

Aspirin Has a Protective Effect Against Adverse Outcomes in Patients with Nonvariceal Upper Gastrointestinal Bleeding

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Abstract

Objective To determine the effect of aspirin and anticoagulants on clinical outcomes and cause of in-hospital death in patients with nonvariceal upper gastrointestinal bleeding (NVUGIB).

Methods Patients were identified from a tertiary center database that included all patients with UGIB. Clinical outcomes including (1) in-hospital mortality, (2) severe bleeding, (3) rebleeding, (4) in-hospital complications, and (5) length of hospital stay were examined in patients taking (a) aspirin only, (b) anticoagulants only, and (c) no antithrombotics.

Results Of 717 patients with NVUGIB, 56 % (402) were taking at least one antithrombotic agent. Seventy-eight (11 %) patients died in hospital, and 310 (43 %) had severe bleeding (BP < 90 mmHg, HR > 120 b/min, Hb < 7 g/dL on presentation, or transfusion of >3 units). On multivariate analysis, being on aspirin was protective against in-hospital mortality [OR 0.26 (0.13–0.53)], rebleeding [OR 0.31 (0.17–0.59)], and predictive of a shorter hospital stay

(coefficient = −4.2 days; 95 % CI −8.7, 0.3). Similarly, being on nonaspirin antiplatelets was protective against in-hospital mortality ($P = 0.03$). However, being on anticoagulants was predictive of in-hospital complications [OR 2.0 (1.20–3.35)] and severe bleeding [OR 1.69 (1.02–2.82)]. Compared to those not taking any antithrombotics, patients who bled on aspirin were less likely to die in hospital of uncontrolled gastrointestinal bleeding (3.6 vs 0 %, $P \leq 0.01$) and systemic cancer (4.9 vs 0 %, $P \leq 0.002$), but equally likely to die of cardiovascular/thromboembolic disease, sepsis, and multiorgan failure.

Conclusion Patients who present with NVUGIB on aspirin had reduced in-hospital mortality and fewer adverse outcomes, while those on anticoagulants had increased in-hospital complications.

Keywords Hemorrhage · Aspirin · Anticoagulant · Outcome · Morbidity · Mortality

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Abbreviations

UGIB	Upper gastrointestinal bleeding
NVUGIB	Nonvariceal upper gastrointestinal bleeding
AC	Anticoagulant
AP	Antiplatelet

Introduction

Nonvariceal upper gastrointestinal bleeding (NVUGIB) is a common condition associated with high morbidity and mortality [1]. It accounts for about 300,000 hospital admissions per year [2]. Despite improvements in pharmacologic and endoscopic therapy, mortality rates have not decreased and range between 10 and 14 % [3, 4].

Antithrombotic drugs, including aspirin and anticoagulants, are commonly and increasingly being prescribed for various cardiovascular conditions [5, 6]. These drugs are known to increase the risk of gastrointestinal bleeding about twofold to threefold [7–9] via different mechanisms: Aspirin is known to cause ulcers, and anticoagulants are thought to increase bleeding from existing gastrointestinal lesions [10]. In fact, it has been reported that 31 % of patients with UGIB were on aspirin and 5.5 % on anticoagulants at baseline [9]. While peptic ulcer disease was thought to be the most common cause of NVUGIB, recent data suggest that other causes play an equally important role [11]. Regardless of the cause, it was common practice to withhold antiplatelets (AP) and anticoagulants (AC) in the setting of active UGIB until data emerged in recent years questioning the value of such a practice [12–16].

The available data on the effects of antiplatelet agents on morbidity and mortality in patients with NVUGIB are still controversial. Some reports suggest that aspirin use does not affect mortality [17, 18], while others suggest that it has protective effects [12, 13, 15]. Similarly, studies on the effect of anticoagulant use on outcomes are inconclusive [2, 18, 19]. We have recently reported that patients presenting with peptic disease-related UGIB who were taking aspirin had fewer adverse outcomes, while those taking anticoagulants had worse outcomes compared to patients taking none [20]. This is supported by a recent prospective study suggesting that the use of aspirin was significantly higher in patients who did not have adverse outcomes, whereas the use of anticoagulants was more common in those who developed adverse outcomes [21]. These data raised the possibility that aspirin may have beneficial effects in patients with NVUGIB.

Thus, the aim of this study was to examine outcomes of patients admitted with all forms of NVUGIB while on aspirin only, anticoagulants (AC) only, or combination therapy, and to compare them to patients with NVUGIB not taking these medications. In addition, we analyzed the cause of death in those who suffered in-hospital mortality.

Methods

Study Design

This was a retrospective cohort study of patients admitted to the American University of Beirut Medical Center with NVUGIB between 1993 and 2010. The study was approved by the Institutional Review Board of AUBMC (IM.KB.09).

Patient Population and Data Collection

All patients admitted with gross GI bleeding between 1993 and 2010 were identified using the ICD-9/ICD-10 coding system. These codes encompassed symptoms of hematemesis, coffee ground emesis, and/or melena. UGIB was defined as witnessed or reported hematemesis, hematochezia, or melena in the setting of a decrease in hemoglobin compared to baseline or to a level below normal. We further defined NVUGIB as bleeding from a GI source proximal to the ligament of Treitz in the absence of varices when endoscopy was performed. For patients who did not have endoscopy, the diagnosis of UGIB was based on history of witnessed or reported hematemesis and/or coffee ground emesis and/or melena. All patients diagnosed with NVUGIB during the study period were included. We excluded patients who had variceal bleeding, lower GIB, small bowel bleeding, or occult GI bleeding.

