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Temporal Trends in Gastrointestinal Bleeding Associated with Percutaneous Coronary Intervention: Analysis of the 1998–2006 Nationwide Inpatient Sample (NIS) Database

Anupama Shivaraju, MD[1], **Vikas Patel, MD**[1], **Gregg C. Fonarow, MD**[2], **Hui Xie, PhD**[3], **Adhir R. Shroff, MD, MPH**[1], and **Mladen I. Vidovich, MD, FACC, FSCAI**[1]

[1]Division of Cardiology, University of Illinois at Chicago, Chicago, Illinois

[2]University of California, Los Angeles, California

[3]Division of Epidemiology and Biostatistics and Cancer Center, University of Illinois at Chicago, Chicago, Illinois

Abstract

Background—Gastrointestinal bleeding (GIB) after percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) and coronary artery disease (CAD) is associated with high morbidity and mortality.

Methods—The Nationwide Inpatient Sample (NIS) database from 1998 to 2006 was utilized to identify 1,216,759 PCIs performed for ACS and CAD. We sought to analyze temporal trends in the incidence and in-hospital outcomes of GIB associated with PCI along with its predictors.

Results—The overall incidence of GIB was 1.04% (95% confidence interval (CI), 1.02%–1.06%). The incidence of GIB decreased over the study period (p for trend <0.0001). The overall mortality in the GIB group was 6.0% (95% CI, 5.6%–6.4%). The adjusted odds ratio (OR) for in-hospital mortality and GIB was 4.70 (95% CI, 4.23–5.23; p<0.0001); this remained high and essentially unchanged over the study period. Independent predictors of GIB included rectum/anal cancer (OR, 4.64; 95% CI, 3.20–6.73; p<0.0001), stomach cancer (OR, 2.74; 95% CI, 1.62–4.66; p=0.0002), esophageal cancer (OR, 1.99; 95% CI, 1.08–3.69; p=0.0288), colon cancer (OR, 1.69; 95% CI, 1.43–2.02; p<0.0001), congestive heart failure (OR, 1.43; 95% CI, 1.35–1.52; p<0.0001), and acute myocardial infarction (OR, 1.23; 95% CI, 1.13–1.35; p<0.0001).

Conclusions—Although the incidence of GIB associated with PCI decreased from 1998–2006 in the face of aggressive therapies for ACS and CAD, the risk of GIB-associated death remained high. Underlying GI malignancy is a significant independent predictor of GIB associated with PCI; identifying these patients may reduce the rate of GIB.

INTRODUCTION

Advances in invasive interventional procedures, anti-platelet and anti-thrombotic therapies have led to significant reductions in cardiovascular morbidity and mortality in patients with symptomatic coronary artery disease (CAD) and acute coronary syndrome (ACS);[1–4]

Corresponding Author: Mladen I. Vidovich, MD, FACC, FSCAI, 840 South Wood Street, MC 715, Chicago, IL 60612, Phone 312-413-4951, Fax 312-413-2948, miv@uic.edu.

however, the risk of overall bleeding, which includes access site and gastrointestinal bleeding (GIB), still remains a significant problem.[5–7] The reported incidence of GIB in patients undergoing percutaneous coronary intervention (PCI) ranges between 1.1% and 3.0%[8–12] and development of post-PCI GIB is associated with a 10% in-hospital mortality.[6, 11, 12] We hypothesized that changes in the utilization of antiplatelet, anticoagulant agents, and coronary stents would impact the overall incidence of GIB and associated mortality. The Healthcare Cost and Utilization Project (HCUP) is a family of health care databases which encompasses the most extensive collection of longitudinal hospital care data in the United States enabling research on a broad range of health care policy issues including medical practice patterns and outcomes of treatments.[13] Given the introduction of drug-eluting stents, new antiplatelet and anticoagulation strategies and wider implementation of guideline-recommended care in this period, we sought to examine the temporal trend of in-hospital GIB events among patients with ACS and CAD undergoing PCI in a broad range of patients representing real-world clinical practice in the US from 1998 to 2006.

