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Original Article

Risk factors for upper gastrointestinal bleeding in coronary artery disease patients receiving both aspirin and clopidogrel

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Abstract

Background: Dual therapy (aspirin and clopidogrel) increases the risk of upper gastrointestinal bleeding (UGIB). Acute coronary syndrome (ACS), a critical ill condition, may increase the risk of UGIB due to stress-related mucosal disease and the impact of receiving dual antiplatelet agents. We identified risk factors of UGIB in patients with coronary artery disease (CAD) receiving dual therapy.
Methods: Patients who received dual therapy due to ACS or postpercutaneous coronary intervention (elective, primary, or urgent) were enrolled retrospectively. We assessed the occurrence of UGIB and identified the risk factors for UGIB at early stage (dual therapy $\leq$ 2 weeks) and late stage ($>$ 2 weeks) by Cox regression analysis.
Results: During a mean follow-up period of 125 days, 67 (12.5 %) out of 534 patients developed UGIB (32 patients at early stage, 35 patients at late stage). Cox regression analysis showed that use of proton pump inhibitor therapy has a protective role in these patients [hazard ratio (HR): 0.10, 95% confidence interval (CI): 0.01−0.71]. ACS (HR: 2.67, 95% CI: 1.33−5.34) has a high risk of developing UGIB at an early stage. Old age (>75 years of age) (HR: 2.13, 95% CI: 1.02−4.47) and prior history of peptic ulcer disease (HR: 3.27, 95% CI: 1.28−8.34) each have an associated high risk for developing UGIB at a late stage. The use of mechanical ventilation (HR: 5.85, 95% CI: 2.19−15.58) also increased UGIB risk at both the early and late stages.
Conclusion: ACS and mechanical ventilation are important risk factors of UGIB at the early stage ($\leq$ 2 weeks). Additionally, old age (>75 years), past peptic ulcer disease history, and the use of mechanical ventilation play important roles in the occurrence of UGIB at late stage (>2 weeks). However, it was also noted that use of PPI plays a protective role in patients with CAD receiving aspirin and clopidogrel therapy.

Keywords: acute coronary syndrome; aspirin; clopidogrel; mechanical ventilation; upper GI bleeding

1. Introduction

Combination therapy with aspirin and clopidogrel effectively decreases the risks of cardiovascular (CV) death, nonfatal myocardial infarction (MI), and stroke when compared with the use of aspirin alone in patients with acute coronary syndrome (ACS).[1] The combined use of clopidogrel and aspirin in patients who undergone percutaneous coronary intervention (PCI) showed a 27% reduction of risk of MI and stroke when compared with aspirin use alone.[2] In patients admitted for ACS or ST-elevated MI, combination therapy, including aspirin and clopidogrel, with/without heparin/thrombolytics has become the standard therapy and has been proven to be decrease CV morbidity and mortality.[3,4] However, elevated major gastrointestinal (GI) bleeding was

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observed in dual therapy groups.[1,5,6] A retrospective study showed that upper GI bleeding (UGIB) developed in 4% of patients who were receiving aspirin and clopidogrel co-therapy for their CV disease after a follow-up of approximately 6 months.[7]

Stress-related mucosal disease (SRMD) has been known to develop in critically ill patients and cause clinically significant GI bleeding. Respiratory failure with mechanical ventilation, coagulopathy [platelet count $<$ 50,000 mm,[3] prolonged international normalized ratio (INR) of prothrombin time (PT)], acute renal failure, sepsis, shock/hypotension, and severe trauma are considered to be risk factors for SRMD-associated GI bleeding.[8,9] ACS may increase the risk of UGIB, especially when patients with ACS are receiving antiplatelet agents and/or thrombolytics.[10]

In this retrospective study, we assessed the occurrence of UGIB in patients with coronary artery disease (CAD) who received dual therapy (aspirin and clopidogrel) after PCI and/or ACS and identified the possible risk factors for UGIB at early (dual therapy $\leq$ 2 weeks) and late stages (dual therapy $>$ 2 weeks).

