Upper Gastrointestinal Bleeding in Patients Receiving Dual Antiplatelet Therapy after Coronary Stenting

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Abstract

Objective We investigated the risk of upper gastrointestinal (UGI) bleeding and the protective effect of concomitant anti-secretory drugs during dual antiplatelet therapy administered following implantation of drug-eluting stents (DES) for coronary heart disease. Because proton pump inhibitors (PPIs) are reported to decrease the platelet inhibitory effects of clopidogrel, we also assessed cardiovascular outcomes in patients taking thienopyridine derivatives with or without anti-secretory drug.

Methods We retrospectively analyzed 243 patients, who underwent DES implantation between January 2006 and December 2007 and were receiving dual anti-platelet therapy post-surgery. The main outcome measurement was the presence of UGI bleeding. Cardiovascular outcomes were assessed by follow-up coronary angiography (CAG) findings. Data were collected from medical records.

Results Eight cases of UGI bleeding were observed during the follow-up period, none of whom were taking anti-secretory drugs. Among the 243 cases, 108 cases were taking anti-secretory drugs: a PPI (67 cases), and an H2 receptor antagonist (41 cases). No UGI bleeding was observed among patients who were taking concomitant anti-secretory drugs. The 1- and 2-year cumulative incidences of UGI bleeding among patients who were not taking anti-secretory drugs were 4.5% and 9.2%, respectively. When CAG findings were compared between patients not taking any anti-secretory drug, taking PPI, or taking H2RA, significantly more stenotic lesions of the coronary artery were observed in the PPI-treatment group.

Conclusion Concomitant use of an anti-secretory agent was associated with a reduced risk of UGI bleeding. Use of PPI may be associated with an attenuation of the effect of dual antiplatelet therapy.

Key words: UGI bleeding, dual antiplatelet therapy, ticlopidine, clopidogrel, proton pump inhibitor

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Introduction

The widespread use of drug-eluting stents (DESs) for coronary heart disease has significantly reduced the risk for in-stent restenosis, but has been associated with an increased risk for stent thrombosis (1). To prevent stent thrombosis after implantation of a DES, dual antiplatelet therapy, mainly combinations of aspirin with various thienopyridine derivatives (which inhibit the platelet ADP receptor, P2Y₁₂), has become a standard treatment for the management of patients with symptomatic coronary artery disease (2). It has been

demonstrated that the premature discontinuation of antiplatelet therapy is an important risk factor for stent thrombosis.

Currently, a course of at least 12 months of dual antiplatelet therapy has been recommended for the prevention of DES thrombosis (3). However, antiplatelet therapy is associated with bleeding complications, and gastrointestinal bleeding has been reported as one of the most common causes of life-threatening complications (4-6). The upper gastrointestinal (UGI) tract is a frequent site of such bleeding, but also a potential target for preventative strategies including anti-secretory drugs such as proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs).

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The thienopyridine derivatives ticlopidine and clopidogrel are prodrugs, and their pharmacological activity depends on cytochrome P-450 (CYP)-dependent oxidation to the active anti-thrombotic agent. Several CYP isoforms, including CYP2C19 and CYP 2B6, are reported to be involved in these metabolic processes (7, 8). CYP2C19 is also involved in the metabolism of PPIs such as omeprazole, lansoprazole and rabeprazole. Platelet studies have demonstrated that PPIs reduce the antiplatelet effects of clopidogrel (9). Possible drug interactions might be present between thienopyridine derivatives and PPIs.

The aim of this study was to determine the risk of UGI bleeding during dual antiplatelet therapy after percutaneous coronary intervention (PCI), and to evaluate the protective effects of anti-secretory drugs in such circumstances. We also compared the cardiovascular outcomes between patients taking dual antiplatelet drugs with or without anti-secretory drugs after coronary stenting.

Patients and Methods

This was a retrospective study of 520 consecutive patients who had undergone PCI at Showa University Fujigaoka Hospital, Yokohama, Japan between January 2006 and December 2007. Of these 520 patients we retrieved the records of those who also received dual antiplatelet therapy, and reviewed them to determine their baseline demographic and clinical characteristics, including age, sex, history of ulcer disease or UGI bleeding, current smoking habit, and use of anti-secretory drugs. We excluded patients with cardiogenic death within 1 week of PCI or hypoxic encephalopathy, malignancies, or chronic hemodialysis, as well as patients who were taking warfarin or single antiplatelet therapy, or who had been transferred to other hospitals after a successful PCI.

Clinically-important UGI bleeding was identified by hematemesis and/or melena, and a reduction of hemoglobin level of at least 2 g/dL, leading to a gastroenterology consultation, and confirmed by an endoscopic diagnosis of peptic ulcer lesions as the cause of bleeding. For the purposes of our study, peptic ulcer lesions included either gastroduodenal peptic ulcers or acute mucosal lesions of the gastroduodenal tract. The consultation results and endoscopic findings were analyzed. On follow-up coronary angiography (CAG), 75% or more stenosis of coronary artery was considered as significant stenosis. The study was approved by the Institutional Research Board of the Showa University Fujigaoka Hospital.

