Background: Acid-suppressive medications are increasingly prescribed for noncritically ill hospitalized patients, although the incidence of nosocomial gastrointestinal (GI) tract bleeding (GI bleeding) and magnitude of potential benefit from this practice are unknown. We aimed to define the incidence of nosocomial GI bleeding outside of the intensive care unit and examine the association between acid-suppressive medication use and this complication.

Methods: We conducted a pharmacoepidemiologic cohort study of patients admitted to an academic medical center from 2004 through 2007, at least 18 years of age, and hospitalized for 3 or more days. Admissions with a primary diagnosis of GI bleeding were excluded. Acid-suppressive medication use was defined as any order for a proton pump inhibitor or histamine-2-receptor antagonist. The main outcome measure was nosocomial GI bleeding. A propensity matched generalized estimating equation was used to control for confounders.

Results: The final cohort included 78,394 admissions (median age, 56 years; 41% men). Acid-suppressive medication was ordered in 59% of admissions, and nosocomial GI bleeding occurred in 224 admissions (0.29%). After matching on the propensity score, the adjusted odds ratio for nosocomial GI bleeding in the group exposed to acid-suppressive medication relative to the unexposed group was 0.63 (95% confidence interval, 0.42-0.93). The number needed to treat to prevent 1 episode of nosocomial GI bleeding was 770.

Conclusions: Nosocomial GI bleeding outside of the intensive care unit was rare. Despite a protective effect of acid-suppressive medication, the number needed to treat to prevent 1 case of nosocomial GI bleeding was relatively high, supporting the recommendation against routine use of prophylactic acid-suppressive medication in noncritically ill hospitalized patients.


The use of acid-suppressive medication in hospitalized patients has increased significantly over the last several decades. Studies estimate that 40% to 70% of medical inpatients receive acid-suppressive medications during their hospitalization. Although some of these patients have clear indications for acid suppression, research has consistently found that most do not. This practice appears to have stemmed from the use of acid suppression to prevent stress-related gastrointestinal (GI) tract bleeding (GI bleeding) in critically ill patients, where the incidence of nosocomial GI bleeding and the effect of acid-suppressive medication have been well characterized. While current guidelines recommend against the routine use of prophylactic acid suppression in patients outside of the intensive care unit (ICU), this recommendation is based on expert consensus; there are little data available on the incidence of nosocomial GI bleeding in the non-ICU population and whether these patients would benefit from acid-suppressive medication.

In addition to the financial cost incurred by this practice, several recent studies have demonstrated increased risks of infection associated with use of acid-suppressive medication in hospitalized patients, including Clostridium difficile infection and hospital-acquired pneumonia. In this context, balancing the risks and benefits of acid-suppressive medication in hospitalized patients requires a better understanding of possible benefits of these medications, particularly potential reductions in the competing risk of nosocomial GI bleeding.

Two randomized controlled trials have evaluated the effect of acid-suppressive medication in hospitalized patients with clear indications for acid suppression, but these studies did not find a significant benefit. Additionally, recent studies have suggested that the use of acid-suppressive medication may increase the risk of infection, including Clostridium difficile infection and hospital-acquired pneumonia. In this context, balancing the risks and benefits of acid-suppressive medication in hospitalized patients requires a better understanding of possible benefits of these medications, particularly potential reductions in the competing risk of nosocomial GI bleeding.
medications on GI bleeding outside of the ICU. Both trials were small, lacked double blinding, did not evaluate proton pump inhibitors, and were restricted to patients with very severe illness and presumed risk factors for stress ulceration, limiting their generalizability to the average inpatient receiving acid-suppressive medication outside of the ICU. To our knowledge, the incidence of nosocomial GI bleeding and the effect of acid-suppressive medication on this complication have not been well examined in a large cohort of noncritically ill patients. We sought to examine these issues, hypothesizing that while acid-suppressive medication use would be associated with a reduced incidence of nosocomial GI bleeding, the incidence of this complication would be low, causing the number needed to treat (NNT) to be high.