2. Methods

2.1. Patients

Patients who had stable angina and received elective PCI, who had ACS (unstable angina, non-ST-elevated MI, ST-elevated MI) with or without receiving PCI were indicated to receive regular dual therapy (aspirin 100 mg daily and clopidogrel 75 mg daily after loading dose) to reduce further CV death and MI.[3,4,11] Patients were enrolled in this study after initial screening, and those patients who had previously taken either aspirin or clopidogrel before screening were deemed acceptable. However, patients were excluded if they received dual therapy before screening, clinical severe thrombocytopenia (platelet count $<$ 50,000/mm^3), unstable and progressive malignancy, a positive stool occult blood (OB) before screening, recent peptic ulcer disease (PUD) without checking healing by scopy, prior surgical intervention due to PUD complications (bleeding, perforation, obstruction), or if they had gastric cancer in the past. The study was approved by the Institutional Review Committee of the Taipei Veterans General Hospital (VGHIRB 201002027IC) and was conducted in accordance with the guidelines of the Declaration of Helsinki.

2.2. Procedure

After enrollment, patient age, sex, smoking and drinking habit, previous medications including antiplatelet agents (aspirin, clopidogrel), nonsteroidal anti-inflammatory drugs (NSAIDs), and gastroprotective agents [proton pump inhibitor (PPI), histamine receptor-2 antagonist (H_2RA)], and past history of endoscopic proven PUD were recorded.[12] Underlying coronary artery condition [stable angina with elective PCI, ACS with primary PCI (within 12 hours after attack), urgent PCI (12−48 hours after attack) or without PCI due to persistent unstable condition], critical condition [hypotension, post-cardiopulmonary resuscitation (CPR), use of mechanical ventilator, use of extracorporeal membrane oxygenation (ECMO), use of intra-aortic balloon counterpulsation (IABC)], laboratory data (clearance of creatinine (CCr), INR of PT, platelet count, hemoglobin) while beginning dual therapy were recorded. Medication including thrombolytic-enoxaparin, glycoprotein IIb/IIIa receptor antagonists, anticoagulants, H_2RA, PPI, traditional NSAIDs, selective cyclooxygenase-2 inhibitors (coxibs), and glucocorticoids were monitored during hospitalization and were followed-up at outpatient visit after discharge. Habits of smoking and drinking after dual therapy were also recorded.[12] Patients received routine follow-up examinations both at the date when first notified dual therapy during hospitalization, and at our outpatient clinic after discharge. During the follow-up period, data concerning hemoglobin and stool OB, evidence of GI bleeding (GIB) or ulcer complications (i.e., melena, hematemesis, hematochezia, or sudden-onset severe epigastric pain),[13,14] and esophagogastroduodenoscopy (EGD) finding were recorded. GIB was defined as melena, hematemesis, hematochezia, or positive stool OB with reduced hemoglobin $\geq$2 g/dl. UGIB was defined as GIB with positive OB in nasogastric aspirate, or a positive finding of EGD (nonmalignant ulcer or $>$five erosions).[15] Non-UGIB was defined as GIB with negative finding of EGD or without positive OB in nasogastric aspirate if EGD was not performed. The observation was terminated at the date of first occurrence of GIB, Day 7 after cessation of dual therapy, or upon patients death. Medications of thrombolytics, glycoprotein IIb/IIIa receptor antagonists, NSAIDs, coxibs, glucocorticoids, and anticoagulants (warfarin) were considered to be associated with patients' UGIB if any of these medications were used within 1 week prior to the index day (the day on which UGIB started).[16]

2.3. End points

The primary end point was the occurrence of UGIB in the patients with CAD receiving dual therapy and to analyze the risk factors for UGIB at early (dual therapy $\leq$ 2 weeks) and late stages (dual therapy $>$ 2 weeks), respectively.

