Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

ORIGINAL RESEARCH

Inappropriate Prescribing of Proton Pump Inhibitors in Hospitalized Patients

Mark Reid, MD[1,2*], Angela Keniston, MSPH[1], J. Christie Heller, MD[1,2], Marshall Miller, MD[1,2], Sofia Medvedev, PhD[3], Richard K. Albert, MD[1,2]

[1]Department of Medicine, Denver Health Medical Center, Denver, Colorado; [2]Department of Medicine, University of Colorado Denver, Denver, Colorado; [3]University HealthSystem Consortium, Denver, Colorado.

BACKGROUND: Proton pump inhibitors have numerous important side effects, yet they are prescribed for outpatients who do not have recognized indications. Less is known with respect to prescribing for inpatients.

OBJECTIVE: To determine the rate of inappropriate prescribing of protein pump inhibitors and to assess reasons why they are prescribed.

DESIGN AND PARTICIPANTS: The study was a retrospective review of administrative data for adult hospital patients discharged from the Medicine service of Denver Health (DH) and from the University HealthSystem Consortium (UHC) between January 1, 2008 and December 31, 2009.

MEASUREMENTS: Valid indications for proton pump inhibitors were sought from discharge diagnoses, prescription records, and, in a randomly selected group of patients from DH, from direct review of records.

RESULTS: Inclusion criteria were met by 9875 DH patients and 6,592,100 UHC patients; of patients receiving a proton pump inhibitor, 61% and 73%, respectively, did not have a valid indication. Increased rates of *Clostridium difficile* infection were found in both groups of patients receiving proton pump inhibitors. Chart reviews found valid indications for proton pump inhibitors in 19% of patients who did not have a valid indication on the basis of the administrative data, and "prophylaxis" was the justification for inappropriate prescribing in 56%.

CONCLUSION: Proton pump inhibitors are frequently inappropriately prescribed to Medicine inpatients who do not have a valid indication and this practice is associated with an increase in *C. difficile* infection. Interventions are needed to curtail this inappropriate prescribing practice. *Journal of Hospital Medicine* 2012;7:421–425. © 2011 Society of Hospital Medicine

Proton pump inhibitors (PPIs) are the third most commonly prescribed class of medication in the United States, with $13.6 billion in yearly sales.[1] Despite their effectiveness in treating acid reflux[2] and their mortality benefit in the treatment of patients with gastrointestinal bleeding,[3] recent literature has identified a number of risks associated with PPIs, including an increased incidence of *Clostridium difficile* infection,[4] decreased effectiveness of clopidogrel in patients with acute coronary syndrome,[5] increased risk of community- and hospital-acquired pneumonia, and an increased risk of hip fracture.[6–9] Additionally, in March of 2011, the US Food and Drug Administration (FDA) issued a warning regarding the potential for PPIs to cause low magnesium levels which can, in turn, cause muscle spasms, an irregular heartbeat, and convulsions.[10]

Inappropriate PPI prescription practice has been demonstrated in the primary care setting,[11] as well as in small studies conducted in the hospital setting.[12–16] We hypothesized that many hospitalized patients receive these medications without having an accepted indication, and examined 2 populations of hospitalized patients, including administrative data from 6.5 million discharges from US university hospitals, to look for appropriate diagnoses justifying their use.

METHODS

We performed a retrospective review of administrative data collected between January 1, 2008 and December 31, 2009 from 2 patient populations: (a) those discharged from Denver Health (DH), a university-affiliated public safety net hospital in Denver, CO; and (b) patients discharged from 112 academic health centers and 256 of their affiliated hospitals that participate in the University HealthSystem Consortium (UHC). The Colorado Multiple Institution Review Board reviewed and approved the conduct of this study.

Inclusion criteria for both populations were age >18 or <90 years, and hospitalization on a Medicine service. Prisoners and women known to be pregnant were excluded. In both cohorts, if patients had more than 1 admission during the 2-year study period, only data from the first admission were used.

We recorded demographics, admitting diagnosis, and discharge diagnoses together with information pertaining to the name, route, and duration of administration of

***Address for correspondence and reprint requests:** Mark Reid, MD, Denver Health Medical Center, Department of Medicine, MC 4000, 777 Bannock St, Denver, CO 80204; Tel.: 303-436-7439; E-mail: Mark.Reid@dhha.org

Additional Supporting Information may be found in the online version of this article.