**METHODS**

**SETTING, DATA COLLECTION, AND INCLUSION AND EXCLUSION CRITERIA**

We studied admissions to a large academic medical center in Boston, Massachusetts, from January 2004 through December 2007. The study was approved by the institutional review board and granted a waiver of informed consent. Data were obtained from the medical center's electronic medical information databases, which are collected prospectively for clinical purposes, and contain patient-specific information related to each admission.

We included admissions of patients 18 years or older and hospitalized for 3 or more days. We chose 3 days to allow sufficient time for development of this nosocomial complication. We excluded admissions with a primary diagnosis of GI bleeding.

**ACID-SUPPRESSIVE MEDICATION EXPOSURE**

We defined acid-suppressive medication exposure as any pharmacy-dispensed proton pump inhibitor or histamine-2 receptor antagonist during the admission. Exposure status was censored at the occurrence of GI bleeding. In those exposed, medication orders were reviewed to ensure that exposure preceded the outcome, where an outcome occurred.

**NOSOCOMIAL GI BLEEDING OUTCOMES**

The primary outcome was nosocomial GI bleeding occurring outside of the ICU, defined as any overt GI bleeding (hematemesis, nasogastric aspirate containing "coffee grounds" material, melena, or hematochezia) occurring more than 24 hours after hospital admission, in a patient outside of the ICU. To identify such cases, we reviewed the medical charts of all admissions identified as having a discharge International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for GI bleeding listed as a secondary discharge diagnosis. ICD-9-CM codes used for this administrative outcome definition were based on the Clinical Classifications Software (CCS)—a diagnosis and procedure categorization scheme maintained by the Agency for Healthcare Research and Quality (AHRQ)—with modification as noted in the eAppendix (http://www.archinternmed.com).

The secondary outcome was clinically significant nosocomial GI bleeding, defined as our primary outcome, with the additional requirement of either an ICD-9-CM procedure code for upper endoscopy or receipt of at least 2 units of packed red blood cells during the admission.

We reviewed the medical records of all administratively identified cases to validate presence of overt bleeding, timing of the bleeding, and patient location at the time of the bleeding. All medical charts were reviewed by 1 of 2 reviewers (S.J.H. and B.P.V.), and any ambiguous cases were reviewed by the other. If the 2 reviewers did not come to an agreement, the case was adjudicated by a third reviewer (E.R.M.). Admissions with overt GI bleeding occurring on or within the first 24 hours of admission were excluded. Bleeding episodes precipitating ICU transfer were counted as an outcome occurrence; however, those occurring during an ICU stay or within 48 hours of transfer out of the ICU were not counted as an outcome occurrence. Admissions with overt bleeding that was thought by the treating physicians to represent bleeding from anatomic locations other than the upper GI tract (eg, the oropharynx or colon) were reclassified as not having our outcome of interest.

**COVARIATES**

We included covariates that were thought to predict use of acid-suppressive medications, as well as variables thought to increase the risk of GI bleeding. These included age; sex; race; season and day of the week of admission; admitting service (medicine vs other); emergency admission; and use of specific classes of medications during the hospitalization, including nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, prophylactic-dose and therapeutic-dose anticoagulants, and antiplatelet medications.

Using discharge ICD-9-CM codes, we controlled for all of the comorbidities included in the Charlson Comorbidity Index, as operationalized from administrative data by Quan et al, except for peptic ulcer disease because this is an intermediate to our outcome of interest. We therefore included a separate category for history of peptic ulcer, defined via ICD-9-CM code V127.1. Rather than using a summary index score, each comorbidity was incorporated into the model as an independent measure, as advocated by Elixhauser et al. We additionally controlled for ICD-9-CM discharge codes indicative of several GI conditions as categorized by the AHRQ CCS, including esophageal disorders, gastritis and duodenitis, other disorders of stomach and duodenum, other GI disorders, nausea and vomiting, abdominal pain, biliary tract disease, pancreatic disorders, and upper GI tract cancer, with modifications as noted in the eAppendix. We controlled for nonspecific chest pain and acute and unspecified renal failure, also as categorized by the AHRQ CCS except where noted in the eAppendix.