Antithrombotic Medications

Information about medication use at time of diagnosis was abstracted from medical records, including nurses and physicians' clinical notes devoted to the patient's medications intake at home. Patients were divided into five groups based on intake of aspirin, anticoagulants, combination therapy, or none upon admission to the hospital as follows: None group included patients on no aspirin, antiplatelet drugs, or anticoagulants (also "no antithrombotics," control group); aspirin group consisted of patients on aspirin only; AC group included patients on anticoagulants (warfarin, heparin, or low molecular weight heparin) only; AP group were patients on nonaspirin antiplatelet agents (clopidogrel, ticlopidine, or dipyridamole) with or without aspirin; AP + AC group were on both antiplatelets and anticoagulants. The use of NSAIDs was also recorded.

Study Variables

The following information was abstracted from medical records: demographic data—including age and gender, social history—including smoking and alcohol use, past medical history—including history of hypertension, coronary artery disease, valvular heart disease, congestive heart

failure, atrial fibrillation, deep vein thrombosis, cerebrovascular accident including transient ischemic attacks, diabetes mellitus, chronic renal failure, gastrointestinal or systemic cancer, dyslipidemia, as well history of peptic ulcer disease. We also recorded the mode of clinical presentation, vital signs upon presentation, initial blood studies obtained upon arrival to the emergency room, management in the emergency room and in the hospital, findings on upper gastrointestinal endoscopy when performed, type of therapeutic endoscopic procedure undertaken (if any), angiography and embolization if any, surgical treatment if any, severe bleeding or rebleeding, in-hospital complications, length of hospital stay, and in-hospital mortality. For patients who died in the hospital, the cause of death was determined as previously described [22].

Definition of Clinical Outcomes

The primary outcome of this study was in-hospital mortality. Secondary outcomes included the following: rebleeding, need for surgery, severe bleeding, in-hospital complications, and length of hospital stay. Criteria for severe bleeding were as follows: systolic blood pressure (BP) < 90 mmHg, heart rate (HR) > 120 b/min, hemoglobin (Hb) < 7 g/dL on presentation, or transfusion of >3 units of blood during hospitalization. Rebleeding was defined as recurrence of hematemesis, coffee ground emesis, or melena occurring after 24 h from the initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a change in vital signs or decrease in hemoglobin concentration by 2 g/L or more. Rebleeding events during the same hospitalization or requiring another hospitalization were combined. In-hospital complications included a definitive diagnosis of a cardiovascular or thromboembolic event (myocardial infarction, angina, deep vein thrombosis, pulmonary embolism, stroke, or transient ischemic attack), infectious complications (pneumonia, urinary tract infection, skin infections, and sepsis), or the following: acute respiratory distress syndrome, acute renal failure, need for mechanical ventilation, and disseminated intravascular coagulopathy. These specific diagnoses were made using standard and commonly accepted clinical criteria. We considered the occurrence of any of those events as one in-hospital complication.

The frequencies of the following causes of death were compared among the groups: gastrointestinal bleeding (if death was due to uncontrolled bleeding or occurred subsequent to interventions undertaken to control it, such as surgery), cardiovascular/thromboembolic events, systemic cancer, sepsis, and multi-organ failure. Need for blood transfusion and number of blood units transfused were also determined.

Statistical Analysis

Data management and analyses were carried out using the Statistical Analysis Software (SAS, version 9.1). Univariate analyses were carried out by calculating the number and percent for categorical variables, and the mean and standard deviation (SD) for the continuous ones. Bivariate analyses were performed using the Chi-square test or the independent Student's *t* test, as appropriate.

To control for the effect of potentially confounding variables, multivariate analyses were carried out while controlling for different risk factors. For categorical outcomes (such as primary outcomes), multivariate logistic regression analyses were carried out where the odds ratio (OR), 95 % confidence interval (CI), and *p* value were reported. For continuous outcomes (such as duration of hospital stay), multivariate linear regression was carried out where the β coefficient, 95 % CI, and *p* value were reported. Multivariate analysis was done for the aspirin only group and anticoagulant only group, with the “none” group as a control for each. Variables included in the regression model were those of either statistical or clinical significance, and these comprised age, comorbidities, and endoscopic therapy. A *p* value < 0.05 was considered to indicate statistical significance.