Received: May 9, 2011; **Revised:** October 22, 2011; **Accepted:** November 13, 2011
 DOI 10.1002/jhm.1901
Published online in Wiley Online Library (Wileyonlinelibrary.com).

TABLE 1. Valid Indications for Proton Pump Inhibitors

Indication	ICD-9 Code
Helicobacter pylori	041.86
Abnormality of secretion of gastrin	251.5
Esophageal varices with bleeding	456.0
Esophageal varices without mention of bleeding	456.1
Esophageal varices in diseases classified elsewhere	456.2
Esophagitis	530.10–530.19
Perforation of esophagus	530.4
Gastroesophageal laceration-hemorrhage syndrome	530.7
Esophageal reflux	530.81
Barrett's esophagus	530.85
Gastric ulcer	531.00–31.91
Duodenal ulcer	532.00–532.91
Peptic ulcer, site unspecified	533.00–533.91
Gastritis and duodenitis	535.00–535.71
Gastroparesis	536.3
Dyspepsia and other specified disorders of function of stomach	536.8
Hemorrhage of gastrointestinal tract, unspecified	578.9

NOTE: "Stress ulcer prophylaxis" was not included in the list due to methodological limitations.
Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision.

all PPIs (ie, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole). We created a broadly inclusive set of valid indications for PPIs by incorporating diagnoses that could be identified by International Classification of Diseases, Ninth Revision.

(ICD-9) codes from a number of previously published sources including the National Institute of Clinical Excellence (NICE) guidelines issued by the National Health Service (NHS) of the United Kingdom in 2000[12,17–21] (Table 1).

To assess the accuracy of the administrative data from DH, we also reviewed the Emergency Department histories, admission histories, progress notes, electronic pharmacy records, endoscopy reports, and discharge summaries of 123 patients randomly selected (ie, a 5% sample) from the group of patients identified by administrative data to have received a PPI without a valid indication, looking for any accepted indication that might have been missed in the administrative data.

All analyses were performed using SAS Enterprise Guide 4.1 (SAS Institute, Cary, NC). A Student *t* test was used to compare continuous variables and a chi-square test was used to compare categorical variables. Bonferroni corrections were used for multiple comparisons, such that *P* values less than 0.01 were considered to be significant for categorical variables.

TABLE 3. Patients Receiving PPIs With and Without a Valid Indication

	DH (N = 9875)	UHC (N = 6,592,100)
Patients receiving PPIs (% of total)	3962 (40)	918,474 (14)
Any ICU stay, N (% of all patients)	1238 (31)	
General Medicine ward only, N (% of all patients)	2724 (69)	
Patients with indication for PPI (% of all patients receiving PPIs)*	1540 (39)	247,142 (27)
Any ICU stay, N (% of all ICU patients)	434 (35)	
General Medicine ward only, N (% of all ward patients)	1106 (41)	
Patients without indication for PPI (% of those receiving PPIs)*	2422 (61)	671,332 (73)
Any ICU stay, N (% of all ICU patients)	804 (65)†	
General Medicine ward only, N (% of all ward patients)	1618 (59)†	

Abbreviations: DH, Denver Health; ICU, intensive care unit; PPI, proton pump inhibitor; UHC, University HealthSystem Consortium.
* From International Classification of Diseases, Ninth Revision (ICD-9) codes at time of discharge.
† *P* value 0.001.

RESULTS

Inclusion criteria were met by 9875 patients in the Denver Health database and 6,592,100 patients in the UHC database. The demographics and primary discharge diagnoses for these patients are summarized in Table 2.

Only 39% and 27% of the patients in the DH and UHC databases, respectively, had a valid indication for PPIs on the basis of discharge diagnoses (Table 3). In the DH data, if admission ICD-9 codes were also inspected for valid PPI indications, 1579 (40%) of patients receiving PPIs had a valid indication (admission ICD-9 codes were not available for patients in the UHC database). Thirty-one percent of Denver Health patients spent time in the intensive care unit (ICU) during their hospital stay and 65% of those patients received a PPI without a valid indication, as