**STATISTICAL ANALYSIS**

Unadjusted incidence rates of the primary outcome in exposed and unexposed patients were compared using the Fisher exact test. To address confounding by indication, we derived a propensity score using a multivariable generalized estimating equation (GEE) model with logit link and exchangeable working correlation structure, where the use of acid-suppressive medication was the dependent variable, and the covariates listed in the previous subsection were independent variables. We used a GEE model to account for within-participant correlated data resulting from patients having multiple admissions. The fitted probability from this model was used as the propensity score. This score was assigned to each patient admission reflecting the propensity to have received the exposure of interest. The C statistic for the propensity score model was 0.82, indicating excellent ability to discriminate between admissions with and without acid-suppressive medication exposure.

We then matched admissions on their propensity score using a greedy matching algorithm. With this approach, each ad-
mission in which acid-suppressive medication was ordered was matched to the admission with the closest propensity score in which acid-suppressive medication was not ordered, thus addressing confounding by indication. The algorithm initially sought a match out to 5 decimals of the propensity score. If a 5-decimal match could not be found, the program then moved to 4, then 3, and so on, until the closest match was found. Once admissions were matched on their propensity to have received acid-suppressive medication, baseline characteristics were compared between the matched groups to gauge the effectiveness of the matching. Any baseline characteristics with residual imbalance (defined as a 10% prevalence and a difference between matched groups of at least 3 percentage points for dichotomous variables and \( P < 0.05 \) for continuous variables) were incorporated into a GEE model to obtain the adjusted odds ratio (OR) of nosocomial GI bleeding.

We calculated the NNT to prevent 1 episode of nosocomial GI bleeding using the prevalence of exposure, the incidence of nosocomial GI bleeding, and the estimate of the adjusted OR for our outcome, all from our propensity matched cohort, to derive the absolute adjusted risk difference. The inverse of this value is the NNT.

A 2-sided type I error of 0.05 or less was used to indicate statistical significance for all comparisons. Based on a prior study, we assumed a rate of 0.4 nosocomial GI bleeds per 100 admissions\(^2\); using this estimate, a sample size of 30,540 admissions would be necessary to achieve 90% power to detect a relative risk of 0.5 in exposed vs unexposed patients. All analyses were carried out using SAS software, version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

OUTCOME VALIDATION STUDY

As previously discussed herein, the presence of nosocomial GI bleeding was validated in all administratively identified cases via medical chart review, ensuring 100% specificity of our outcome. To ensure full capture of our outcome and assess the potential for underrepresentation of the outcome incidence, we performed 3 additional validation studies. First, we reviewed the medical charts of 100 randomly selected admissions with GI bleeding coded as the primary discharge diagnosis (admissions that had been excluded) to validate the absence of nosocomial GI bleeding in these admissions. In addition, we reviewed the medical charts of 100 randomly selected admissions that did not have a discharge code for GI bleeding (either primary or secondary). Lastly, we reviewed the medical charts of 100 randomly selected admissions that had a code for upper endoscopy but did not have a discharge code for GI bleeding.

SENSITIVITY ANALYSES

We performed 2 sensitivity analyses to address the possibility of outcome misclassification. After identifying the estimated number of “missed cases” of nosocomial GI bleeding via the validation study, we recalculated the NNT using the new incidence estimate.

Although we excluded cases of overt bleeding that were deemed to represent lower GI bleeding by the patient care team, the inclusion of hematochezia in our outcome definition likely led to inclusion of some cases of bleeding secondary to lesions in the lower GI tract. We therefore conducted a sensitivity analysis in which we reran our analysis using an outcome definition of GI bleeding restricted to hematemesis, nasogastric aspirate containing “coffee grounds” material, or melena.

EXPOSURE SUBGROUP ANALYSIS

To investigate the independent effect of proton pump inhibitors on our primary outcome, we repeated our main analysis after excluding patients with exposure to histamine-2 receptor antagonists. We did not assess the independent effect of histamine-2 receptor antagonists because we lacked sufficient power for this comparison.