METHODS

Data Source

The Nationwide Inpatient Sample (NIS) is the largest all-payer U.S. inpatient care database that contains over a hundred clinical and nonclinical data elements from approximately 8 million hospital stays each year.[13] Included in these data elements are primary and secondary diagnoses, primary and secondary procedures, admission and discharge status, patient demographics, expected payment source, length of stay, hospital characteristics. All patients are considered for inclusion. The most recent NIS database contains data from about 1050 hospitals from 44 States in the U.S. sampled to approximate a 20% stratified sample of U.S. community hospitals as defined by the American Hospital Association. NIS was developed as part of HCUP, which is sponsored by the Agency for Healthcare Research and Quality. NIS data are available yearly, beginning with 1988, and allow for analyzing trends over time. It is the only national hospital database with charge information on all patients regardless of payer.

Study Patients and Definitions

From 1998 to 2006, a total of 1,216,759 PCI procedures performed in patients for symptomatic CAD and acute myocardial infarction (AMI) diagnoses, which encompass ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), were identified. The Clinical Classifications Software (CCS) developed by HCUP was used in analyzing our dependent and independent variables. CCS is a diagnosis and procedure categorization scheme that is based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM); a uniform and standardized coding system. The multitude of ICD-9-CM codes are collapsed into a manageable number of clinically meaningful categories. CCS consists of a single-level and multi-level classification systems. The single-level CCS system classifies all diagnoses and procedures into unique groups, and the multi-level CCS expands the single-level CCS into a hierarchical system and also splits single-level CCS categories to provide more detail. The specific single-level CCS diagnosis category used to define GIB in this study was “153 – Gastrointestinal Hemorrhage.” GIB was the dependent variable. Additional data on covariates were collected and include year, age, race, gender, in-hospital mortality, length of stay, cost of hospitalization, esophageal cancer, stomach cancer, colon cancer, rectum/anal cancer, gastroduodenal ulcer/gastritis/duodenitis, diabetes mellitus (DM), dyslipidemia, heart valve disorder, hypertension, AMI, CAD, congestive heart failure (CHF), atrial fibrillation/flutter, transient ischemic attack (TIA)/cerebrovascular accident (CVA),

peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), diverticulosis/diverticulitis, chronic renal insufficiency (CRI), upper endoscopy, lower endoscopy, pulmonary artery catheter monitoring, blood transfusion, bare-metal stents (BMS), drug-eluting stents (DES), and percutaneous transluminal coronary angioplasty (PTCA).

Primary Analysis

Our primary analysis was to assess the incidence of GIB and its trend over the study period.

Secondary Analysis

Our secondary analysis looked at independent predictors of GIB, mortality rate in patients with GIB, and temporal trend in mortality rate in patients with GIB over the study years.

Statistical Analysis

The study population were separated into two groups – those with GIB and those without GIB. The summary statistics with baseline characteristics were generated for the entire population separated into the “GIB” and “No GIB” groups as well as for the subpopulations stratified by the year.

All tests were 2-tailed, and a *P* value of less than 0.05 was considered significant for all tests. Univariate analysis was initially conducted to summarize the data. The Pearson chi-square tests were used to test for categorical variables and are presented as percentages. The nonparametric Wilcoxon rank sum tests were employed to test for all continuous variables and are presented as mean ± standard deviation.

The logistic regressions were fit to the data to evaluate the trend for incidence of GIB over the years 1998 to 2006. Wald test with a 0.05 level of significance was used to test the null hypothesis of no trend. The logistic regression model was then used to assess independent predictors of GIB after adjusting for the observed baseline demographic and clinical characteristics. The logistic regression model was also used to investigate the trends for incidence of in-hospital mortality with and without GIB as well as to assess the trends for the adjusted and unadjusted odds ratio (OR) for the association between death and GIB over the study years.

Finally, we used propensity-score method to evaluate the effect of GIB on the mortality rate. Propensity scores were estimated using a logistic regression model with GIB as the outcome and all the observed baseline demographic and clinical characteristic variables. We then used the method of regression adjustment by the estimated propensity scores to estimate the effect of GIB on the mortality rate, taking into account all the other observed baseline demographic and clinical characteristic variables. Advantage of this two-step propensity score procedure is that this allows us to fit a complicated propensity score model with interactions and higher order terms for more accurate estimation of GIB probability.[14]

The missing data were omitted as follows: in the No GIB group (n=1204065) age (n=20, 0.002%), death (n=296, 0.02%), female gender (n=97, 0.008%), length of stay (n=20, 0.002%), mean financial cost (n=17295, 1.4%), race (n=337586, 28%). In the GIB group (n=12694) death (n=13, 0.1%), female gender (n=1, 0.008%), mean financial cost (n=211, 1.7%), race (n=3672, 29%).