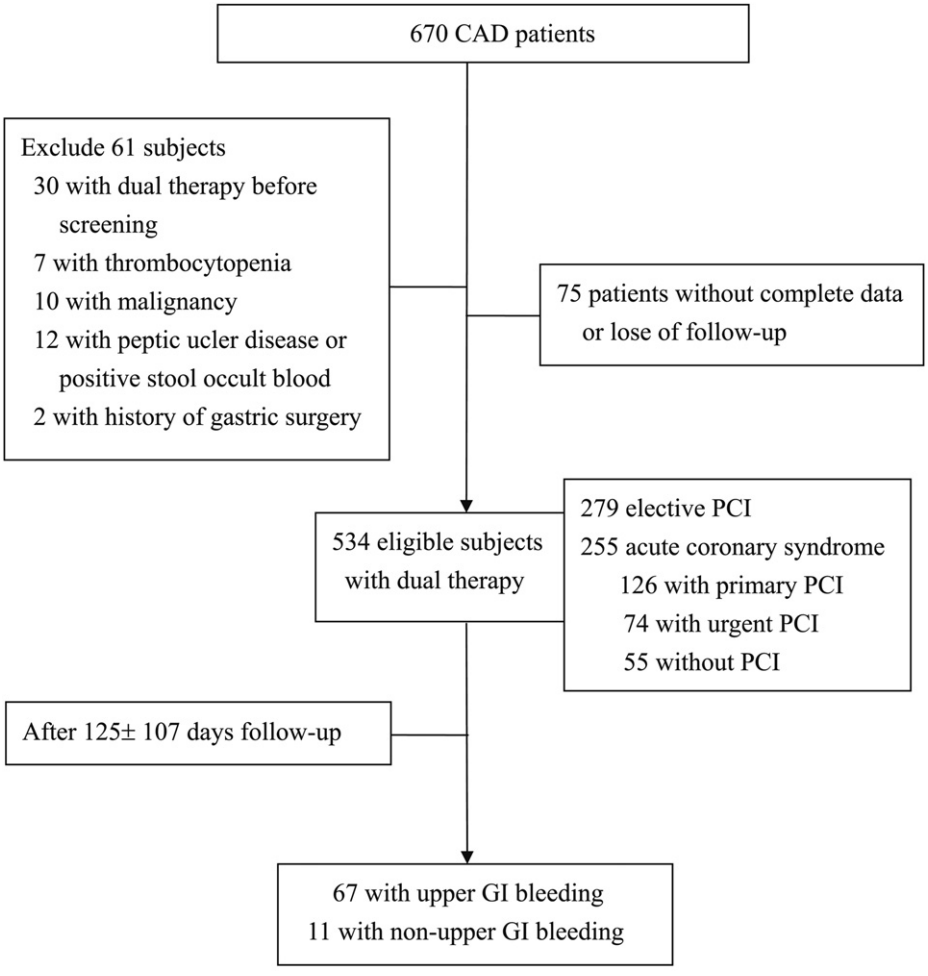
2.4. Statistical analysis

The occurrence of UGIB was analyzed with the use of Kaplan-Meier survival estimates. All data were expressed as mean $\pm$ standard deviation. The calculations were performed using SPSS software (SPSS for Windows version 14.0, SPSS Inc., Chicago, IL, USA). Results were compared between groups depending on the type of data analyzed using either the Chi-square test, Fisher's exact test, Student's t test or Mann-Whitney U test where appropriate. Cox's regression analysis was performed to evaluate the risk factors for UGIB at early and late stages in patients with CAD receiving dual therapy.

All p values were two-tailed, and a p value less than 0.05 was considered statistically significant.

