GASTROINTESTINAL SYMPTOMS are common: annually, 20% to 40% of the general population has at least 1 episode of dyspepsia or gastroesophageal reflux disease, and 5% consult a general practitioner for these complaints.\(^2\) The most effective treatment strategy for these symptoms in primary care is reduction of gastric acid secretion, which can be achieved by using H\(_2\)-receptor antagonists (H\(_2\)RAs) or proton pump inhibitors (PPIs).\(^3\) Currently, a common approach in western countries is to prescribe acid-suppressive drugs for upper gastrointestinal tract symptoms without suspicion of a malignancy and to refer nonresponders for gastrointestinal endoscopy.\(^4\) The consequence of this policy is that acid-suppressive drugs are among the most frequently prescribed drugs, whereas their use is not without risk.

H\(_2\)-receptor antagonists and PPIs increase susceptibility to infections by increasing gastric pH.\(^5,6\) Intragastric acidity constitutes a major nonspecific defense mechanism of the stomach to ingested pathogens. In normal gastric juice with a pH below 4, most pathogens are promptly killed, whereas they survive in hypochlorhydric to achlorhydric circumstances. For the effective management of upper gastrointestinal tract symptoms, the intragastric pH should, however, be maintained above 4 for at least 18 hours. Treatment with acid-suppressive drugs may therefore lead to an insufficient elimination, or even increased colonization, of ingested pathogens.\(^7,12\) There is some evidence that acid-suppressive therapy facilitates nosocomial infections.\(^13\)

To our knowledge, there are no large-scale studies of the association be-
between use of acid-suppressive drugs and the risk of infections. We examined the association between the use of gastric acid-suppressive drugs and community-acquired pneumonia in a population-based cohort study.

METHODS
Setting
All data were retrieved from the Integrated Primary Care Information (IPCI) project, a general practice research database containing data from electronic patient records of a group of about 150 general practitioners in the Netherlands. Details of the database have been described. Briefly, the database contains the complete medical records of approximately 500,000 patients. The electronic records contain coded and anonymous data on patient demographics, reasons for visit (in free text), diagnoses (using the International Classification for Primary Care and free text) from general practitioners and specialists, referrals, laboratory findings, hospitalizations, and drug prescriptions, including their indications and dosage regimen. To maximize completeness of the data, general practitioners participating in the IPCI project are not allowed to maintain a system of paper-based records aside from the electronic medical records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmacoepidemiologic research. The Scientific and Ethical Advisory Board of the IPCI project approved the study.

Source Population and Exposure Cohorts
The study started on January 1, 1995, and ended on December 31, 2002. The source population comprised all individuals with at least 1 year of valid database history, which means that the general practitioner supplied standard data for at least 1 year and the patient was registered for 1 year with the general practitioner. We required this pre-enrollment period to be able to characterize the patient and verify previous use of drugs and a history of pneumonia. All individuals were followed up from the moment they had 1 year of valid history until one of the following events: pneumonia, death, moving out of the practice area, or end of the study period, whichever came first. To retain patients without recent occurrence of pneumonia, we excluded all individuals who had a diagnosis of pneumonia in the pre-enrollment period.

From the source population, a study cohort of incident (no use in the year before enrollment) acid-suppressive drug users (those with at least 1 H2RA or PPI prescription) was identified. From this exposure cohort, we excluded all individuals who received acid-suppressive drugs in combination with antibiotics to eradicate *H. pylori* infection. The duration of use of individual acid-suppressive drugs was calculated from the prescribed quantity and prescribed dosing regimen. Person-time of exposure was accumulated during follow-up time for calculation of incidence rates. Individuals who never used acid-suppressive drugs before or during the study period were considered unexposed; follow-up time was accumulated for calculation of incidence rates.

Identification and Ascertainment of Pneumonia
The first occurrence of pneumonia for each individual was identified through searches on diagnoses and free-text indicators of pneumonia. The medical records of all potential cases were reviewed manually to classify the pneumonia as certain (proven by thorax radiography or microbiological culture), probable (clinical symptoms consistent with pneumonia but no objective evidence), possible, or no pneumonia. Definitions of pneumonia vary widely. Some require only the presence of infiltrates on chest radiography, whereas others require only certain symptoms or signs. In our analysis, we included pneumonia proven by chest radiography or sputum culture (certain) or presence of respiratory symptoms (probable). Cases with certain or probable pneumonia caused by aspiration (n=5), obstruction (n=6), or nosocomial infection (n=13) were excluded. The date of first pneumonia was defined as the index date.

Nested Case-Control Analysis
To reduce confounding by indication, a nested case-control analysis was conducted within the cohort of persons who used acid suppressants during the study period. For each case of pneumonia, we randomly selected up to 10 controls from the cohort, matched on sex, year of birth, and index date to the case. Exposure to H2RAs and PPIs was classified separately by time since last use. Drug use was defined as current if the prescription length covered the index date and as past if the end of the last prescription was before the index date. Past use was further categorized into recent past, past, and distant past if the end of the last prescription was less than 30 days ago, between 30 and 180 days ago, and more than 180 days ago, respectively.