For statistical analysis, Mann-Whitney U-test and χ^2 -test were used to compare categorical data. The observation period started the day of DES implantation. Follow-up finished either on the day of UGI bleeding, the day of stopping anti-secretory drug, or the day of the latest visit to our outpatient clinic. The cumulative incidence of UGI bleeds among patients who were or were not taking an anti-secretory drug was plotted using the Kaplan-Meier method. The differences

between the groups were assessed using log-rank test. $p < 0.05$ was considered to be statistically significant.

Abbreviation: CAG: coronary angiography

Result

Among 520 PCI cases between 2006 and 2007, 277 patients were excluded for the following reasons: the patient had been transferred to another hospital immediately after a successful PCI (N=90); chronic hemodialysis (N=60); the patient was taking warfarin or single antiplatelet therapy (N=44); cardiogenic death within 1 week of PCI or hypoxic encephalopathy (N=35); malignancies (N=24). We identified 243 patients as having received an implanted DES for coronary heart disease, and who had been subsequently discharged from hospital on dual antiplatelet therapy. These cases included 183 men and 60 women with a mean age of 68 years (range, 36-88 years). Regarding the dual antiplatelet therapy, 234 cases received aspirin (100 mg/d) plus thienopyridine derivatives (ticlopidine; 100-200 mg/d 201 cases, clopidogrel 50-75 mg/d; 33 cases), and 8 received aspirin plus cilostazol (200-300 mg/d). EGD endoscopic examination was performed in 47 patients (19%) after DES implantation. The endoscopic findings and *H. pylori* status (determined in 38 cases) of these patients are presented in Table 1. We analyzed the UGI bleeding events, which had occurred in these patients until July 2008; mean follow-up period was 15.8 months (maximum follow-up period was 30 months). We found that 8 patients (3.3%) had developed UGI bleeding during the period; their clinical characteristics are summarized in Table 2. They included 6 men, and 2 women, average age 70 years; there were 4 gastric ulcer cases, 2 acute gastric mucosal lesion cases, 2 duodenal ulcer cases. None of the 8 patients was taking concomitant anti-secretory drugs. The dual antiplatelet therapy in all 8 cases was aspirin and ticlopidine. One patient had a prior history of peptic ulcer. Four cases developed UGI bleeds within 1 month of DES implantation; they all were ACS cases (2 for acute myocardial infarction (AMI), and 2 for unstable angina). One case (No. 8 in Table 2) developed anemia without melena, and was found to have a gastric ulcer on endoscopic examination. Seven cases required hospitalization and a blood transfusion of at least 2 units of packed red blood cells. Endoscopic hemostasis was performed in 5 cases, and they were all successful. After confirming that no sign of bleeding (Forrest type III) was present in the ulcer lesion(s) on endoscopic examination, we restarted dual antiplatelet therapy with PPI prophylaxis before discharge. No bleeding-associated mortality or recurrent UGI bleeding occurred among these 8 patients during 6 months of follow-up. Among them, 7 cases were *H. pylori* positive. *H. pylori* eradication was performed after healing of ulcer lesion (scar stage) had been confirmed on endoscopic examination in each patient. Six of the cases were eradicated successfully. The 1- and 2-year cumulative incidences of UGI bleeds among the entire study population of 243 patients were

Table 1. Demographic and Baseline Characteristics of the Patients

total n	without anti-secretory drug 135	with anti-secretory drug 108	p
age (mean 68)	67 (34-86)	71 (38-89)	n.s.
male : female (183 : 60)	111 : 24	72 : 36	0.005
clinical presentation			
stable angina	82	52	0.05
acute myocardial infarction	36	43	0.03
unstable angina	17	13	n.s.
current smoking	40	29	n.s.
previous peptic ulcer	7	5	n.s.
previous UGI bleeding	0	1	n.s.
previous EGD endoscopy	24	23	n.s.
gastritis	11	12	n.s.
GERD	2	5	n.s.
PUD	4	2	n.s.
polyp	2	0	n.s.
positive <i>H. pylori</i>	15/19	14/19	n.s.