3. Results

From February 2010 to August 2011, 670 patients who admitted to coronary care and intensive care units were screened. Of the total 670 screened candidates, 30 patients were reported with dual therapy before screening, seven patients with thrombocytopenia, 10 patients with malignancy, 12 patients with recent PUD or positive stool OB, two patients with past surgical intervention for PUD complications or gastric cancer, and 75 patients had no detailed data or who were lost to follow-up during the study period. Ultimately, 534 eligible patients (male: 453, female: 81 with age of 71 ± 14) were enrolled (Fig. 1). Prior to enrollment, 157 (29.4%) of 534 patients used antiplatelet agents (136 aspirin, 21clopidogrel), 26 (4.9%) used NSAIDs, including coxibs, eight (1.5%) used H_2RA, and 20 (3.7%) used PPI. Eighty-one (15.2%) were smokers, 25 (4.7%) consumed alcohol, and 39 (7.3%) had a past history of endoscopic proven PUD. Regarding the coronary artery condition, 279 (52.2%) patients received elective PCI, and another 255 (47.8%) patients had ACS (126 with primary PCI, 74 with urgent PCI, 55 without PCI due to unstable clinical condition). Seventy-four (13.9%) patients received glycoprotein IIb/IIIa receptor antagonists, and 192 (36.0%) patients received enoxaparin. Fifty-six (10.5%) patients needed mechanical ventilation, 90 (16.9%) patients had hypotension, seven (1.3%) patients needed ECMO, 28 (5.2%) needed IABC, 34 (6.4%) received CPR; all the aforementioned critical condition occurred within 7 days of ACS. During the follow-up period, 33 (6.2%) smoked, 14 (2.6%) consumed alcohol, 47 (8.8%) patients used PPI once daily (11 with intravenous administration for 3 days, other with oral), 48 (9.0%) patients used oral H_2RA (twice daily), three (0.6%) patients used warfarin, 28 (5.2%) patients used non-selective NSAIDs, 6 (1.1%) patients received coxib, and 26 (4.9%) received glucocorticoid.



CAD: coronary artery disease
PCI: percutaneous coronary intervention
GI: gastrointestinal

Fig. 1. Flowchart of patient disposition and follow-up.

After 125 ± 107 days of follow-up, a total of 67 (12.5%) out of 534 patients developed UGIB, 32 within 2 weeks (1−14 days) and 35 after 2 weeks (14−399 days). Another 11 (2.1%) of 534 patients had non-UGIB. Forty-four of the 67 patients had received EGD, and gastric ulcer was noted in 17 patients, duodenal ulcer in 13 patients, gastric and duodenal ulcers in six patients, erosive gastritis in six patients, and erosive esophagitis in two patients. Forty (7.5%) patients died during the follow-up period.

When comparing the 67 patients with UGIB with those 456 patients without GIB, patients with UGIB were significantly older in age, had a higher rate of past history of PUD, more frequently used mechanical ventilation, had a higher incidence of hypotension and ACS, were more likely to use enoxaparin, and used PPI less frequently after dual therapy than patients without UGIB (Table 1, $p < 0.05$). There were no significant differences between these two groups with regards to sex, INR value, platelet counts, CCr, drinking or smoking habits before and after dual therapy, use of H_2RA, use of NSAIDs before and after dual therapy, use of aspirin, clopidogrel, or PPI before dual therapy, use of glycoprotein IIb/IIIa receptor antagonists, coxib, warfarin, and steroid after dual therapy, or use of ECMO, IABC, and post-CPR (Table 1).

Cox multivariate regression analysis including risk factors of age (>75 years), CCr (<30 ml/minute), smoking after dual therapy, past history of PUD, use of enoxaparin, use of PPI, mechanical ventilation, status of hypotension, and ACS showed that patients with age >75 years, past history of PUD, ACS, mechanical ventilation were independent risk factors for UGIB in patients with CAD receiving dual therapy, while use of PPIs was a protective factor for UGIB in these patients (Table 2).

The mean length of hospitalization in the intensive care unit after dual therapy in 248 ACS patients in our study was 7 ± 6 days, so we chose 2 weeks as a staging cutoff point. In order to identify whether different risk factors existed for UGIB at the early and late stages in patients with CAD receiving dual therapy, we divided patients with UGIB into early (≤2 weeks) and late (>2 weeks) stages. Cox regression analysis showed that ACS and use of mechanical ventilation were important risk factors for developing UGIB at the early stage of dual therapy. Furthermore, patients with age >75 years, a past

Table 1
Characteristics between patients with UGIB and patients without GIB during dual therapy.