Results

Patient Demographics

In total, 717 patients with NVUGIB were included. Their mean age was 65 years and 31 % were women. Of this total, 315 were on no antithrombotics (none group), 202 were on aspirin only (aspirin group), 89 were on anticoagulants only (AC group), 53 were on nonaspirin antiplatelet agents with or without aspirin (AP \pm aspirin group), and 58 were on both antiplatelet agents and anticoagulants (AP + AC group) (Table 1). Patients on aspirin and those on anticoagulants were significantly older and had more co-morbidities than controls, including hypertension, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and dyslipidemia. Both groups were also less likely to have a history of peptic ulcer disease than controls. In addition, atrial fibrillation and deep vein thrombosis were more prevalent in anticoagulant users than in controls (Table 1). The frequency of proton pump inhibitors (PPI) use was higher in AP + AC group compared to controls (21 vs 11 %, *P* = 0.053) but was otherwise similar in all groups with an average prevalence of 12 %. NSAIDs use was less common in AP \pm aspirin and AP + AC groups compared to the other groups (Table 1). The prevalence of alcohol consumption in the cohort was 13 %, similar in all groups. There were

Table 1 Demographics and clinical characteristics of 717 patients with NVUGIB

Group (N)	None (315)	Aspirin (202)	AC (89)	AP ± aspirin (53)	AP + AC (58)	All (717)
Age, years (mean ± SD)	60 ± 19	68 ± 12**	69 ± 12**	70 ± 12**	73 ± 11**	65 ± 16
Male gender, <i>n</i> (%)	208 (66)	155 (77)**	47 (53)*	42 (79)‡	41 (71)	493 (69)
<i>PMH, n (%)</i>						
Diabetes	43 (14)	75 (37)**	26 (29)**	19 (36)**	21 (36)**	184 (26)
Hypertension	99 (31)	116 (57)**	51 (57)**	42 (79)**	33 (57)**	341 (48)
CAD	44 (14)	88 (44)**	35 (39)**	37 (70)**	40 (69)**	244 (34)
PVD	9 (3)	14 (7)*	9 (10)**	3 (6)	4 (7)	39 (5)
CRF	30 (10)	25 (12)	10 (11)	8 (15)	7 (12)	80 (11)
Valvular disease	10 (3)	4 (2)	16 (18)**	0 (0)*	9 (16)**	39 (5)
CVA	7 (2)	16 (8)**	9 (10)**	4 (8)*	10 (17)**	46 (6)
Atrial fibrillation	9 (3)	8 (4)	20 (22)**	2 (4)	11 (19)**	50 (7)
CHF	13 (4)	10 (5)	7 (8)	4 (7)	15 (26)**	49 (7)
DVT	0 (0)	2 (1)	7 (8)**	0 (0)	1 (2)*	10 (1)
Dyslipidemia	27 (9)	61 (30)**	15 (17)*	28 (53)**	17 (29)**	148 (21)
Cancer	67 (21)	20 (10)**	22 (25)	6 (11)	3 (5)**	118 (16)
History of PUD	69 (22)	25 (12)**	8 (9)**	4 (8)*	10 (17)	116 (16)
Nonaspirin NSAIDs use	63 (20)	31 (15)	13 (15)	3 (6)*	1 (2)**	111 (15)
<i>Symptoms at presentation, n (%)</i>						
Hematemesis	86 (27)	38 (19)*	22 (25)	14 (26)	11 (19)	171 (24)
Melena	136 (43)	105 (52)*	40 (45)	16 (30)	33 (57)‡	330 (46)
Hematemesis + Melena	59 (19)	39 (19)	22 (25)	14 (26)	10 (17)	144 (20)
Hematochezia	9 (3)	7 (3)	2 (2)	4 (8)	3 (5)	25 (3)
Syncope	39 (12)	40 (20)*	11 (12)	15 (28)**	10 (17)	115 (16)
<i>Initial laboratory results, mean ± SD</i>						
Hemoglobin (g/dl)	9.1 ± 2.9	9.1 ± 2.4	8.2 ± 2.5**	8.8 ± 1.7	9.0 ± 2.2	8.9 ± 2.6
Hematocrit (%)	27 ± 8	27 ± 7	25 ± 8*	26 ± 5	27 ± 7	27 ± 7
Drop in hematocrit	11 ± 7	11 ± 7	13 ± 8**	11 ± 6*	12 ± 7	11 ± 7.0
INR	1.3 ± 0.7	1.1 ± 0.5*	3.2 ± 2.0**	1.2 ± 0.6	2.6 ± 1.8**	1.7 ± 1.4
<i>Endoscopic diagnosis, n (%)</i>						
Ulcer disease	115 (37)	105 (52)**	25 (28)	25 (47)	15 (26)	285 (40)
Erosive disease	83 (26)	88 (44)**	17 (19)	20 (38)	17 (29)	225 (31)
Mallory–Weiss tear	21 (7)	9 (4)	0 (0)*	6 (11)	3 (5)	39 (5)
AVM	13 (4)	5 (2)	5 (6)	4 (8)	0 (0)	27 (4)
Cancer	10 (3)	0 (0)*	0 (0)	1 (2)	0 (0)	11 (2)
Hiatal Hernia	28 (9)	20 (10)	11 (12)	5 (9)	5 (9)	69 (10)

Aspirin: those on aspirin only; AC: those on anticoagulants only; AP ± aspirin: those on non-aspirin antiplatelet (clopidogrel, ticlopidine, or dipyridamole) with or without aspirin; AP + AC: those taking antiplatelet agents combined with anticoagulants; PMH, past medical history; SD, standard deviation; CAD, coronary artery disease; PVD, peripheral vascular disease; CRF, chronic renal failure; CVA, cerebro-vascular accident; CHF, congestive heart failure; DVT, deep vein thrombosis; NSAIDs, nonsteroidal anti-inflammatory drugs; INR, international normalized ratio; AVM, arteriovenous malformation; NVUGIB, nonvariceal upper gastrointestinal bleeding

* *P* value <0.05; ** *P* value < 0.01; ‡ *P* value = 0.05–0.06 compared to the none group

10 patients out of the 717 (1.4 %) who had documented hepatitis or cirrhosis, and they all fell in the control group.