Table 2. Characteristics of the 8 Patients with UGI Bleeding

	age	sex	cardiac profile	time after PCI	current smoking	medication	previous PUD	melen	hematemesis	endoscopy	Hb (g/dL)	<i>H. pylori</i>	transfusion
1	51	M	AMI	22 days	yes	aspirin/ticlopidine	no	yes	no	DU	10.4	positive	2 units
2	75	M	uAP	20 days	no	aspirin/ticlopidine	no	yes	no	AGML	5.4	positive	8 units
3	77	M	uAP	23 days	no	aspirin/ticlopidine	no	yes	no	GU	10.6	positive	2 units
4	79	M	EAP	4 months	yes	aspirin/ticlopidine	no	yes	no	AGML	7.0	negative	4 units
5	70	M	uAP	2 months	no	aspirin/ticlopidine	no	no	yes	GU	8.6	positive	4 units
6	78	F	EAP	21 months	no	aspirin/ticlopidine	no	no	yes	GU	9.8	positive	no
7	62	M	AMI	11 days	yes	aspirin/ticlopidine	yes	yes	no	DU	9.6	positive	4 units
8	70	F	EAP	16 months	no	aspirin/ticlopidine	no	no	no	GU	6.9	positive	4 units

PUD; peptic ulcer disease

2.5% and 5.0%, respectively (Fig. 1).

Among the 243 cases, 108 (44.4%) were given anti-secretory drugs: 67 a PPI, and 41 an H2RA. Regarding the administration of PPIs, all cases were taking “half the standard dose” (lansoprazole 15 mg/d, rabeprazole 10 mg/d and omeprazole 10 mg/d). Regarding the administration of an H2RA, 23 cases were taking “half the standard dose” and 18, the “standard dose”. Because of the retrospective nature of this study, the doses of anti-secretory drugs were determined by the physician for each patient. Among the 108 cases who were taking anti-secretory drugs, observation was discontinued in 3 cases because they stopped taking the anti-secretory drugs.

Table 2 defines the baseline characteristics of the patients in the 2 sub-groups (concomitant anti-secretory drug and no concomitant anti-secretory drug). There were more women than men (33% vs. 18%) in the group taking a concomitant anti-secretory drug. In terms of history of heart disease, more cases of prior AMI was found in the group taking a concomitant anti-secretory drug (40% vs. 27%), and more stable angina was found in the group not taking a concomitant anti-secretory drug (60% vs. 48%). No significant differences were seen when comparing age, current smoking habit and peptic ulcer history between the two groups. The 1- and 2-year cumulative incidences of UGI bleeds among patients who were not taking an anti-secretory drug were 4.5% and 9.2%, respectively. On the other hand, as reported above, there were no cases of UGI bleeding among patients who were taking an antiplatelet drug plus an anti-secretory

drug. As depicted in Fig. 2, there was a significant protective effect against UGI bleeding among patients taking an anti-secretory drug compared with those who were not (any anti-secretory drug, $p=0.01$; PPI $p=0.044$).

We then evaluated the follow-up CAG findings after DES implantation. Among 243 patients, follow-up CAG was performed in 214 patients, 6-16 months after DES implantation. When CAG findings were compared between patients who were not taking any anti-secretory drug, and those who were taking PPI or H2RA, significantly more stenotic lesions in coronary arteries (in-stent restenosis, new stenotic lesions or AMI) were observed in the PPI-treatment group compared with the group not taking any anti-secretory drug ($p<0.05$, Table 3).

Abbreviation: ACS: acute coronary syndrome

Discussion

In the present study, we found that UGI bleeding during dual antiplatelet therapy was relatively high, and that anti-secretory drug use was associated with a profound reduction in this risk. Co-administration of PPIs reduced the risk of UGI bleeding significantly; however, increase in stenotic lesions of coronary arteries after stenting was also observed.

While the beneficial effects of dual antiplatelet therapy on stent thrombosis have been established, unfortunately it has also been associated with several hemorrhagic complications. The GI tract is the most frequent site of bleeding during anti-thrombotic therapy. The risk of bleeding with aspi-

Figure 1. Kaplan-Meier estimates of UGI bleeding-free patients receiving dual antiplatelet therapy.

Figure 2. Kaplan-Meier estimates of UGI bleeding-free patients with and without concomitant anti-secretory drug.

Table 3. Follow-up CAG Finding during Antiplatelet Therapy with or without Anti-secretory Therapy

without anti-secretory drug (n=117; M:F = 97:20, mean age 67)	no stenosis		92
	stenosis (+) n=25; 22%	ISR (+)	17
		ISR (-), new lesion	8
		AMI	0
PPI (n=62; M:F = 43:19, mean age 70)	no stenosis		(LPZ/OPZ/RPZ; 38: 1: 1) 40
	stenosis (+) n=22 (35%)	ISR (+)	(LPZ/OPZ/RPZ; 15: 0: 0) 15
		ISR (-), new lesion	(LPZ/OPZ/RPZ; 3: 1: 0) 4
		AMI	(LPZ/OPZ/RPZ; 3: 0: 0) 3
H2RA (n=35; M:F = 22:13, mean age 73)	no stenosis		(standard dose: half dose; 7 :19) 26
	stenosis (+) n=9; 26%	ISR (+)	(standard dose:half dose; 3: 4) 7
		ISR (-), new lesion	(half dose; 1) 1
		AMI	(standard dose; 1) 1