TABLE 2. Admission Characteristics of Denver Health and UHC Study Population

DH (N = 9875)				UHC (N = 6,592,100)	
	Received a PPI	No PPI		Received a PPI	No PPI
No. (%)	3962 (40)	5913 (60)		918,474 (14)	5,673,626 (86)
Age (mean ± SD)	53 ± 15	51 ± 16		59 ± 17	55 ± 18
Gender (% male)	2197 (55)	3438 (58)		464,552 (51)	2,882,577 (51)
Race (% white)	1610 (41)	2425 (41)		619,571 (67)	3,670,450 (65)
Top 5 primary discharge diagnoses					
Chest pain	229 (6)	462 (8)	Coronary atherosclerosis	35,470 (4)	186,321 (3)
Alcohol withdrawal	147 (4)	174 (3)	Acute myocardial infarction	26,507 (3)	132,159 (2)
Pneumonia, organism unspecified	142 (4)	262 (4)	Heart failure	21,143 (2)	103,751 (2)
Acute pancreatitis	132 (3)	106 (2)	Septicemia	20,345 (2)	64,915 (1)
Obstructive chronic bronchitis with (acute) exacerbation	89 (2)	154 (3)	Chest pain	16,936 (2)	107,497 (2)

Abbreviations: DH, Denver Health; PPI, proton pump inhibitor; UHC, University HealthSystem Consortium.

TABLE 4. Incidence of Pneumonia and *Clostridium difficile* Infection

	Denver Health			UHC		
Concurrent diagnosis	(+) PPI 3962	(–) PPI 5913	*P*	(+) PPI 918,474	(–) PPI 5,673,626	*P*
C. difficile	46 (1.16)	26 (0.44)	<0.0001	12,113 (1.32)	175 (0.0031)	<0.0001
Pneumonia	400 (10.1)	517 (8.7)	0.0232	75,274 (8.2)	300,557 (5.3)	<0.0001

NOTE: After Bonferroni correction, *P* value < 0.01 is statistically significant.
Abbreviations: PPI, proton pump inhibitor; UHC, University HealthSystem Consortium.

compared to 59% of patients who remained on the General Medicine ward (Table 3).

Higher rates of concurrent *C. difficile* infections were observed in patients receiving PPIs in both databases; a higher rate of concurrent diagnosis of pneumonia was seen in patients receiving PPIs in the UHC population, with a nonsignificant trend towards the same finding in DH patients (Table 4).

Chart review in the DH population found valid indications for PPIs in 19% of patients who were thought not have a valid indication on the basis of the administrative data (Table 5). For 56% of those in whom no valid indication was confirmed, physicians identified "prophylaxis" as the justification.

DISCUSSION

The important finding of this study was that the majority of patients in 2 large groups of Medicine patients hospitalized in university-affiliated hospitals received PPIs without having a valid indication. To our knowledge, the more than 900,000 UHC patients who received a PPI during their hospitalization represent the largest inpatient population evaluated for appropriateness of PPI prescriptions.

Our finding that 41% of the patients admitted to the DH Medicine service received a PPI during their hospital stay is similar to what has been observed by others.[9,14,22] The rate of PPI prescription was lower in the UHC population (14%) for unclear reasons. By our definition, 61% lacked an adequate diagnosis to justify the prescription of the PPI. After performing a chart review on a randomly selected 5% of these records, we found that the DH administrative database had failed to identify 19% of patients who had a valid indication for receiving a PPI. Adjusting the administrative data accordingly still resulted in 50% of DH patients not having a valid indication for receiving a PPI. This is consistent with the 54% recorded by Batuwitage and colleagues[11] in the outpatient setting by direct chart review, as well as a range of 60%-75% for hospitalized patients in other studies.[12,13,15,23,24]

Stomach acidity is believed to provide an important host defense against lower gastrointestinal tract infections including *Salmonella*, *Campylobacter*, and *Clostridium difficile*.[25] A recent study by Howell et al[26] showed a dose–response effect between PPI use and *C. difficile* infection, supporting a causal connection between loss of stomach acidity and development of *Clostridium difficile*-associated diarrhea (CDAD). We found that *C. difficile* infection was more common in both populations of patients receiving PPIs (although the relative risk was much higher in the UHC database) (Table 5). The rate of CDAD in DH patients who received PPIs was 2.6 times higher than in patients who did not receive these acid suppressive agents.

The role of acid suppression in increasing risk for community-acquired pneumonia is not entirely clear. Theories regarding the loss of an important host defense and bacterial proliferation head the list.[6,8,27] Gastric and duodenal bacterial overgrowth is significantly more common in patients receiving PPIs than in patients receiving histamine type-2 (H2) blockers.[28] Previous studies have identified an increased rate of hospital-acquired pneumonia and recurrent community-acquired pneumonia[27] in patients receiving any form of acid suppression therapy, but the risk appears to be greater in patients receiving PPIs than in those receiving H2 receptor antagonists (H2RAs).[9] Significantly more patients in the UHC population who were taking PPIs had a concurrent diagnosis of pneumonia, consistent with previous studies alerting to this association[6,8,9,27] and consistent with the nonsignificant trend observed in the DH population.