All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA).

All authors have read and agree to the manuscript as written. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. This study has been approved by the University of Illinois at Chicago Institutional Review Board. This study is supported in part by the Division of Cardiology, University of Illinois at Chicago (Chicago, Illinois) and the University of Illinois at Chicago Center for Clinical and Translational Science, which is funded in part by the National Center for Research Resources, National Institutes of Health (Bethesda, Maryland), grant number UL1RR029879.

RESULTS

GIB after PCI

From 1998 to 2006, there were 1,216,759 PCI procedures performed for AMI and CAD diagnoses. Patients' baseline characteristics and clinical presentation are shown in Table I. GIB during the PCI hospitalization occurred in 12,694 (1.04%, 95% confidence interval (CI), 1.02%–1.06%) patients. The overall incidence in GIB associated with PCI decreased during the study period from 0.98% in 1998 to 0.88% in 2006 (p for trend <0.0001 univariate analysis, p=0.0008 multivariate analysis, Figure 1).

The independent predictors for GIB after adjusting for covariates were identified (Figure 2). Important independent predictors included rectum/anal cancer (adjusted OR, 4.64; 95% CI, 3.20–6.73; p<0.0001), stomach cancer (OR, 2.74; 95% CI, 1.62–4.66; p=0.0002), esophageal cancer (OR, 1.99; 95% CI, 1.07–3.69; p=0.0288), colon cancer (OR, 1.69; 95% CI, 1.43–2.02; p<0.0001), and CHF (OR, 1.43; 95% CI, 1.35–1.52; p<0.0001). Other predictors included COPD, gastroduodenal ulcer/gastritis/duodenitis and AMI. Female gender and atrial fibrillation/atrial flutter were not significant independent predictors for GIB.

The number of procedures performed (upper endoscopy, lower endoscopy, pulmonary artery catheter monitoring, and blood transfusion [p<0.0001 for all]), length of stay (p<0.0001), mean financial cost (p<0.0001), utilization of bare-metal stents (p<0.0001) and drug-eluting stents (p=0.0004) were significantly associated with GIB after adjusting for covariates.

Death and GIB Associated with PCI

The overall mortality in the GIB group was 6.0% (95% CI, 5.6%–6.4%). Patients who died were 8.31 (95% CI, 7.71–8.97; p<0.0001) times more likely to have GIB than the patients who were alive; this OR decreased to 4.70 (95% CI, 4.23–5.23; p<0.0001) after adjusting for covariates. The in-hospital mortality in patients with GIB (p=0.1499 multivariate analysis) and without GIB (p=0.2004 multivariate analysis) was *unchanged* from 1998 to 2006 (Figures 3A and 3B respectively). Both the adjusted and unadjusted OR for in-hospital mortality associated with GIB were high for each individual year when compared to in-hospital mortality without GIB (p<0.0001 for all years). The temporal trend of the unadjusted and adjusted OR for in-hospital mortality associated with GIB (p for trend = 0.64 and 0.72, respectively) remained *unchanged* over the study period (Table II).

Propensity matching analysis was also performed to reduce the confounding effects of baseline demographics and clinical characteristic variables. After propensity matching the association of GIB with in-hospital mortality remained statistically significant (p<0.001).