RESULTS

PATIENT ADMISSION CHARACTERISTICS, EXPOSURE TO ACID-SUPPRESSIVE MEDICATION, AND PROPENSITY MATCHING

There were 136,529 adult admissions to the medical center from January 1, 2004, through December 31, 2007. After excluding admissions with a length of stay less than 3 days (n=56,430) and a primary diagnosis of GI bleeding (n=812), 79,287 admissions were included in the analytic cohort. The median age of the cohort was 56 years (range, 18-107 years), and 31,798 (41%) were men. Acid-suppressive medication was ordered in 45,882 admissions (59%). Of the group exposed to acid-suppressive medications, 37,392 (81%) received proton pump inhibitors and 13,194 (29%) received histamine-2 receptor antagonists, with some exposed to both. There were significant differences in baseline characteristics between those exposed and unexposed to acid-suppressive medication (Table 1).

We successfully matched 18,983 admissions with acid-suppressive medication exposure to 18,983 admissions without exposure. After this matching process, the group exposed to acid-suppressive medication was much more similar in baseline characteristics to the unexposed group (Table 2).

INCIDENCE OF NOSOCOMIAL GI BLEEDING AND ITS RELATIONSHIP WITH ACID-SUPPRESSIVE MEDICATION

Our administrative outcome definition identified 1,776 potential cases of nosocomial GI bleeding. After reviewing the medical charts of these admissions and applying our exclusion and reclassification criteria (Figure), our final cohort included 78,394 admissions. The primary outcome of nosocomial GI bleeding occurred in 224 admissions (0.29%); the secondary outcome of clinically significant GI bleeding occurred in 176 admissions (0.22%).

The unadjusted incidence of nosocomial GI bleeding was higher in the group exposed to acid-suppressive medication than in the unexposed group (0.33% vs 0.22%; OR, 1.53; 95% confidence interval [CI] 1.15-2.03 [Table 3]). The unadjusted incidence of clinically significant GI bleeding was also higher in the group exposed to acid-suppressive medication than in the unexposed group (0.26% vs 0.18%; OR, 1.44; 95% CI, 1.05-1.98 [Table 3]).

PROPENSITY-MATCHED ANALYSIS

After matching admissions by propensity score, the incidence of GI bleeding was identical to that in our full
Table 1. Admission Characteristics of Study Population§