Clinical Presentation and Etiology of Bleeding

Compared to controls, patients taking aspirin only were less likely to report hematemesis and more likely to report

melena. Interestingly, patients on aspirin therapy were more likely to report syncope, which was also the case in AP ± aspirin group. Overall, the mean hematocrit of patients in this cohort was 27 ± 7 % at initial evaluation. The anticoagulant group had a significantly lower hematocrit (25 ± 8 %) than the control group (27 ± 8 %, *P* < 0.01) and had a significantly higher drop in hematocrit as well.

The mean INR was higher in the anticoagulant group (3.2 ± 2.0) and lower for the aspirin only group (1.1 ± 0.5) than in controls (1.3 ± 0.7 , $P < 0.01$ and < 0.05 , respectively).

Endoscopy was performed on 512 patients, revealing ulcer disease in 285 patients (40 %) and erosive disease in 225 (31 %); 39 (5 %) had Mallory–Weiss tears, and 69 (10 %) had large hiatal hernia with or without Cameron lesions. Twenty-seven (4 %) had AVM, and 11 (2 %) had gastrointestinal cancer. Three hundred and ninety-eight patients (56 %) of this cohort had peptic disease (ulcers and/or erosions) as reported previously by us [20]. Multiple patients had more than one lesion identified. The prevalence of gastric ulcers and erosive disease was significantly higher in the aspirin only group than in controls. Endoscopic therapy was performed on 124 patients, as follows: thermo-coagulation alone (31 patients), epinephrine injection alone (29 patients), hemostatic clips alone (1 patient), argon plasma coagulation alone (13 patients), dual therapy (47 patients), triple therapy (2 patients), and quadruple therapy in one.

Clinical Outcomes

Patients in the aspirin only group had lower in-hospital mortality and rebleeding rates compared to controls (5 and 7 vs 14 and 17 %, respectively, $P < 0.01$, Table 2). The aspirin only group also required surgery less frequently than the control group. Their hospital stay was shorter than for controls (5.7 vs 8.6 days), but this was of borderline statistical significance on univariate analysis ($P = 0.16$).

Patients on aspirin only were more likely to be transfused (77 vs 63 %, $P < 0.01$); however, they were given less blood units per patient compared to controls (3.6 vs 4.8, $P < 0.05$). Similarly, patients on nonaspirin antiplatelet agents with or without aspirin had a lower overall mortality rate than controls (4 vs 14 %, $P < 0.01$). This difference remained significant on multivariate analysis ($P = 0.03$). They also had shorter hospital stay and received fewer blood transfusions than controls (Table 2).

By contrast, patients in the anticoagulant group had similar mortality, rebleeding rate, and hospital stay to patients not taking any antithrombotic agents. They were, however, more likely to be transfused (88 vs 63 %, $P < 0.01$) and required a similar number of transfused blood units per transfused patient (7.3 ± 18.0 vs 4.8 ± 5.7 , $P = 0.23$). They were also more likely to develop in-hospital complications (58 vs 34 %, $P < 0.01$) and severe bleeding (61 vs 40 %, $P < 0.01$). When compared to the aspirin group, the anticoagulant group had a higher mortality rate ($P = 0.004$), in-hospital complications ($P < 0.001$), severe bleeding ($P = 0.001$), and rebleeding ($P = 0.002$).

For patients on combination antiplatelet and anticoagulant therapy, the frequency of in-hospital mortality, rebleeding, severe bleeding, and surgery was similar to that of the control group (Table 2). The same is true for length of hospital stay. The frequency of hospital complications and that of patients requiring transfusions, however, was higher in that group than in controls. However, the increase in hospital complications was not significant on multivariate analysis.

Table 2 Clinical outcomes in 717 patients with NVUGIB

Group (n)	None (315)	Aspirin (202)	AC (89)	AP ± aspirin (53)	AP + AC (58)	All (717)
Complications, n (%)	107 (34)	73 (36)	52 (58)**	15 (28)	32 (55)**	279 (39)
Severe bleeding, n (%)	131 (42)	83 (41)	55 (62)**	15 (28)	26 (45)	310 (43)
Rebleeding, n (%)	54 (17)	15 (7)**	18 (20)	9 (17)	6 (10)	102 (14)
Surgery, n (%)	24 (8)	6 (3)*	7 (8)	1 (2)	1 (2)	39 (5)
Mortality, n (%)	45 (14)	11 (5)**	14 (16)	2 (4)*	6 (10)	78 (11)
Endoscopic therapy, n (%)	50 (16)	41 (20)	9 (10)	19 (36)**	7 (12)	126 (18)
Transfusion, n (%)	197 (63)	155 (77)**	78 (88)**	47 (89)**	45 (78)*	522 (73)
Transfusion units, mean ± SD	4.8 ± 5.7	3.6 ± 2.9*	7.3 ± 18.0	3 ± 2.0*	4.1 ± 3.9	4.6 ± 8.1
Hospital stay (days), mean ± SD	8.6 ± 30.3	5.7 ± 4.4	11.2 ± 16.9	5.0 ± 3.3	7.9 ± 8.9	7.8 ± 21.2