DISCUSSION

GI bleeding is a serious and often fatal complication after PCI.[5, 15, 16] Although post-PCI bleeding most frequently occurs at the access site, the GI tract is the second most common

site of hemorrhage.[10, 12, 17, 18] The overall observed incidence of GIB associated with PCI from 1998 to 2006 in this large, contemporary, national registry was 1.04%. This is lower compared with the reported incidence of GIB associated with PCI in previous studies which ranged from 1.1% to 3.0%.[8–12] This finding is important since more intensive anti-platelet and anti-thrombotic therapies associated with increased GIB rates were introduced during this period.[1, 12, 19, 20]

During the observation period, bivalirudin, a direct thrombin inhibitor was approved for use in 2000. In the National Cardiovascular Data Registry (NCDR) Catheterization PCI (CathPCI) registry, the use of UFH, LMWH and glycoprotein IIb/IIIa inhibitors (GPI) significantly decreased and the use of bivalirudin increased among patients with ACS and non-ACS from 2005 to 2009.[3] GIB occurred significantly more frequently in patients randomized to heparin + GPI when compared with bivalirudin monotherapy (0.6% vs. 0.1%).[6, 12, 21, 22] A sharp decline in the incidence of GIB was noted from 2003 to 2006 in this study, which coincides with the publication of the REPLACE-2 results that brought the reduction in bleeding complications with the use of bivalirudin to the forefront. Similarly, the use of thienopyridines underwent dramatic changes in this period.

Among the NSTE-ACS patients enrolled in 4 large prospective, multicenter US registries from 1999 to 2008, the use of thienopyridines increased from 8.9% to 76.2% with a significant increase in dual anti-platelet therapy use.[23] Dual antiplatelet therapy with clopidogrel and aspirin increases GI bleeding complications – GI is the site of major bleeding in 1.3% of patients treated with clopidogrel and aspirin versus 0.7% in those treated with aspirin alone.[24] Prasugrel, a more potent thienopyridine, further increases the risk of major, life-threatening and fatal bleeding; and the GI site was one of the most frequent site for life-threatening bleeding.[25] It is very encouraging that the wide adoption of intensive dual antiplatelet regimens did not result in an increase in GIB in the NIS patient population.

With an increase in PCI with stents, utilization of anticoagulants, dual oral anti-platelet medications, and GPI in patients with AMI and NSTE-ACS as noted from 1990 to 2008,[23, 26] a parallel increase in the incidence of GIB would have been expected. The observation of risk factors for GIB associated with PCI, including age, AMI, and CRI (Table I) are consistent with other trials.[10, 12] Focused efforts in identifying these high bleeding risk patients [5, 27] and tailoring therapies [23] to reduce GIB in these patients may have contributed partially to the lower observed GIB rates. Implementation of societal guidelines [26] and quality-improvement techniques targeting bleeding complications, such as renal function and weight-adjusted dosing of anti-platelet/anti-thrombotic therapies, preferential use of medications such as bivalirudin that cause less bleeding,[4, 22] prophylactic treatment of high bleeding risk patients with proton pump inhibitors (PPIs),[11, 28, 29] may have also contributed to the observed decrease in the rates of GIB in this period.

Previous studies have reported a 10% in-hospital mortality with development of GIB associated with PCI.[8] The overall mortality in this NIS GIB group was 6.0%. The high mortality noted in patients developing GIB associated with PCI is likely multifactorial in etiology. The practice of discontinuing effective anti-platelet/anti-thrombotic agents in patients who develop GIB, has been associated with the increased risk of further ischemia, infarction, stent thrombosis and need for repeat PCI and death.[5, 10, 30] Aspirin and/or thienopyridines were noted to be frequently discontinued in patients with GIB.[12] Among patients triaged to PCI, 5.8% of patients with GIB developed stent thrombosis compared with 2.4% of patients without GIB.[12] Other proposed mechanisms for the association between GIB and mortality are anemia and hypotension-related reduction in myocardial oxygen delivery, hemodynamic instability, blood transfusions and thrombocytopenia.[8, 9, 12]

The risk-adjusted in-hospital mortality did not change significantly among the ACS and non-ACS patients in the NCDR CathPCI registry from 2005 to 2009.[3] A very concerning finding in this NIS PCI registry is that the adjusted risk of death after developing GIB associated with PCI remained high and largely unchanged from 1998 to 2006 (Table II); this finding is consistent with the findings of the NCDR CathPCI registry and was noted over a longer study period.