Our study has a number of limitations. Our database comes from a single university-affiliated public hospital with residents and hospitalists writing orders for all medications. The hospitals in the UHC are also teaching hospitals. Accordingly, our results might not generalize to other settings or reflect prescribing patterns in private, nonteaching hospital environments. Because our study was retrospective, we could not confirm the decision-making process supporting the prescription of PPIs. Similarly, we could not temporarily relate the existence of the indication with the

TABLE 5. Chart Review of 123 (5%) DH Patients Receiving PPI Without Valid Indication

Characteristic	N (%)
Valid indication found on chart review only	23 (19)
No valid indication after chart review	100 (81)
Written indication: "prophylaxis"	56 (56)
No written documentation of indication present in the chart	33 (33)
Written indication: "continue home medication"	9 (9)
Intubated with or without written indication of "prophylaxis"	16 (16)

Abbreviations: DH, Denver Health; PPI, proton pump inhibitor.

time the PPI was prescribed. Our list of appropriate indications for prescribing PPIs was developed by reviewing a number of references, and other studies have used slightly different lists (albeit the more commonly recognized indications are the same), but it may be argued that the list either includes or misses diagnoses in error.

While there is considerable debate about the use of PPIs for stress ulcer prophylaxis,[29] we specifically chose not to include this as one of our valid indications for PPIs for 4 reasons. First, the American Society of Health-System Pharmacists (ASHP) Report does not recommend prophylaxis for non-ICU patients, and only recommends prophylaxis for those ICU patients with a coagulopathy, those requiring mechanical ventilation for more than 48 hours, those with a history of gastrointestinal ulceration or bleeding in the year prior to admission, and those with 2 or more of the following indications: sepsis, ICU stay >1 week, occult bleeding lasting 6 or more days, receiving high-dose corticosteroids, and selected surgical situations.[30] At the time the guideline was written, the authors note that there was insufficient data on PPIs to make any recommendations on their use, but no subsequent guidelines have been issued.[30] Second, a review by Mohebbi and Hesch published in 2009, and a meta-analysis by Lin and colleagues published in 2010, summarize subsequent randomized trials that suggest that PPIs and H2 blockers are, at best, similarly effective at preventing upper gastrointestinal (GI) bleeding among critically ill patients.[31,32] Third, the NICE guidelines do not include stress ulcer prophylaxis as an appropriate indication for PPIs except in the "prevention and treatment of NSAID [non-steroidal anti-inflammatory drug]-associated ulcers."[19] Finally, H2RAs are currently the only medications with an FDA-approved indication for stress ulcer prophylaxis. We acknowledge that PPIs may be a reasonable and acceptable choice for stress ulcer prophylaxis in patients who meet indications, but we were unable to identify such patients in either of our administrative databases.

In our Denver Health population, only 31% of our patients spent any time in the intensive care unit, and only a fraction of these would have both an accepted indication for stress ulcer prophylaxis by the ASHP guidelines and an intolerance or contraindication to an H2RA or sulcralfate. While our administrative database lacked the detail necessary to identify this small group of patients, the number of patients who might have been misclassified as not having a valid PPI indication was likely very small. Similar to the findings of previous studies,[15,18,23,29] prophylaxis against gastrointestinal bleeding was the stated justification for prescribing the PPI in 56% of the DH patient charts reviewed. It is impossible for us to estimate the number of patients in our administrative database for whom stress ulcer prophylaxis was justified by existing guidelines, as it would be necessary to gather a number of specific clinical details for each patient including: 1) ICU stay; 2) presence of coagulopathy; 3) duration of mechanical ventilation; 4) presence of sepsis; 5) duration of ICU stay; 6) presence of occult bleeding for >6 days; and 7) use of high-dose corticosteroids. This level of clinical detail would likely only be available through a prospective study design, as has been suggested by other authors.[33] Further research into the use, safety, and effectiveness of PPIs specifically for stress ulcer prophylaxis is warranted.