Definition of variables: severe bleeding as BP < 90 mmHg, HR > 120 b/min, Hb < 7 g/dL on presentation, or transfusion of >3 units of blood during hospitalization; rebleeding as recurrence of hematemesis, coffee ground emesis, or melena occurring after 24 h from initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a decrease in hemoglobin concentration of at least 2 g/L or change in vital signs; in-hospital complications included one or more events belonging to these three main categories: cardiovascular or thromboembolic events, infectious complications, and other complications; surgery as any type of surgical procedure performed to control GI bleeding

Aspirin: those on aspirin only; AC: those on anticoagulants only; AP ± aspirin: those on nonaspirin antiplatelet (clopidogrel, ticlopidine, or dipyridamole) with or without aspirin; AP + AC: those taking antiplatelet agents combined with anticoagulants

* P value < 0.05; ** P value ≤ 0.01 compared to the none group

Table 3 Predictors of in-hospital mortality, re-bleeding, severe bleeding, and in-hospital complications in patients with NVUGIB at univariate analysis

	Mortality, n (%)		P value	In-hospital complications, n (%)		P value	Severe bleeding, n (%)		P value	Re-bleeding, n (%)		P value
	Yes	No		Yes	No		Yes	No		Yes	No	
<i>Number of comorbidities^a</i>			0.09			<0.0001			<0.0001			0.53
0	25 (32)	254 (40)		80 (29)	199 (45)		92 (30)	187 (46)		33 (32)	246 (40)	
1	30 (38)	206 (32)		95 (34)	141 (32)		115 (37)	121 (30)		38 (37)	198 (32)	
2	11 (14)	124 (19)		62 (22)	73 (17)		65 (21)	70 (17)		21 (21)	114 (19)	
≥3	12 (15)	55 (9)		42 (15)	25 (6)		38 (12)	29 (7)		10 (10)	57 (9)	
<i>Severe bleeding</i>												
Yes	51 (65)	259 (41)	<0.0001	167 (60)	143 (33)	<0.0001	NA	NA	NA	NA	NA	NA
No	27 (35)	380 (59)		112 (40)	295 (67)							
<i>Aspirin^b</i>												
Yes	11 (20)	191 (41)	0.002	73 (41)	129 (38)	0.61	83 (39)	119 (39)	0.91	15 (22)	187 (42)	0.002
No	45 (80)	270 (59)		107 (59)	208 (62)		131 (61)	184 (61)		54 (78)	261 (58)	
<i>AC^b</i>												
Yes	14 (24)	75 (22)	0.73	52 (33)	37 (15)	<0.0001	55 (30)	34 (16)	0.0007	18 (25)	71 (21)	0.50
No	45 (76)	270 (78)		107 (67)	208 (85)		131 (70)	184 (84)		54 (75)	261 (79)	
Age (years), mean ± SD	68.9 ± 16.8	64.9 ± 15.7	0.04	70.8 ± 13.5	61.8 ± 16.3	<0.0001	66.6 ± 15.2	64.4 ± 16.4	0.067	67.9 ± 14.3	64.9 ± 16.1	0.07

Definition of outcomes: mortality as in-hospital death from any cause; severe bleeding as BP < 90 mmHg, HR > 120 b/min, Hb < 7 g/dL on presentation, or transfusion of >3 units of blood during hospitalization; re-bleeding as recurrence of hematemesis, coffee ground emesis, or melena occurring after 24 h from initial endoscopic evaluation and/or hemostatic therapy and initial stabilization, accompanied by either a decrease in hemoglobin concentration of at least 2 g/L or change in vital signs; in-hospital complications included one or more events belonging to these three main categories: cardiovascular or thromboembolic events, infectious complications, and other complications

NA not applicable

^a Comorbidities include: coronary artery disease, congestive heart failure, cerebral vascular accident, systemic cancer, chronic renal failure, and diabetes mellitus

^b For the analysis in the aspirin group, we purposely limited the cohort to patients not taking any antithrombotic (i.e., none group) and to those who are taking aspirin as the only antithrombotic (i.e., aspirin only group), similarly for the AC group which was limited to the none group and AC only group

Table 4 Independent predictors of in-hospital mortality, in-hospital complications, severe bleeding, and rebleeding on multivariable logistic regression analysis

	Mortality			In-hospital complications			Severe bleeding			Rebleeding		
	OR	95 % CI	P value	OR	95 % CI	P value	OR	95 % CI	P value	OR	95 % CI	P value
<i>Aspirin use</i>												
Aspirin only ^b	0.26	0.13–0.53	0.0002	0.77	0.52–1.15	0.2	0.78	0.53–1.15	0.21	0.31	0.17–0.59	0.0003
Comorbidities ^a	1.32	0.97–1.80	0.07	1.39	1.13–1.71	0.002	1.40	1.12–1.69	0.002	1.03	0.77–1.38	0.85
Age > 60 years ^c	2.41	1.17–5.00	0.02	2.81	1.77–4.46	0.0001	1.30	0.88–1.97	0.18	2.30	1.21–4.37	0.01
Endoscopic therapy	0.42	0.16–1.1	0.08	0.88	0.53–1.44	0.56	1.02	0.64–1.63	0.92	1.92	1.04–3.54	0.04
<i>AC use</i>												
AC only ^b	0.94	0.47–1.85	0.85	2.0	1.20–3.35	0.004	1.69	1.02–2.82	0.04	1.06	0.56–2.00	0.9
Comorbidities ^a	1.04	0.76–1.43	0.79	1.32	1.03–1.68	0.03	1.59	1.25–2.04	0.0002	1.16	0.87–1.55	0.3
Age > 60 years ^c	1.94	0.99–3.83	0.054	2.71	1.65–4.45	0.0001	1.37	0.87–2.16	0.18	1.94	1.03–3.71	0.04
Endoscopic therapy	0.73	0.31–1.71	0.47	1.08	0.59–1.96	0.81	0.99	0.56–1.77	0.98	2.60	1.38–4.89	0.003