The significant association between GI malignancies and GIB associated with PCI has not been previously observed. Patients with malignancies are generally excluded from clinical trials, and other large nationwide registries have not reported this particular information. Our findings indicate that the presence of an underlying GI malignancy is an additional significant independent predictor of GIB associated with PCI. Identifying patients with GI malignancies may reduce the rate of GIB associated with PCI. Currently, there are no systematic strategies to screen for GI malignancy in the elective PCI population. Such measures, however, may not be effective in the emergent STEMI or NSTEMI setting. While the rate of GIB in the elective PCI population was lower than that in the AMI population, elective PCI may allow substantial improvement in the processes of care and procedural outcomes. It is important to emphasize that the findings of this study does not imply causality but only an association of GI malignancy with GIB.

Study Limitations

Data about management patterns, utilization rates or dosing of the various anti-platelet/anti-thrombotic medications and utilization rates of PPIs that have been associated with decreased GIB were not collected. The database does not allow for evaluation of practice patterns that account for the noted reduction in GIB. This precludes us from confirming an association between the trends in the utilization of specific anti-platelet/anti-thrombotic medications and PPI with the incidence of GIB. Data on other bleeding complications such as access site and retroperitoneal bleeds were not available in our dataset. The details on the type and temporal relationship of GIB to PCI were not available. The identification of GIB was determined by the local sites and not centrally adjudicated. The underreporting of smaller GIB cannot be excluded, and could have biased the estimation of the true incidence of GIB, in addition to the mortality rate associated with GIB. Importantly, the cause-effect relationship between PCI, anti-platelet/anti-thrombotic therapy, GIB and the observed outcome of mortality cannot be determined. Additional unmeasured confounders may have accounted for the observed differences. The race data was missing in about 29% of all cases. NIS does not collect long-term outcomes of GIB associated with PCI. Finally, participation in the NIS registry is voluntary and only selected centers may have participated in this registry, the results may not be generalized to all U.S. hospitals/population at large.

Summary

A temporal trend in GIB associated with PCI has not been studied, and as such this study addresses an important gap in the literature. This very large sample study represents the contemporary, real-world practice in the US and encompasses a broad range of patients who would have otherwise been excluded from randomized clinical trials. This study describes a period during which important changes in PCI management have occurred. From 1998 to 2006 the incidence of GIB associated with PCI decreased in the face of more aggressive therapies for ACS and CAD. The risk of GIB-associated death has remained high and unchanged. Underlying GI malignancy is a significant independent predictor of GIB associated with PCI. The findings of this study may help develop a basis for future investigation to better define causes of GIB associated with PCI and provide pertinent information regarding preventive management strategies to reduce morbidity and mortality.

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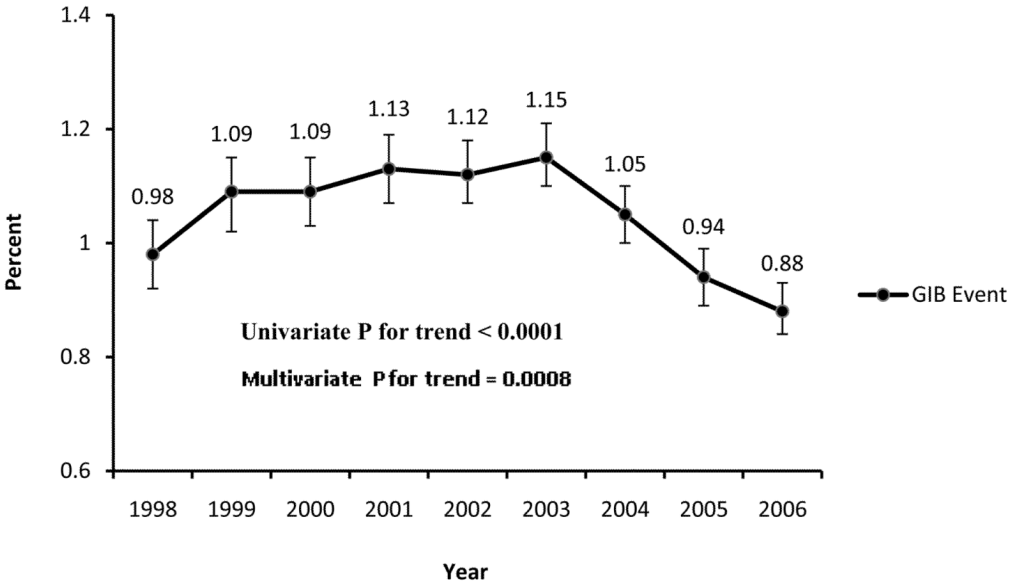

Figure 1.
Incidence of gastrointestinal bleeding from 1998 to 2006.
The error bars indicate 95% confidence intervals.