In conclusion, we found that 73% of nearly 1 million Medicine patients discharged from academic medical centers received a PPI without a valid indication during their hospitalization. The implications of our findings are broad. PPIs are more expensive[31] than H2RAs and there is increasing evidence that they have significant side effects. In both databases we examined, the rate of *C. difficile* infection was higher in patients receiving PPIs than others. The prescribing habits of physicians in these university hospital settings appear to be far out of line with published guidelines and evidence-based practice. Reducing inappropriate prescribing of PPIs would be an important educational and quality assurance project in most institutions.

Disclosure: Nothing to report.

References

1. IMS Health Web site. Available at: http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2009%20Top-line%20Market%20Data/Top%20Therapy%20Classes%20by%20U.S.Sales.pdf. Accessed May 1, 2011.
2. Bate CM, Keeling PW, O'Morain C, et al. Comparison of omeprazole and cimetidine in reflux oesophagitis: symptomatic, endoscopic, and histological evaluations. *Gut*. 1990;31(9):968–972.
3. Lau JY, Leung WK, Wu JC, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med*. 2007;356(16):1631–1640.
4. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA*. 2005;294(23):2989–2995.
5. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301(9):937–944.
6. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16):1955–1960.
7. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296(24):2947–2953.
8. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med*. 2007;167(9):950–955.
9. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301(20):2120–2128.
10. US Food and Drug Administration (FDA) Website. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm245275.htm. Accessed March 2, 2011.
11. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J*. 2007;83(975):66–68.
12. Grube RR, May DB. Stress ulcer prophylaxis in hospitalized patients not in intensive care units. *Am J Health Syst Pharm*. 2007;64(13):1396–1400.
13. Afif W, Alsulaiman R, Martel M, Barkun AN. Predictors of inappropriate utilization of intravenous proton pump inhibitors. *Aliment Pharmacol Ther*. 2007;25(5):609–615.
14. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol*. 2000;95(11):3118–3122.

15. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns and predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. *Intern Med* 2010;49(23):2561–2568.
16. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment Pharmacol Ther*. 2003;17(12):1503–1506.
17. Choudhry MN, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with Clostridium difficile-associated disease. *QJM*. 2008;101(6):445–448.
18. Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. *Ann Pharmacother*. 2006;40(7–8):1261–1266.
19. National Institute of Clinical Excellence (NICE), National Health Service (NHS), Dyspepsia: Management of dyspepsia in adults in primary care. Web site. Available at: http://www.nice.org.uk/nicemedia/live/10950/29460/29460.pdf. Accessed May 1, 2011.
20. Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? *Curr Opin Crit Care*. 2009;15(2):139–143.
21. Walker NM, McDonald J. An evaluation of the use of proton pump inhibitors. *Pharm World Sci* 2001;23(3):116–117.
22. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. *J Clin Pharm Ther*. 2000;25(5):333–340.
23. Alsultan MS, Mayet AY, Malhani AA, Alshaikh MK. Pattern of intravenous proton pump inhibitors use in ICU and non-ICU setting: a prospective observational study. *Saudi J Gastroenterol*. 2010;16(4):275–279.
24. Ramirez E, Lei SH, Borobia AM, et al. Overuse of PPIs in patients at admission, during treatment, and at discharge in a tertiary Spanish hospital. *Curr Clin Pharmacol*. 2010;5(4):288–297.
25. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol*. 2007;102(9):2047–2056.
26. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. *Arch Intern Med*. 2010;170(9):784–790.
27. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med*. 2010;123(1):47–53.
28. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut*. 1996;39(1):54–59.
29. Hussain S, Stefan M, Visintainer P, Rothberg M. Why do physicians prescribe stress ulcer prophylaxis to general medicine patients? *South Med J* 2010;103(11):1103–1110.
30. ASHP therapeutic guidelines on stress ulcer prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. *Am J Health Syst Pharm*. 1999;56(4):347–379.
31. Mohebbi L, Hesch K. Stress ulcer prophylaxis in the intensive care unit. *Proc (Bayl Univ Med Cent)*. 2009;22(4):373–376.
32. Lin PC, Chang CH, Hsu PI, Tseng PL, Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med*. 2010;38(4):1197–1205.
33. Pongprasobchai S, Kridkratoke S, Nopmaneejumruslers C. Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: a meta-analysis. *J Med Assoc Thai*. 2009;92(5):632–637.
34. Yachimski PS, Farrell EA, Hunt DP, Reid AE. Proton pump inhibitors for prophylaxis of nosocomial upper gastrointestinal tract bleeding: effect of standardized guidelines on prescribing practice. *Arch Intern Med*. 2010;170(9):779–783.