Original Article

Gastrointestinal Complications from Antiplatelet Therapy in Acute Coronary Syndrome Patients in Maharaj Nakorn Chiang Mai Hospital

Iamworanirun C[1]
Pisespongsa P[1]
Kuanprasert S[2]
Thongsawat S[1]
Chitapararux T[1]
Leerapun A[1]
Kijdamrongthum P[1]

ABSTRACT

Background & Aims: Antiplatelets drugs are widely used and may cause GI complications. This study was aimed at assessing the incidence and the risk factors of antiplatelet-induced gastrointestinal (GI) complication.

Methods: Patients ≥ 18 years old with newly diagnosed coronary artery disease who were admitted for coronary angiography at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand, between January 1, 2010 and December 31, 2012 were included for study. The GI complications were classified as the CSULGIE composite end points.

Results: Of 729 patients, 66 developed gastrointestinal complications (9.05%; 6.03 events per 100 patient-years), of which clinically significant anemia of presumed occult GI origin was most common (44 cases, 66.7%). Patients with GI complications were more often re-hospitalized. No significant risk factors for the occurrence of GI complications were identified.

Conclusion: Clinically significant anemia of presumed occult GI origin was the most common gastrointestinal complication in patients receiving antiplatelet therapy in Maharaj Nakorn Chiang Mai hospital.

Key words : Antiplatelet therapy, gastrointestinal complication, risk factor

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[1]*Gastroenterology and Hepatology unit,* [2]*Cardiology unit, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.*

Address for Correspondence: *Apinya Leerapun, M.D., Gastroenterology and Hepatology unit, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.*

INTRODUCTION

Antiplatelets drugs are widely used for the prevention of cardiovascular events worldwide[1]. Although there are clear benefits concerning the cardiovascular system, these have to be balanced against the adverse effects and potential damages to the gastrointestinal mucosa[2-6].

Gastroduodenal hemorrhage is the most common complication from antiplatelet therapy, with increasing mortality in patients with coronary artery disease[7-9]. A recent consensus guideline concludes that proton pump inhibitor (PPI) should be considered in any person with risk factors for gastrointestinal bleeding who receives antiplatelet therapy[10, 11]. It has become clear over the last few years that antiplatelets can also injure the lower gastrointestinal tract as well as the small bowel mucosa[2, 12-14].

To our knowledge, There are no studies to data in Thai patients on anti-platelet therapy specifically examining the types and the characteristics of gastrointestinal complications. The main objective of this study was to evaluate the rate, type, and risk factors of gastrointestinal complications in routine clinical practice, in patients on antiplatelet therapy after PCI at Maharaj Nakorn Chiang Mai Hospital.

METHODS

Study design and setting

This was a retrospective study of data from patients admitted for coronary angiography at Maharaj Nakorn Chiang Mai hospital during January 1, 2010 and December 31, 2012.

Patients ≥ 18 years old with newly diagnosed coronary artery disease who had received anti-platelet therapy and had been followed up for at least 6 months were included. Exclusion criteria were advanced liver or kidney disease, long term antiplatelet usage before PCI, bleeding diathesis, malignancy within the previous 5 years, Inflammatory bowel disease, rheumatologic disease, and prior gastrointestinal or biliary bypass surgery.

Demographics, past medical history, prescription of PPIs or H_2- receptor antagonists, gastrointestinal and cardiovascular events requiring hospitalization, endoscopic findings, medications during follow-up, and laboratory data were collected from the hospital electronic medical data base, and chart reviews of all patients were made. The study was approved by The Hospital Ethics Committee.

The primary end-point was a composite of clinically significant events occurring throughout the gastrointestinal tract. The definitions of the endpoint criteria (clinically significant upper and lower GI events (CSULGIE) composite end points) were as described by Chan and colleagues[15].

Statistical methods

The association between two categorical variables was analyzed by the Fisher's exact test. Comparisons of means or medians of a continuous variable between independent samples with normal and skewed distributions were made by the independent sample Student's *t*-test and Mann-Whitney test, respectively. The predictive factors for the primary end-point were analyzed by multiple logistic regression analysis. All statistical tests were performed with the use of SPSS software (SPSS Version 19).

RESULTS

A total of 802 patients were screened for the study, of whom 73 were excluded. The reasons for exclusion during screening were long-term antiplatelet therapy before PCI (45), end stage renal disease (22), and history of malignancy (6). Finally, 729 patients were analyzed (Figure 1).