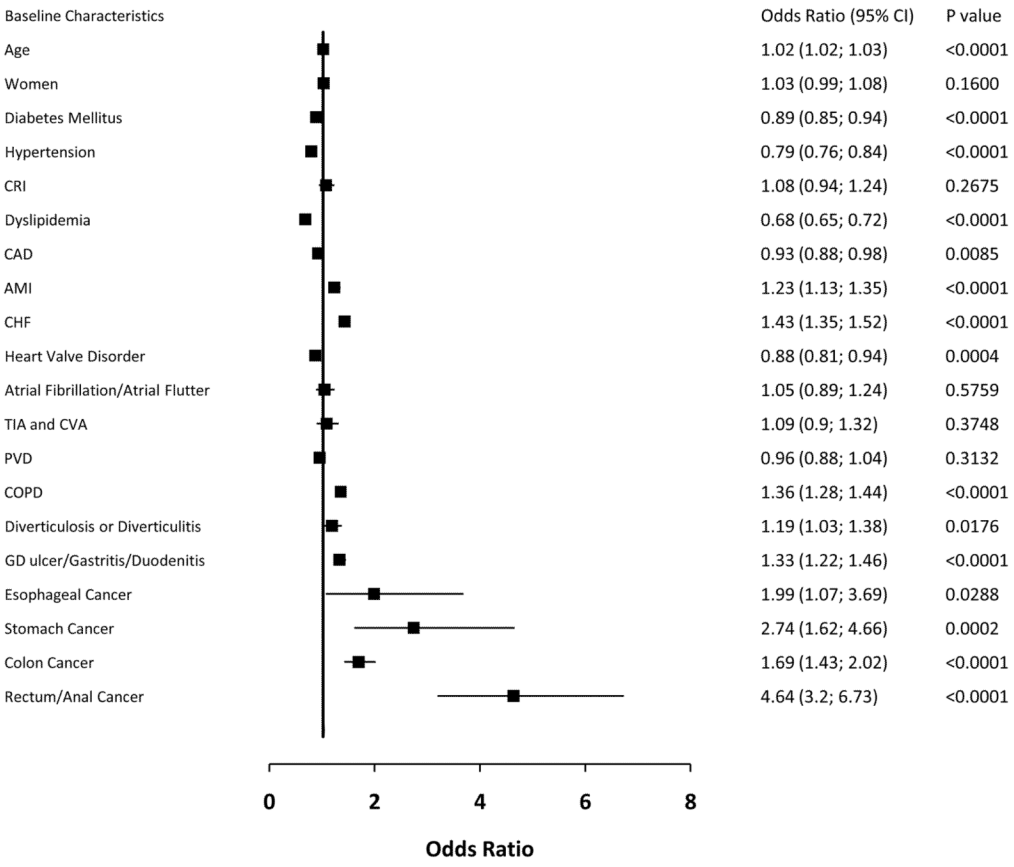

Figure 2.
Independent predictors for GIB after adjusting for covariates.