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acid-Suppressive Medication (n=45 882)</th>
<th>No Acid-Suppressive Medication (n=32 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4462 (9.7)</td>
<td>1444 (4.4)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 558 (23.0)</td>
<td>3026 (9.3)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4085 (8.9)</td>
<td>1672 (5.1)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3073 (6.7)</td>
<td>937 (2.9)</td>
</tr>
<tr>
<td>Delirium/dementia</td>
<td>2595 (5.7)</td>
<td>1189 (3.7)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>9082 (19.8)</td>
<td>3167 (9.7)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1482 (3.2)</td>
<td>414 (1.3)</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>3538 (7.7)</td>
<td>897 (2.8)</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>1005 (2.2)</td>
<td>108 (0.3)</td>
</tr>
<tr>
<td>Diabetes without complications</td>
<td>9525 (20.8)</td>
<td>3806 (11.7)</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>3440 (7.5)</td>
<td>1485 (4.6)</td>
</tr>
<tr>
<td>Paraplegia/hemiplegia</td>
<td>596 (1.3)</td>
<td>208 (0.6)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>6463 (14.1)</td>
<td>2046 (6.3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>6810 (14.8)</td>
<td>2524 (7.8)</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>3892 (8.5)</td>
<td>1017 (3.1)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>631 (1.4)</td>
<td>406 (1.3)</td>
</tr>
<tr>
<td>Esophageal disorder</td>
<td>8010 (17.5)</td>
<td>801 (2.5)</td>
</tr>
<tr>
<td>Prior peptic ulcer</td>
<td>52 (0.1)</td>
<td>12 (0.04)</td>
</tr>
<tr>
<td>Gastritis/duodenitis</td>
<td>641 (1.4)</td>
<td>37 (0.1)</td>
</tr>
<tr>
<td>Other gastrointestinal disorders</td>
<td>1029 (2.2)</td>
<td>154 (0.5)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>5198 (11.3)</td>
<td>1372 (4.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>792 (1.7)</td>
<td>153 (0.5)</td>
</tr>
<tr>
<td>Acute and unspecified renal failure</td>
<td>6752 (14.7)</td>
<td>1729 (5.3)</td>
</tr>
<tr>
<td><strong>Admitting service</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>23 938 (52.2)</td>
<td>9446 (29.1)</td>
</tr>
<tr>
<td>Other</td>
<td>21 944 (47.8)</td>
<td>23 066 (71.0)</td>
</tr>
<tr>
<td><strong>Admission type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergent</td>
<td>35 282 (76.9)</td>
<td>15 704 (48.3)</td>
</tr>
<tr>
<td>Nonemergent</td>
<td>10 620 (23.2)</td>
<td>16 808 (51.7)</td>
</tr>
<tr>
<td><strong>In-hospital medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid</td>
<td>10 992 (24.0)</td>
<td>2157 (6.6)</td>
</tr>
<tr>
<td>NSAID</td>
<td>9025 (19.7)</td>
<td>14 693 (45.2)</td>
</tr>
<tr>
<td>Prophylactic anticoagulantb</td>
<td>28 590 (62.3)</td>
<td>10 256 (31.6)</td>
</tr>
<tr>
<td>Treatment anticoagulantc</td>
<td>10 425 (22.7)</td>
<td>3538 (10.9)</td>
</tr>
<tr>
<td>Antiplateletd</td>
<td>17 962 (39.2)</td>
<td>6651 (20.5)</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NSAID, nonsteroidal anti-inflammatory drugs.

§Data are given as number percentage of patients unless otherwise specified.

bIncludes subcutaneous unfractionated heparin and enoxaparin at doses of 60 mg/d or lower.

Includes intravenous heparin, warfarin, fondaparinux, argatroban, bivalirudin, and lepirudin.

cIncludes aspirin, clopidogrel, eptifibatide, tirofiban, ticlopidine, and dipyridamole.

dIncludes aspirin, clopidogrel, eptifibatide, tirofiban, ticlopidine, and dipyridamole.

cohort (109 cases [0.29%]). After adjusting for residual imbalances using a GEE model, there was a significant association between exposure to acid-suppressive medi-

cation and nosocomial GI bleeding in the opposite direction of the unadjusted analysis, with an OR of 0.63 (95% CI, 0.42-0.93) (Table 3). There was a similar as-
association between acid-suppressive medication and our secondary outcome of clinically significant GI bleeding (OR, 0.58; 95% CI, 0.37-0.91) (Table 3). Based on these estimates of incidence and effect, 770 patients would need to be treated with acid-suppressive medication to prevent 1 episode of nosocomial GI bleeding and 834 to prevent 1 episode of clinically significant nosocomial GI bleeding.

OUTCOME VALIDATION STUDY

Of 100 randomly selected admissions with GI bleeding coded as the primary discharge diagnosis (admissions that had been excluded), we identified 1 additional case of nosocomial GI bleeding, for a misclassification rate estimate of 1%. Of 100 randomly selected admissions that did not have a discharge code for GI bleeding (either primary or secondary), we did not identify any additional cases of nosocomial GI bleeding. Lastly, of 100 randomly selected admissions that had an ICD-9-CM code for upper endoscopy but no discharge code for GI bleeding, we identified 1 additional case of nosocomial GI bleeding, for a misclassification rate estimate of 1%.

SENSITIVITY ANALYSES

An estimated misclassification rate of 1% for both admissions with GI bleeding coded as the primary discharge diagnosis (n=812) and admissions with a code for upper endoscopy but no discharge code for GI bleeding (n=1907) would imply that we potentially missed 27 cases of nosocomial GI bleeding. This would make the incidence of our primary outcome 0.32%, with an NNT of 715.