Because all persons had used an acid-suppressive drug during the study period, we had no unexposed subjects. In analyses of the dose and duration effects of H2RAs and PPIs separately, we restricted the cases and controls to individuals who never used the other type of acid suppressant. Among current users of H2RAs or PPIs, we studied the active compound (cimetidine, famotidine, nizatidine, ranitidine, roxatidine, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole), the daily dosage (less than, equal to, and more than the defined daily dose), and the duration of use (<14 days, 14-28 days, 28-42 days, and ≥42 days). The defined daily dose for the PPIs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole is 20, 20, 30, 40, and 20 mg, respectively. The defined daily dose for the H2RAs cimetidine, famotidine, nizatidine, ranitidine, and roxatidine is 800, 40, 300, 300, and 150 mg, respectively.

Covariates
As covariates in the case-control analysis, we considered age, sex, and calen-
null
Excluding pneumonia without a laboratory confirmation led to higher risk estimates for developing pneumonia: 2.2 (95% CI, 1.4-3.5) for PPIs and 1.7 (95% CI, 0.8-2.9) for H2RAs. There was no significant effect modification by age, season, or presence of cancer.

The adjusted attributable risk percentage is 42% for PPIs and 37% for H2RAs. Therefore, 1.05 pneumonia cases per 100 person-years of PPI exposure can be attributed directly to the use of PPIs and 0.86 pneumonia cases during 100 person-years of H2RA exposure. Because the average duration of use was 0.23 years for H2RAs and 0.42 years for PPIs, this roughly translates to 1 case of pneumonia per 226 patients treated with PPIs and 1 case of pneumonia per 508 persons treated with H2RAs.

**COMMENT**

In this large cohort, current use of acid-suppressive drugs was associated with an increased risk of community-acquired pneumonia. The increase in risk was most pronounced for PPIs and showed a clear dose-response relationship, which supports a real biological effect. The results are in agreement with a previous small study that was conducted ad hoc in a clinical setting. This study showed that subjects using acid-suppressive drugs more often reported clinical manifestations of respiratory tract infections and complications compared with those who did not use acid-suppressive drugs.19

Gastric acid is an important barrier against pathogen invasion through the gastrointestinal tract. Although it is well known that a raised pH increases bacterial and virus colonization, the clinical consequences of gastrointestinal pathogen overgrowth have not been convincingly demonstrated.5,6 Reports on the clinical consequences have been only anecdotal or nonclinical. Already in 1934, Hurst20 suggested that bacillary and amoebic dysentery occurred much more frequently in subjects with achlorhydria or hypochlorhydria. More recent studies suggested that acid-suppressive drugs might be responsible for the development of esophageal candidiasis and enteric infections, although this was not solidly supported by clinical evidence.10,13,14,20-22 Furthermore, experimental evidence suggests that acid-suppressive drugs inhibit polymorphonuclear neutrophil functions and cytotoxic T lymphocyte and natural killer cell activity,23-26 which might add to the increased susceptibility to infection because of these drugs.

Studies in mechanically ventilated patients support the results from our study that the use of acid-suppressive drugs modifies the risk of pneumonia. These studies showed that during mechanical ventilation, intestinal pathogens colonize the oral space via the stomach.13,14 The colonized secretions may gain access to the lower airways and cause lower respiratory infections. Aspiration of gastric acid itself carries a risk of developing chemical pneumonia.27 Backflow of gastric acid and content into the esophagus because of incompetent barriers at the gas-
troesophageal junction is a prevalent gastrointestinal disorder. Reflux of gastric contents into the lower esophagus even occurs in the majority of healthy individuals but usually does not result in clinical sequelae.

In this study, we were able to take advantage of the fact that in the Dutch health care system, all medical information is prospectively collected at general practices that cover the total population instead of subjects presenting in a clinical setting. As a consequence, the data are generalizable to the general population and are not prone to selection bias. Nevertheless, given its observational nature, this study should be interpreted in the light of its limitations. First, we cannot exclude that some misclassification of outcome occurred. Such misclassification might be false negative or false positive. False-negative misclassification by underestimation of pneumonia may have occurred because of the exclusion of the possible cases (ie, cases for which we had insufficient diagnostic information). False-positive misclassification was possible in the group of probable pneumonia; most of the mild pneumonia is dealt with in primary care and therefore is not confirmed by chest radiograph or microbiological testing. Although we classified as probable pneumonia only infections with all clinical symptoms of pneumonia, we may have included some patients with bronchitis. When we excluded all probable cases from the analysis, the detected associations became stronger. Diagnostic bias could have occurred if patients who were taking acid-suppressive drugs had better diagnostic evaluation than distant-past users; however, the percentage of certain cases confirmed by radiograph or sputum was similar for current users (32%) and distant-past users.

