1.20)	0.07
>180 d	2316 (2.9)	7064 (0.9)	1.77 (1.68–1.87)	<0.001	0.96 (0.90–1.02)	0.20
Past recipients	2785 (3.5)	16 968 (2.1)	1.40 (1.34–1.47)	<0.001	0.92 (0.87–0.97)	0.002
120-d exposure window						
Nonrecipients	73 187 (91.4)	770 626 (96.3)	1.0 (reference)	–	1.0 (reference)	–
Current recipients	4274 (5.3)	13 102 (1.6)	2.05 (1.96–2.14)	<0.001	1.03 (0.98–1.08)	0.24
Daily dose						
≤1.5 DDD	3778 (4.7)	11 844 (1.5)	1.95 (1.86–2.03)	<0.001	1.02 (0.97–1.07)	0.47
>1.5 DDD	496 (0.6)	1258 (0.2)	2.78 (2.46–3.13)	<0.001	1.19 (1.03–1.37)	0.02
Duration of use before index date						
<30 d	664 (0.8)	2160 (0.3)	2.42 (2.19–2.68)	<0.001	1.32 (1.17–1.49)	<0.001
New recipients	361 (0.5)	595 (0.1)	4.34 (3.72–5.07)	<0.001	2.45 (2.03–2.95)	<0.001
Others§	303 (0.4)	1565 (0.2)	1.61 (1.40–1.85)	<0.001	0.85 (0.72–1.00)	0.06
30–180 d	1248 (1.6)	3719 (0.5)	2.36 (2.20–2.55)	<0.001	1.08 (0.98–1.18)	0.11
>180 d	2362 (3.0)	7223 (0.9)	1.78 (1.69–1.88)	<0.001	0.95 (0.90–1.02)	0.20
Past recipients	2605 (3.3)	16 144 (2.0)	1.38 (1.32–1.45)	<0.001	0.92 (0.90–0.97)	0.004

DDD = defined daily dose.

* Case patients and control participants were matched on practice site, calendar year, and duration of follow-up before index date.

† Adjusted for sex, age at index date, current smoking status, alcoholism, total number of general practice visits during the past year, total number of hospitalizations during the past year, community-acquired pneumonia before General Practice Research Database enrollment, chronic obstructive pulmonary disease or asthma, myocardial infarction, congestive heart failure, chronic renal failure, cirrhosis, diabetes mellitus, stroke, cancer other than basal-cell carcinoma, and dementia. We also considered use of histamine-2-receptor antagonists, anxiolytics, antidepressants, antiparkinson drugs, antipsychotics, barbiturates, opiates, corticosteroids, antibiotics, and nonsteroidal anti-inflammatory drugs.

‡ Current recipients who began proton-pump inhibitor therapy <30 d before the index date.

§ Patients whose first prescription was >30 d before the index date but whose use extended into the 30-d window before the index date.