Definition of outcomes: mortality, in-hospital complications, severe bleeding, and rebleeding are defined as in Table 3

^a Comorbidities include: coronary artery disease, congestive heart failure, cerebral vascular accident, systemic cancer, chronic renal failure, and diabetes mellitus

^b Multivariable analyses for aspirin use and anticoagulant (AC) use were done using the none group (those who were not taking any antithrombotics) as the control group. Variables included were age, comorbidities, and endoscopic therapy

^c Outcomes were compared in patients >60 years to those in patients ≤60 years of age

On univariate analysis (Table 3), the frequencies of severe bleeding ($P < 0.001$) and in-hospital complications ($P < 0.001$) increased as the number of co-morbidities increased. The mean age of patients who died in-hospital was higher than in those who did not ($P = 0.04$). Furthermore, patients who had in-hospital complications were on average 9 years older than those who did not ($P < 0.001$). Finally, the likelihood of severe bleeding was higher in patients who suffered in-hospital complications and mortality than in those who did not ($P < 0.001$ for both). Compared to patients who presented with NVUGIB on aspirin, those who were not on aspirin were twice as likely to have in-hospital mortality and twice as likely to experience rebleeding. On the other hand, the frequency of being on anticoagulants at presentation was greater in patients who developed severe hemorrhage and those who had in-hospital complications ($P < 0.001$, Table 3).

On multivariate analysis (Table 4), older age was found to be independently predictive of in-hospital complications, rebleeding, and mortality. In addition, being on aspirin on presentation was an independent predictor of better outcomes, including lower in-hospital mortality ($P < 0.001$) and rebleeding rate ($P < 0.001$). Furthermore, patients presenting on aspirin had a shorter hospital stay by 4.2 days compared to those on no antithrombotics after adjusting for age and comorbidities (95 % CI –8.7, 0.3, $P = 0.07$). On the other hand, being on anticoagulants on presentation was predictive of in-hospital complications ($P = 0.004$) and severe bleeding ($P = 0.04$), but not in-hospital mortality ($P = 0.85$). Multivariate analysis in the

aspirin group versus none showed a protective effect of endoscopic therapy on mortality that was of borderline significance (OR 0.42, $P = 0.08$). This was not the case in the anticoagulant group. On the other hand, endoscopic therapy was an independent predictor of rebleeding in patients who were either on aspirin or on anticoagulation at baseline ($P = 0.01$ and 0.003, respectively).

The presence of comorbidities was independently predictive of severe hemorrhage and in-hospital complications in both the aspirin and anticoagulant groups ($P < 0.05$). PPI use at baseline was not associated with mortality (OR 1.52, CI 0.78–2.95, $P = 0.22$), in-hospital complications (OR 0.97, CI 0.60–1.59, $P = 0.92$), severe bleeding (OR 0.80, CI 0.50–1.29, $P = 0.4$), or rebleeding (OR 0.90, CI 0.46–1.76, $P = 0.75$).

To evaluate the possibility that endoscopy influenced outcomes, multivariate analysis was done for the 512 patients who underwent endoscopy. Again, a protective effect of aspirin against in-hospital mortality and rebleeding was observed (OR 0.07, $P = 0.01$ and OR 0.37, $P = 0.004$, respectively). Anticoagulation continued to be predictive of in-hospital complications (OR 2.52, $P = 0.006$). A further analysis was done after excluding patients with CAD and CVA, and using aspirin for primary prophylaxis was still protective against in-hospital mortality (data not shown).

We did a separate multivariate analysis on the effect of aspirin on clinical outcomes in the 319 patients that we did not include in our previous study [20]. Of those, 116 patients had NVUGIB from non-peptic sources on UGI endoscopy and 203 patients did not have endoscopic

Table 5 Causes of death in 78 patients in relation to intake of antithrombotics

Cause of death	None (315)	Aspirin only (202)	AC only (89)	Combination (111)	Total (717)
Gastrointestinal bleeding	10 (3.6 %)	0 (0 %)**	3 (3.9 %)	2 (1.9 %)	15
Cardiovascular or thromboembolic event	7 (2.5 %)	3 (1.6 %)	3 (3.9 %)	1 (1.0 %)	14
Malignancy	14 (4.9 %)	0 (0 %)**	4 (5.1 %)	0 (0 %)*	18
Sepsis	7 (2.5 %)	5 (2.6 %)	1 (1.3 %)	2 (1.9 %)	15
Multi-organ failure	7 (2.5 %)	3 (1.6 %)	3 (3.9 %)	3 (2.8 %)	16
Total	45	11	14	8	78