	Patients with UGIB, $n = 67$	Patients without GIB, $n = 456$	p
Male (%)	52 (77.6)	390 (85.5)	0.104
Age (yrs ± SD)	75 ± 13	70 ± 14	0.006
INR of prothrombin time	1.1 ± 0.3	1.0 ± 0.2	0.101
Platelet count (/mm^3)	219,800 ± 86,000	219,900 ± 68,000	0.994
CCr (ml/min)	50 ± 29	57 ± 19	0.058
Past history of PUD (%)	11 (16.4)	27 (5.9)	0.005
Hypotension (%)	20 (29.8)	66 (14.5)	0.004
Mechanical ventilation (%)	18 (26.9)	38 (8.3)	<0.001
IABC (%)	5 (7.5)	22 (4.8)	0.386
Post-CPR (%)	3 (4.5)	30 (65.8)	0.603
ECMO (%)	0 (0)	7 (1.5)	0.603
ACS (%)	48 (71.6)	200 (43.9)	<0.001
Medication and habit before dual therapy			
Use of H_2RA (%)	1 (1.5)	6 (1.3)	>0.99
Use of PPI (%)	1 (1.5)	19 (4.2)	0.494
Use of NSAIDs (%)	3 (4.5)	22 (4.8)	>0.99
Use of aspirin (%)	22 (32.8)	109 (23.9)	0.131
Use of clopidogrel (%)	5 (7.5)	16 (3.5)	0.170
Smoking (%)	13 (19.4)	64 (14.0)	0.267
Drinking (%)	5 (7.5)	20 (4.4)	0.350
Medication and habit after dual therapy			
Use of glycoprotein IIb/IIIa receptor antagonist (%)	11 (16.4)	59 (12.9)	0.443
Use of enoxaparin (%)	34 (50.7)	153 (33.6)	0.009
Use of H_2RA (%)	8 (11.9)	40 (8.8)	0.370
Use of PPI (%)	1 (1.5)	39 (8.6)	0.046
Use of NSAIDs (%)	3 (4.5)	23 (5.0)	>0.99
Use of coxibs (%)	0 (0)	5 (1.1)	>0.99
Use of warfarin (%)	1 (1.5)	3 (0.7)	0.886
Use of steroid (%)	6 (9.0)	20 (4.4)	0.127
Smoking (%)	7 (1.5)	24 (5.3)	0.099
Drinking (%)	2 (2.9)	12 (2.6)	0.697

ACS = acute coronary syndrome; CCr = clearance of creatinine; coxib = selective cyclooxygenase-2 inhibitors; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; H_2RA = histamine 2 receptor antagonist; IABC = intra-aortic balloon counterpulsation; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PUD = peptic ulcer disease; UGIB = upper gastrointestinal bleeding.

Table 2
Independent predictors of UGIB in coronary artery disease patients receiving dual therapy identified by Cox regression analysis.

Risk factors	Hazard ratio	95% confidence interval	*p*
Age > 75 yrs	1.94	1.11−3.39	0.020
CCr < 30 (ml/min)	1.91	0.92−3.95	0.083
Smoking after dual therapy	1.78	0.80−4.00	0.160
Past history of PUD	3.45	1.62−7.35	0.001
Hypotension	1.37	0.68−2.78	0.381
Use of enoxaparin	0.81	0.43−1.54	0.519
Use of mechanical ventilation	2.94	1.38−6.27	0.005
Acute coronary syndrome	2.67	1.33−5.34	0.006
Use of PPI	0.10	0.01−0.71	0.022

CCr = clearance of creatinine; PPI = proton pump inhibitor; PUD = peptic ulcer disease; UGIB = upper gastrointestinal bleeding.

history of PUD, and mechanical ventilation were important risk factors for developing UGIB at late stage of dual therapy (Table 3).

4. Discussion

This retrospective study in patients with CAD receiving dual therapy (aspirin plus clopidogrel) showed that ACS and a past history of PUD are important risk factors for UGIB at the early and late stages respectively; mechanical ventilation has an important impact on the likelihood of occurrence of UGIB at both early and late stages, while use of PPI plays a protective role in these patients.

As we know, dual therapy significantly decreases the risks of CV death, MI, and stroke when compared with the use of aspirin alone in patients with CAD,[1,2] but increased the occurrence of UGIB with an incidence of 4−7% in a period of 1 half-year.[10,17] The higher occurrence rate (12.5%) of UGIB in our study was probably due to the fact that fewer patients in our subject group used prophylactic PPI before (3.7 % vs. 11%) and after (8.8% vs. 21%) dual therapy when compared with previous studies.[10,17] The finding that PPI rather than H_2RA had a protective role for UGIB in patients with CAD receiving dual therapy was consistent with previous studies.[10,17] However, the prophylactic use of PPI to prevent UGIB in the patients with dual therapy is currently not reimbursed by Taiwan Health Insurance.[18,19] and should be considered only in high GI risk patients, such as patients with ACS, mechanical ventilation, a past history of PUD, and those patients older than 75.[20]

Table 3
Independent predictors of UGIB in early and late stage in coronary artery disease patients receiving dual therapy identified by Cox regression analysis.