Figure 3a

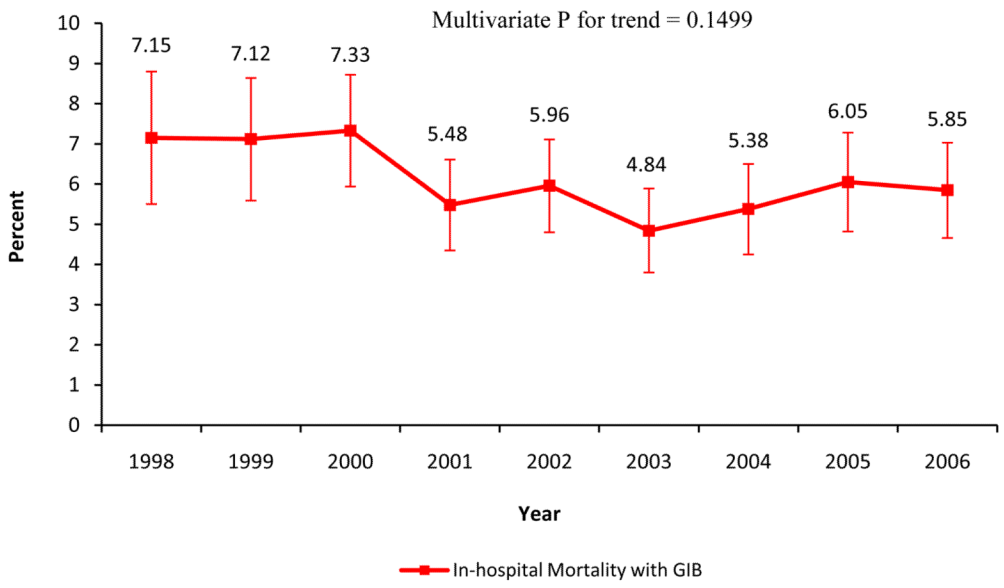

Figure 3b

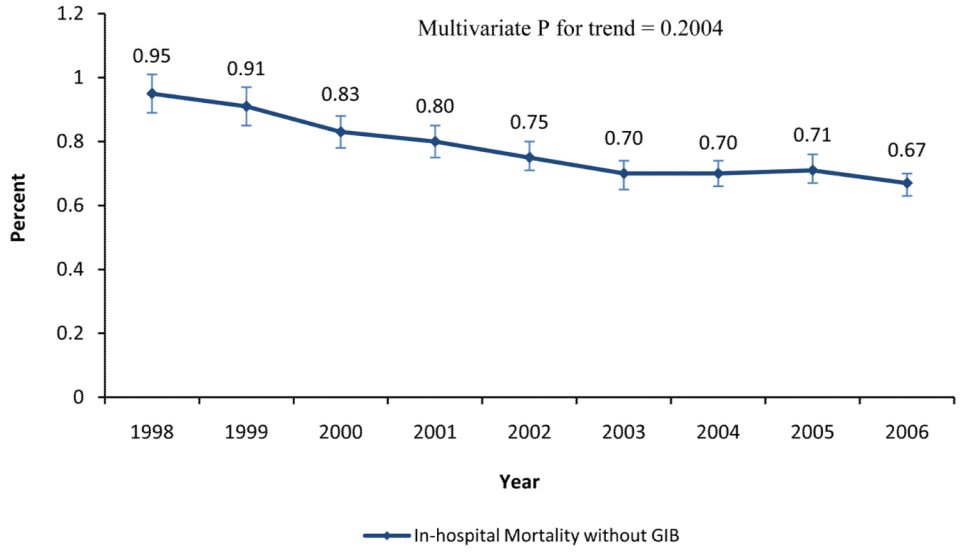

Figure 3.

Figure 3A. Incidence of in-hospital mortality with gastrointestinal bleeding from 1998 to 2006.

The error bars indicate 95% confidence intervals.

Figure 3B. Incidence of in-hospital mortality without gastrointestinal bleeding from 1998 to 2006.

The error bars indicate 95% confidence intervals.