Second, misclassification of exposure may have occurred because we used outpatient prescription data and had no information about whether the prescription was actually dispensed and taken. It is likely, however, that such exposure misclassification was random and evenly distributed among cases and controls.

Third, one could suspect that pneumonia would be diagnosed especially when the patient was treated by the general practitioner, the so-called diagnostic classification bias. However, the results from our study showed that the risk for pneumonia was increased in current drug users (pneumonia was reported during prescription length) but also in patients for whom the last prescription was at least 30 days old (recent past). These patients were prob-

<table>
<thead>
<tr>
<th>Drug classes</th>
<th>No. (%)</th>
<th>Cases</th>
<th>Controls</th>
<th>Unadjusted OR</th>
<th>Adjusted OR (95% CI)*</th>
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<tr>
<td>Current PPIs</td>
<td>99 (20.8)</td>
<td>697 (14.1)</td>
<td>1.79</td>
<td>1.73 (1.33-2.25)</td>
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<tr>
<td>Current H2RAs</td>
<td>48 (10.1)</td>
<td>417 (8.4)</td>
<td>1.43</td>
<td>1.59 (1.14-2.23)</td>
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<td>Current use of H2RAs and PPIs</td>
<td>36 (7.6)</td>
<td>247 (5.0)</td>
<td>1.89</td>
<td>1.76 (1.18-2.61)</td>
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<tr>
<td>Recent use of H2RAs or PPIs</td>
<td>26 (5.6)</td>
<td>3010 (60.7)</td>
<td>1.00</td>
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<tr>
<td>Past plus distant past use of H2RAs or PPIs</td>
<td>264 (55.6)</td>
<td>3356 (67.7)</td>
<td>1.00</td>
<td></td>
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</tbody>
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Table 3. Odds Ratios for Community-Acquired Pneumonia in Patients Using Proton Pump Inhibitors or H2-Receptor Antagonists

Abbreviations: CI, confidence interval; DDD, defined daily dose; H2RAs, H2-receptor antagonists; NA, not applicable; OR, odds ratio; PPIs, proton pump inhibitors.

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ACID-SUPPRESSIVE DRUGS AND PNEUMONIA

ably no longer being treated by the general practitioner, making classification bias less likely.

Finally, protopathic bias (ie, pneumonia symptoms) may have resulted in an acid-suppressive-drug prescription if patients received acid-suppressive drugs for symptoms related to pneumonia. However, on exclusion of all persons who began receiving acid-suppressive drugs within 1 week before the index date, the relative risk estimates did not change, and therefore protopathic bias can be excluded.

We observed a large difference between the unadjusted incidence rate ratios and the adjusted ORs in the nested case-control study. The incidence rate ratio should be interpreted with caution because it compares users of acid-suppressive drugs (with more comorbidity) with nonusers, which may result in substantial confounding by indication. In fact, we designed the nested case-control study to control for this confounding effect. As confounding factors, we included other respiratory illnesses, comorbidities, and drug use that are strongly associated with pneumonia. Inclusion of these confounders in the model did not change the estimates to a large extent, which implies that confounding was minimal. Despite this outcome, we cannot exclude the presence of uncontrolled confounders, which is a limitation inherent in all unrandomized studies.

The effectiveness of acid-suppressive drugs in the treatment of upper gastrointestinal tract symptoms is excellent. Acid-suppressive drugs neverthless seem to have some significant drawbacks. Persons using acid-suppressive drugs more often develop a community-acquired pneumonia compared with those who do not use acid-suppressive drugs, which is in general not a problem because the risk for developing pneumonia is low. The increased risk for pneumonia is a problem for patients who are at increased risk for infection, especially because community-acquired pneumonia is potentially dangerous.28 Groups of persons who are at increased risk for infection and for whom pneumonia is a major source of mortality have been identified.29 Pneumonia is more pronounced in persons with asthma or chronic obstructive lung disease, immunocompromised persons, children, and elderly persons. Elderly patients are likely to incur severe infection, which is partly due to a decreased immune response, including the natural reduction of gastric acid secretion after age 60 years. To avoid the calculated excess pneumonia, patients with asthma or chronic obstructive lung disease, immunocompromised persons, children, and elderly persons should be treated with acid-suppressive drugs only when necessary and with the lowest possible dose.

In conclusion, our results suggest that acid-suppressive drugs such as H2RAs and PPIs are associated with an increased risk of community-acquired pneumonia, probably because of reduction of gastric acid secretion, facilitating oral infections.

Author Contributions: Dr Laheij had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Laheij, Sturkenboom.

Acquisition of data: Laheij, Sturkenboom, Hassing. Analysis and interpretation of data: Laheij, Sturkenboom, Dieleman, Stricker, Jansen.

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Critical revision of the manuscript for important intellectual content: Hassing, Dieleman.

Statistical analysis: Laheij, Sturkenboom, Stricker. Administrative, technical, or material support: Hassing.

Study supervision: Jansen.

REFERENCES