Of 224 cases of nosocomial GI bleeding, 186 were defined by hematemesis, nasogastric aspirate containing “coffee grounds” material, and/or melena, while 38 were defined by hematochezia. After excluding hematochezia from our outcome, the effect estimate for the association between acid-suppressive medication and nosocomial GI bleeding was relatively unchanged, with an OR of 0.59 (95% CI, 0.39-0.91).

EXPOSURE SUBGROUP ANALYSIS

After excluding patients with exposure to histamine-2 receptor antagonists (n=13 194), the association between proton pump inhibitor use and nosocomial GI bleeding was relatively unchanged, with an OR of 0.58 (95% CI, 0.41-0.84).

COMMENT

In this large cohort, nosocomial GI bleeding outside of the ICU was rare, occurring in only 0.29% of admissions. Acid-suppressive medication use was associated with a 37% reduction in the odds of nosocomial GI bleeding. Despite this protective effect, given the low overall incidence of this outcome, 770 patients would need to be treated with acid-suppressive medication to prevent 1 episode of nosocomial GI bleeding and 834 to prevent 1 episode of clinically significant nosocomial GI bleeding.

Our definition of the primary outcome of nosocomial GI bleeding is consistent with prior studies done in the ICU population. In addition, the incidence of our outcome is almost identical to that found in the nonventilated patients in the latter study (0.18%). A recent retrospective case-control study in the noncritically ill patient population found a rate of nosocomial GI bleeding of 0.41%; however, this study included occult GI bleeding in the outcome and only included cases of bleeding that required upper endoscopy. Allowing for these differences, our observed rate of nosocomial GI bleeding is remarkably similar to those previously reported.

The use of a propensity score approach has been shown to improve control of confounding over traditional logistic regression methods in the setting of scarce outcomes, such as the outcome of interest in this study. The positive association between acid-suppressive medication and nosocomial GI bleeding in the unadjusted analysis suggests confounding by indication; physicians place patients at higher risk for GI bleeding on acid-suppressive medication. The reversal of the direction of the relationship between acid-suppressive medication and GI bleeding from unadjusted to adjusted analyses—a phenomenon seen in observational studies of drug effects, attributed to control of confounding by indication—and suggests that we have controlled for a great deal of such confounding. Although residual confounding is possible, our estimate for the association between acid-suppressive medication use and nosocomial GI bleeding is consistent with the estimates of relative risk identified in randomized controlled trials of histamine-2 receptor antagonists in ICU patients, which was 0.58 in one large meta-analysis of these trials.

Although we have not conducted a formal risk to benefit analysis, our finding of a NNT of 730 should be con-
sidered in the context of prior studies addressing the risks of acid-suppressive medications in similar patient populations. A recent study by Howell et al,\textsuperscript{10} based at the same medical center, found an association between acid-suppressive medication and hospital-acquired $C$ difficile infection, with a number needed to harm of 533. Another study based at the same medical center identified a number needed to harm of 111 for hospital-acquired pneumonia.\textsuperscript{1} While some differences exist in cohort inclusion criteria among these studies and the attributable morbidity and mortality of these outcomes differ, the NNT for nosocomial GI bleeding is similar to or greater than the number needed to harm for $C$ difficile and pneumonia. These findings lend support to the current guidelines, which recommend against prophylactic acid-suppressive medication use in patients outside of the ICU.\textsuperscript{16} Further risk factor and risk to benefit analyses are warranted to develop more specific guidelines that target these medications to the subset of hospitalized patients in whom the benefits might outweigh the risks.

As with all studies using administrative data, there is concern over the validity of ICD-9-CM coding. Our medical chart review of all administratively identified cases of GI bleeding, coupled with adjudication of unclear cases, ensured 100% specificity of our outcome, making bias from outcome misclassification highly unlikely. Furthermore, we performed a sensitivity analysis to investigate the effect of missed cases of GI bleeding on our NNT, which confirmed the robustness of our estimate even in the face of this type of misclassification.