Percentages were calculated as follows: number of cause-specific death/number of alive patients in each subgroup. For example: GI bleeding in the none group = $10/(315 - 45) = 3.6\%$ and similarly for each cause of death

AC anticoagulants, *combination* any combination of antithrombotics excluding aspirin only and anticoagulant only

* P value < 0.05; ** P value < 0.01 for differences in mortality rate between groups

evaluation. The analysis showed that patients who were on aspirin were protected against in-hospital mortality [OR 0.44 (0.18–1.04), $P = 0.06$] and rebleeding [OR 0.057 (0.007–0.45), $P = 0.007$]. We also did the multivariate analyses after excluding 10 patients with cirrhosis and chronic hepatitis. The results were unchanged: The protective effect of aspirin against mortality and other adverse outcomes was still evident (data not shown).

We also did a multivariate analysis for each of our outcomes, and we included the four antithrombotic groups and compared them against the control group, as opposed to doing subset analyses comparing one at a time with the control group. The results remain essentially unchanged. Patients on aspirin are protected against in-hospital mortality [OR 0.27 (0.13–0.55), $P < 0.0001$] and have a reduced risk of re-bleeding [OR 0.30 (0.16–0.56), $P < 0.0001$]. The effects of anticoagulants on clinical outcomes also remain unchanged.

As the prevalence of systemic cancer was higher in the control group than in the aspirin group, we did a multivariate analysis in which systemic cancer was considered a separate covariate and not included in the composite comorbidity score. The protective effect of aspirin against mortality [OR 0.30 (0.15–0.62), $P < 0.001$] and the overall results remain essentially unchanged. As expected, the presence of systemic cancer is an independent predictor of mortality [OR 1.99 (1.14–3.45), $P = 0.02$].

Cause of Death Analysis

The association between intake of antithrombotics and various causes of death was also evaluated (Table 5). Patients who were on aspirin only had the lowest overall mortality. Death due to uncontrolled gastrointestinal bleeding was less common in the aspirin group versus controls ($P < 0.01$). Similarly, patients on aspirin were less likely to die in hospital of systemic cancer ($P < 0.01$), but equally likely to die of other causes. There was no apparent

association between intake of anticoagulants and various causes of death. Due to the small number of patients, multivariate analysis for cause of death data was not performed.

Discussion

Our findings indicate that patients taking aspirin and presenting with NVUGIB had lower morbidity and mortality, and a shorter hospital stay compared to other groups of patients with NVUGIB. The protective effect of aspirin was found to be present in various subgroup analyses, including in particular, patients taking aspirin for primary prophylaxis. In contrast, patients taking anticoagulants at baseline had a higher rate of in-hospital complications and severe bleeding than the other groups.

Our study confirms and extends findings suggesting a protective effect of aspirin on mortality in NVUGIB [12, 13, 15, 20, 21, 23]. However, it was not clear in those studies whether control patients were taking other antithrombotics, and whether patients taking aspirin were using other antithrombotics concomitantly [12, 13, 21, 23]. Here, we compared groups taking aspirin only to a control group (on no antithrombotic medications) within the same cohort. Additionally, we found an association between use of other antiplatelets and reduced mortality, which is also a new finding. In a randomized trial, aspirin continuation in peptic ulcer bleeding decreased mortality as compared to placebo [15], which is consistent with the general theme of our findings, but is different from our study given that we examined aspirin use versus nonuse at baseline. In contrast, two studies reported no association between aspirin use and mortality [4, 17]. In the first one, patients using aspirin or NSAIDs were grouped together, and in the second, aspirin users had lower 30-day mortality than controls, but this was of borderline significance. To our knowledge, there are no studies showing that aspirin increases mortality in NVUGIB.

It is well appreciated that aspirin increases the risk of UGIB, and this risk is further magnified by combination antithrombotic therapy [9, 24–26]. Approximately 36 % of our patients were on antiplatelet agents, 28 % on aspirin only, and 12 % on anticoagulants, consistent with proportions previously reported [9, 23, 27]. However, those who were on aspirin only had lower in-hospital mortality despite being older and having more co-morbidities than patients in the control group. This is even more remarkable given that older age and the presence of co-morbidities are known independent predictors of adverse outcome in UGIB [27].

In this study, we also analyzed the cause of death. Importantly, we found that no patient taking aspirin died of ongoing uncontrolled hemorrhage. Furthermore, the protective effect of aspirin may not be fully explained by its known cardiovascular effects, since most deaths were due to non-cardiovascular causes (Table 5) and since aspirin was protective even in patients taking it for primary prophylaxis. In a previous randomized trial of aspirin versus placebo in patients taking aspirin who presented with peptic ulcer bleeding, half of the deaths in the placebo group were due to non-cardiovascular causes, further suggesting that aspirin's protective effect is not solely due to its cardiovascular benefits [15]. These data, in combination with our own data, raise the possibility that it may not be prudent to discontinue aspirin in patients with NVUGIB. While this would be a more aggressive approach than currently recommended at the 2010 International Consensus on NVUGIB in which it was recommended that “in patients who receive low-dose aspirin and develop acute ulcer bleeding, aspirin therapy should be restarted as soon as the risk of cardiovascular complication is thought to outweigh the risk for bleeding” [28], the data appear to suggest that it may be most appropriate to simply continue aspirin.