Risk factors within 14 d	Hazard ratio	95% confidence interval	*p*
Use of mechanical ventilation	2.94	1.38−6.27	0.005
Acute coronary syndrome	2.67	1.33−5.34	0.006
Risk factors after 14 days			
Age > 75 yrs	2.13	1.02−4.47	0.046
Use of mechanical ventilation	5.59	2.09−14.91	0.001
Past history of PUD	3.27	1.28−8.34	0.013

PUD = peptic ulcer disease; UGIB = upper gastrointestinal bleeding.

Earlier study showed that prior peptic ulcer, cardiogenic shock, cardiac arrest, inotropic agent requirement, and primary PCI are important risk factors for UGIB in patients with CAD.[7,10] Our study showed that ACS (versus stable angina), old age (>75 years), a past history of PUD and mechanical ventilation, but not post-CPR, use of ECMO, and IABC are independent risk factors for UGIB. The diversity of the risk factors observed for UGIB between our study and previous studies could be due to different patient populations, study design, and varying follow-up periods.[10,14]

The study showed that use of mechanical ventilation and ACS in patients with CAD during hospitalization caused an elevated patient risk for UGIB, which implied that SRMD-associated UGIB also plays an essential role in dual-therapy patients with CAD at acute and critical stage. The pathophysiology of SRMD is believed to be multifactorial and not completely understood; splanchnic hypoperfusion and reperfusion injury are important factors.[9] The major two leading factors for SRMD-associated UGIB are respiratory failure requiring mechanical ventilation for more than 48 hours and coagulopathy (INR > 1.5 or platelet count < 50,000/mm^3).[8] Therapeutic coagulopathy during enoxaparin therapy was usually observed in ACS patients. Use of H_2RA to keep gastric pH above 4 significantly decreased SRMD-associated UGIB.[9] However, one-half of our patients are exposed to both critical stress condition and antiplatelet therapy, oral H_2RA could not alone provide effective protection for gastroduodenal mucosa in these patients with CAD, only PPIs have proven efficacious. However, the finding that H_2RA did not decrease the risk of UGIB in our investigation is consistent with findings in previous studies.[17]

There are a number of limitations to this study that are worth noting. First, this is a hospital-based retrospective study, so certain selection biases may exist such that caution must be taken in extrapolating the results. Second, 23 (34 %) of the 67 UGIB patients did not have their conditions confirmed by EGD due to unstable or unsuitable clinical conditions, so they were diagnosed by dropped hemoglobin with positive OB from NG aspirate according to our definition of UGIB. As we known, some duodenal ulcer bleeding could show negative NG aspirate and some non-UGIB patients could show positive NG aspirate due to minimal UGI mucosal injury, so the occurrence of UGIB could be underestimated or overestimated in aforementioned condition. Third, the number of cases involving some potential risk factors is small, including the use of ECMO, and medication with coxibs or warfarin after dual therapy. Consequently, a type II error may exist. Finally, *Helicobacter pylori* infection is an important risk factor for ulcer bleeding in the general population and among aspirin users.[21] We did not check *H. pylori* status in this retrospective study.[22] However, previous studies did not show that *H. pylori* infection is an important risk factor for UGIB in patients with ACS or PCI[10,14] or in patients under stress or suffering a critical condition.[8,9]

In conclusion, ACS and mechanical ventilation are important risk factors of UGIB at the early stage (≤ 2 weeks). Old age (>75 years), past PUD history, and mechanical ventilation play important roles in the occurrence of UGIB at the late stage

(>2 weeks). Additionally, use of PPI plays a protective role in patients with CAD receiving aspirin and clopidogrel therapy.

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