Given that acid-suppressive medication is not expected to affect lower GI bleeding, we attempted to include only cases of upper GI bleeding in our outcome definition. However, we could not rule out that some cases of lower GI bleeding were included, so we performed a sensitivity analysis to address this limitation. The fact that the apparent protective effect of acid-suppressive medication was relatively unchanged when restricting our analysis to more clearly defined cases of upper GI bleeding (excluding hematochezia) strengthens the validity of our findings.

The lack of temporal information related to ICD-9-CM discharge codes is a limitation of our analysis. We addressed this concern with respect to the exposure and outcome via our medical chart review, ensuring that exposure preceded outcome and that outcomes occurred beyond the first 24 hours of admission and not in the ICU. Another limitation is our inability to independently investigate histamine-2 receptor antagonists owing to insufficient power. Given their less potent acid-suppressive effect, however, it is unlikely that they would be more protective than proton pump inhibitors for nosocomial GI bleeding, and thus the NNT with these agents is unlikely to be lower than that observed with proton pump inhibitors. Another limitation relates to our inability to ascertain whether the patient was using acid-suppressive medication prior to hospitalization, which rendered us unable to specifically evaluate the effect of prophylactic use of these medications in patients without other indications for their use. However, it seems likely that patients with preexisting GI conditions necessitating acid-suppressive medication use prior to hospitalization would stand to benefit most from continuation of these medications during hospitalization, and yet despite inclusion of this patient population, we found a relatively high NNT. Further studies are necessary to investigate whether effect modification by prior exposure or prior conditions exists. Lastly, although almost 80 000 admissions were studied over a 4-year period, the single-center nature of our study limits generalizability. Our findings should be validated at other institutions.

In conclusion, we found that in a large cohort of noncritically ill hospitalized patients, nosocomial GI bleeding was rare. Acid-suppressive medication use was associated with a decreased odds of nosocomial GI bleeding; however, because of the low incidence of this complication, the NNT to prevent 1 case of GI bleeding was high at 730. Clinicians should balance the effectiveness of these medications against their cost, their associated risks,\textsuperscript{1,17,18} and the relatively large NNT to prevent 1 case of nosocomial GI bleeding. Our findings support the current recommendations against routine use of prophylactic acid-suppressive medication in patients outside of the ICU.\textsuperscript{16}

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Author Contributions: Dr Herzig 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: Herzig, Vaughn, Howell, Ngo, and Marcantonio. Acquisition of data: Herzig, Vaughn, and

Table 3. Rates of Gastrointestinal Tract (GI) Bleeding According to Acid-Suppressive Medication Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Acid-Suppressive Medication (n=45 882)</th>
<th>No Acid-Suppressive Medication (n=32 512)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial GI bleeding</td>
<td>153 (0.33)</td>
<td>71 (0.22)</td>
<td>1.53 (1.15-2.03)</td>
</tr>
<tr>
<td>Clinically significant GI bleeding</td>
<td>118 (0.26)</td>
<td>58 (0.18)</td>
<td>1.44 (1.05-1.98)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

Propensity score incorporated all variables listed in Table 1, plus season and admission day of the week. Adjusted odds ratio derived using a generalized estimating equation model, controlling for all significantly imbalanced baseline characteristics after matching on the propensity score (categorical variables with >10% incidence and >3% difference between exposure groups after matching and continuous variables using a cutoff of $P<.05$): emergent admission, male sex, nonsteroidal anti-inflammatory drug use, and age.

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Howell. Analysis and interpretation of data: Herzig, Howell, Ngo, and Marcantonio. Drafting of the manuscript: Herzig. Critical revision of the manuscript for important intellectual content: Herzig, Vaughn, Howell, Ngo, and Marcantonio. Statistical analysis: Herzig and Ngo. Administrative, technical, and material support: Herzig, Vaughn, and Howell. Study supervision: Herzig and Marcantonio.

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REFERENCES