Patients taking aspirin who were admitted with NVUGIB were less likely to have rebleeding compared to controls. The mechanism for this effect is unclear but could be secondary to the phenomenon of platelet rebound following acute aspirin discontinuation [29]. This may have also aided in initial hemostasis of bleeding lesions. However, aspirin continuation would be expected to increase the risk of rebleeding, as previously suggested [15]. A similar protective effect of aspirin against rebleeding was suggested by a recent study [21], but aspirin did not influence rebleeding rates in two other studies that also included patients with NVUGIB [13, 23].

In our study, aspirin use was a predictor of a shorter hospital stay after adjusting for age and comorbidities, which reflects the better overall outcome of those patients. This has not been the case in other studies [18, 30]. Another study on patients with UGIB suggested that aspirin use is predictive of a longer hospital stay; however, that study population included patients with variceal bleeding [19].

In contrast to being on aspirin, being on anticoagulants was predictive of more in-hospital complications and more severe bleeding (but not mortality or rebleeding). Severe bleeding, defined a priori according to rigorous criteria, occurred in 42 % of patients, within the range reported by others [12, 13, 23, 31], and is a risk factor for mortality. Our data are consistent with previous data suggesting that the use of anticoagulants is predictive of severe hemorrhage [20, 32]. We are uncertain of the mechanism, but impairment of hemostasis may play a role. Other studies, however, have been inconsistent in their findings, suggesting no effect of anticoagulant use on mortality and rebleeding in UGIB patients [2, 12, 18, 33], and an increase in mortality risk associated with heparin [23] or prolonged hospital length of stay [31, 34].

Patients on aspirin had more peptic ulcers and erosions than controls, in accordance with the known association of aspirin with peptic ulcer bleeding [35]. On the contrary, there was no difference in endoscopic diagnoses between patients on anticoagulants and those on none, consistent with previous reports [18]. Endoscopic therapy was performed on 18 % of patients, and 14 % of the 717 patients had recurrent bleeding. Of note is that we found that endoscopic therapy was independently predictive of rebleeding in patients receiving aspirin or anticoagulants; this could be due to the presence of stigmata of active hemorrhage, at endoscopy, which is reported to be a predictor of rebleeding [36]. Since most of our patients did not receive standard dual endoscopic therapy, this finding should be interpreted with caution.

The hospital mortality in this cohort was 11 %; death from uncontrolled gastrointestinal bleeding occurred in approximately one-fifth of these patients, consistent with previous studies [22, 37]. Malignancies accounted for 29 % of the non-bleeding-related deaths in accordance with previous reports, while cardiovascular causes accounted for 22 %, somewhat higher than the reported 13–14 % [28, 38].

Our study has a number of strengths. First, all potential patients with UGIB were identified using the ICD-9 codes, and then, each case was reviewed individually on the basis of well-developed, prespecified criteria. Second, we included a control group of patients who were not on any antithrombotic therapies. Third, we determined the cause of death in our patients to better understand the association between aspirin or anticoagulant use and mortality. Fourth, subgroup analyses for patients who had endoscopy and for patients who were taking aspirin for primary prophylaxis were performed; these revealed similar findings to the primary analysis.

We also recognize limitations of our study. First, 29 % of patients in our study did not have endoscopy. This may have precluded endoscopic therapy and thus affected outcomes. However, there was no evidence of bias toward

those who underwent endoscopy compared to those who did not. This is consistent with the finding of a protective effect of aspirin specifically in the group who had endoscopic evaluation (512 patients). Also, this study is retrospective, and documentation of aspirin or anticoagulant intake prior to presentation depends primarily on patient recall, and hence, there is a potential for recall bias. Nevertheless, a rigorous history-taking system is implemented at our institution where data on medication intake are collected separately by physicians as well as by nurses and subsequently incorporated into the medical record likely mitigates this concern. Furthermore, the majority of our patients are regular attendants of our hospital/clinics, and the gathered information is also part of the medical record. A further limitation is that complete data on endoscopic stigmata of bleeding and on the *H. pylori* status of patients with ulcer disease were lacking (since this was not recorded during data collection). However, data on endoscopic therapy were carefully collected—and this is likely a reasonable proxy for the presence of stigmata of high-risk lesions. Because our study included patients over a long period of time, changes in clinical practice may have influenced outcomes. However, to account for this temporal variation, we performed analyses after dividing the whole cohort into three consecutive 6-year time periods, and we obtained similar results in each time frame. Finally, this is a single-center study, so the generalizability of the findings to other populations will require further evaluation.

We conclude that patients who present with NVUGIB while receiving aspirin were protected against in-hospital mortality and adverse clinical outcomes, while those on anticoagulants had increased morbidity. The protective effect of aspirin appeared to extend to patients not known to have cardiovascular or cerebrovascular disease, suggesting a non-cardiovascular effect. Further prospective studies are needed to determine the optimal management of aspirin in patients presenting with NVUGIB and to understand its protective effects. While our data add to the body of literature about the potential benefit of aspirin in patients with NVUGIB, when to resume aspirin after an episode of NVUGIB remains an open question, and should be governed at this time by local practice and expertise.

Conflict of interest None.

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