ISR; in-stent restenosis, LPZ; lansoprazole, OPZ; omeprazole, RPZ; rabeprazole, RTD; ranitidine, FTD; famotidine, NTD; nizatidine

rin plus clopidogrel is similar to the risk with aspirin plus ticlopidine (10). Several large randomized trials have compared the combination of clopidogrel and aspirin in patients at high risk of future cardiovascular events (11-15). These studies have reported that there were between 0.6% (28-day follow-up) and 4.8% (12-month follow-up) major bleeds in

patients treated with dual antiplatelet therapy, compared with between 0.6% (28-day follow-up) and 3.8% (12-month follow-up) in patients treated with aspirin alone. Compared with those reports, the 1- and 2-year cumulative incidences of UGI bleeds among our patients during dual antiplatelet therapy were 2.5% and 5%, respectively. Our results indi-

cated that the incidence of UGI bleeds in Japanese patients with dual antiplatelet therapy after PCI seems similar to that of patients living in Western countries.

We analyzed the effect of concomitant anti-secretory drug use in the prevention of UGI bleeding. Due to the retrospective nature of this study, we cannot be certain that patients were randomly assigned to anti-secretory drug treatment or non-treatment. Table 1 shows that more females than males and more patients with a history of AMI were found in the anti-secretory drug-treated group. Reported factors for UGI bleeding include increasing age, female sex, major organ dysfunction (cardiac, respiratory, hepatic), diabetes, hypertension, and hemostatic disorders (5). Hence, if anti-secretory drug treatment is ineffective in the prevention of UGI bleeding, then we would have expected the incidence to have been higher in this sub-group, but this was not found to be the case. Indeed, we observed a significant prophylactic effect on UGI bleeding when an anti-secretory drug (PPI or H2RA) was co-prescribed with dual antiplatelet therapy. PPI use was associated with substantial reductions in the risk of UGI bleeding among both low-dose aspirin and clopidogrel users (16). Although the difference is not statistically significant, the standard or half the standard dose of H2RA also seems to be effective for preventing UGI bleeding. While a high dose, not the standard dose, of an H2RA is reported to be effective for the prevention of NSAID-induced gastroduodenal complications (17), half of the standard dose of famotidine was shown to be effective in preventing NSAID-induced gastric damage in a Japanese study (18). One possible explanation for the discrepancies may be the difference in gastric acid output and *H. pylori* prevalence between Japanese and Western populations.

In the present study, 4 cases (50%) of UGI bleeding occurred within 1 month of PCI; all were ACS cases. In accordance with this, several reports have indicated that the incidence of major bleeding within 1 month of PCI was between 0.6-2.3% (16, 19, 20), indicating that the first month after PCI seems to be a high-risk period for UGI bleeding. Although prophylactic use of an anti-secretory drug in all

patients with dual antiplatelet therapy might be economically unacceptable, it should be considered in those high-risk cases such as patients with ACS, and during the high-risk early period (at least the first 3 months) after PCI.

In the present study, we also analyzed the follow-up CAG findings after coronary stenting, and found significantly more stenotic lesions in the coronary arteries in the PPI-treatment group. The active forms of ticlopidine and clopidogrel arise from complex biochemical reactions involving several CYP isoforms. Several studies have reported an interaction between thienopyridine derivatives and CYP2C19, a known site of PPI metabolism. Notably, poor metabolizers of clopidogrel with CYP2C19 polymorphism have higher platelet aggregability, greater clopidogrel nonresponse, and a higher rate of major adverse cardiovascular events after coronary stenting (21). These earlier studies suggest that attenuation of the antiplatelet effect of thienopyridine derivatives by PPIs leads to adverse clinical outcome. Recently, it has been reported that concomitant use of clopidogrel and PPI after hospital discharge for ACS was associated with an increased risk of adverse outcome (22). Together with our results, the use of PPI may be associated with attenuation of the anti-platelet effect of thienopyridine derivatives. H2RAs could become alternative prophylactic drugs for prevention of UGI, but they might be less effective compared to PPIs. In addition, it is worthy to note that prasugrel, a novel thienopyridine derivative, is as effective as clopidogrel for the prevention of ischemic events (23, 24). Notably, the platelet inhibitory action of prasugrel is not affected by genetic variation of CYP2C19 (25). Concomitant use of PPI with prasugrel may be potentially useful for the prevention of UGI bleeding.

In summary, UGI bleeding during dual antiplatelet therapy without concomitant anti-secretory drugs is relatively common. Prophylaxis with anti-secretory drugs during dual antiplatelet therapy after PCI may prevent UGI bleeding. Concomitant use of PPI seems to be associated with a reduction of the effect of dual antiplatelet therapy.

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