Table I

Baseline patient characteristics

	No Gastrointestinal Bleeding (n = 1,204,065)	Gastrointestinal Bleeding (n = 12694)	p-value
Age, mean ± SD	64.2 ± 12.2	70.5 ± 11.4	< 0.001
Women, %	34.2	44.3	< 0.001
Race, %			<0.0001
White	82.9	81.1	
Black	6.3	8.1	
Hispanic	6.0	6.2	
Asian	1.6	1.9	
Native American	0.3	0.2	
Other	3.1	2.6	
Died during hospitalization, total (%)	9199 (0.8)	763 (6.0)	< 0.001
Length of stay, mean ± SD	2.78 ± 3.1	7.61 ± 7.1	< 0.001
Financial cost, mean ($)	36758	60094	< 0.001
Medical History, total number (%)			
Diabetes mellitus	334395 (27.8)	3411 (26.9)	0.024
Hypertension	736634 (61.2)	6837 (53.9)	< 0.001
CRI	18803 (1.6)	443 (3.5)	< 0.001
Dyslipidemia	620215 (51.5)	3863 (30.4)	< 0.001
CAD	972236 (80.7)	9797 (77.2)	< 0.001
AMI	44367 (3.7)	944 (7.4)	< 0.001
CHF	116754 (9.7)	3469 (27.3)	< 0.001
Heart Valve Disorder	82980 (6.9)	1495 (11.8)	< 0.001
Atrial fibrillation/Atrial flutter	12490 (1.0)	292 (2.3)	< 0.001
TIA and CVA	11115 (0.9)	186 (1.5)	< 0.001
PVD	76305 (6.3)	967 (7.6)	< 0.001
COPD	113365 (9.4)	2437 (19.2)	< 0.001
Diverticulosis or diverticulitis	6777 (0.6)	589 (4.6)	< 0.001
GD ulcer/Gastritis/Duodenitis	22223 (1.9)	1706 (13.4)	< 0.001
Esophageal cancer	475 (0.0)	24 (0.2)	< 0.001
Stomach cancer	378 (0.0)	35 (0.3)	< 0.001
Colon cancer	8234 (0.7)	266 (2.1)	< 0.001
Rectum/Anal cancer	714 (0.1)	62 (0.5)	< 0.001
Procedures, total number (%)			
Upper endoscopy	8143 (0.7)	3382 (26.6)	< 0.001
Lower endoscopy	2192 (0.2)	1000 (7.9)	< 0.001
Pulmonary artery catheter monitoring	3233 (0.3)	226 (1.8)	< 0.001
Blood transfusion	17137(1.4)	2123 (16.7)	< 0.001
BMS	664707 (55.2)	7787 (61.3)	< 0.001
DES	419782 (34.9)	3534 (27.8)	< 0.001

CRI indicates chronic renal insufficiency; CAD, coronary artery disease; AMI, acute myocardial infarct; CHF, congestive heart failure; TIA, transient ischemic attack; CVA, cerebrovascular accident; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; GD ulcer, gastroduodenal ulcer; BMS, bare-metal stent; DES, drug eluting stent.

Table II

Association between death and gastrointestinal bleed by year with and without adjusting for covariates.

	Without adjusting for covariates		With adjusting for covariates*	
Variable	**Odds Ratio (95% Confidence Interval)**	**P-value**	**Odds Ratio (95% Confidence Interval)**	**P-value**
Overall				
Died	8.31 (7.71, 8.97)	< 0.0001	4.70 (4.23, 5.23)	< 0.0001
Individual Year				
1998	8.04 (6.22, 10.40)	< 0.0001	5.43 (3.92, 7.52)	< 0.0001
1999	8.35 (6.57, 10.61)	< 0.0001	4.58 (3.26, 6.42)	< 0.0001
2000	9.48 (7.66, 11.74)	< 0.0001	5.11 (3.76, 6.94)	< 0.0001
2001	7.19 (5.74, 9.01)	< 0.0001	4.22 (3.13, 5.67)	< 0.0001
2002	8.38 (6.76, 10.38)	< 0.0001	5.37 (3.99, 7.21)	< 0.0001
2003	7.24 (5.73, 9.15)	< 0.0001	3.84 (2.71, 5.43)	< 0.0001
2004	8.07 (6.42, 10.16)	< 0.0001	4.14 (2.95, 5.79)	< 0.0001
2005	8.95 (7.14, 11.2)	< 0.0001	5.30 (3.93, 7.14)	< 0.0001
2006	9.27 (7.42, 11.59)	< 0.0001	4.41 (3.21, 6.07)	< 0.0001

* The adjusting covariates are year, age, gender, race, length of stay, financial cost, diabetes mellitus, hypertension, chronic renal insufficiency, dyslipidemia, coronary artery disease, acute myocardial infarction, congestive heart failure, heart valve disorder, atrial fibrillation/flutter, transient ischemic attack/cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, diverticulosis/diverticulitis, gastroduodenal ulcer/gastritis/duodenitis, esophageal cancer, stomach cancer, colon cancer, rectum/anal cancer, upper endoscopy, lower endoscopy, pulmonary artery catheter monitoring, blood transfusion, bare-metal stents, drug-eluting stents, and percutaneous transluminal coronary angioplasty.