Of the 729 patients, the mean age was 64.1±10.8 years, 63.8% were male, 96.4% received a combination of aspirin (ASA) and clopidogrel, and prophylactic PPIs had been prescribed in 362 patients (49.7%). The mean duration of follow up was 18.6±7.2 months. The mean time of events occurring was 4.7±3.9 months after PCI. Re-hospitalization was significantly more frequent in patients with the occurrence of GI complications. The differences in the characteristics of patients with or without gastrointestinal complications are described in Table 1.

A total 66 patients (9.05%; 6.03 events per 100 patient-years) developed GI complications; 44 (66.7%) had clinically significant anemia of presumed occult GI origin (Figure 2). In multivariate analysis, any risk factor had statistical significance (Table 2).

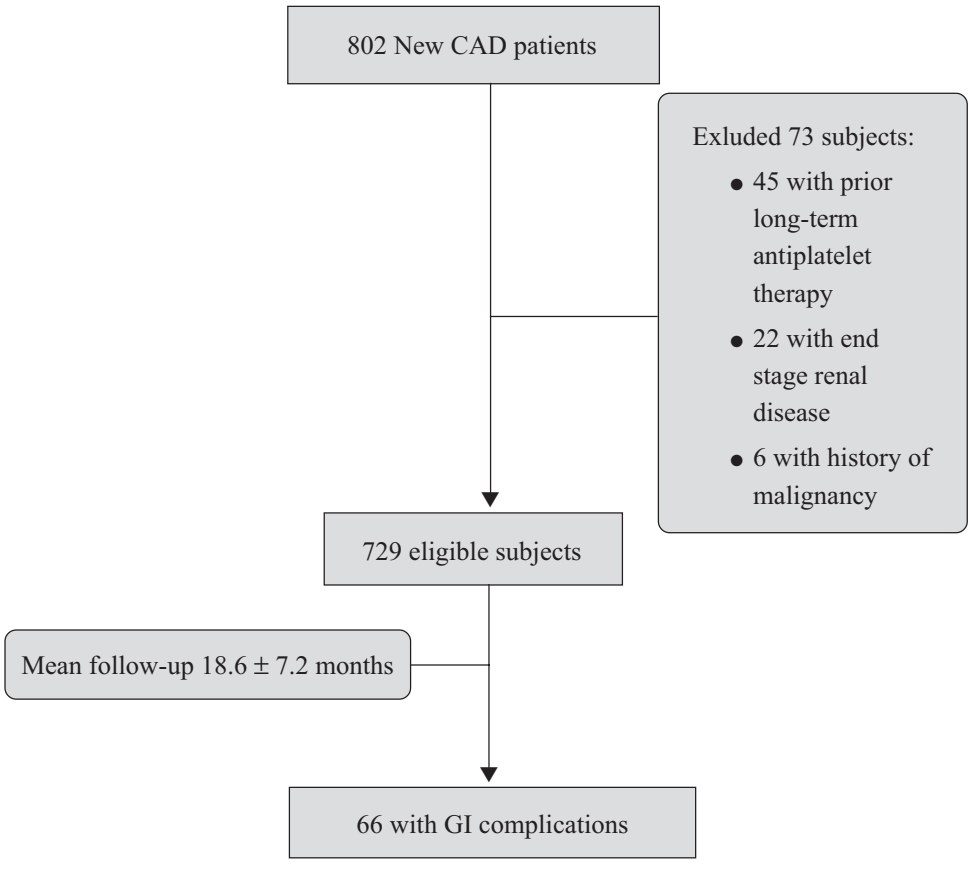

Figure 1. Flow diagram showing the process leading to the final patient sample eligible for analysis.

Table 1. Characteristics of study patients.

	GI events (n, %) n=66	**No GI events (n, %) n=663**	***p*-value**
Age yrs.(mean, SD)	65.0, 9.8	64.0, 10.9	0.115
Age ≥ 60	46 (69.7)	400 (60.3)	0.137
Gender (male)	44 (66.7)	421 (63.5)	0.610
Drugs			
ASA+Clopidogrel	64 (97.0)	639 (96.4)	1.000
NSAIDs	2 (3.0)	7 (1.1)	0.192
Warfarin	2 (3.0)	19 (2.9)	1.000
Steroid	0	0	NS
PPIs	39 (59.1)	323 (48.7)	0.108
H_2RA	2 (3.0)	12 (1.8)	0.628
Baseline (mean, SD)			
Hemoglobin (g/dL)	12.5, 1.6	12.3, 1.5	0.179
Hematocrit (%)	37.7, 5.0	37.3, 4.3	0.159
Follow up time (months)	17.9, 6.3	18.7, 7.3	0.446
Re-hospitalization			
Cardiovascular disease	5 (7.6)	6 (0.9)	0.002
GI disease	9 (13.6)	0	<0.001

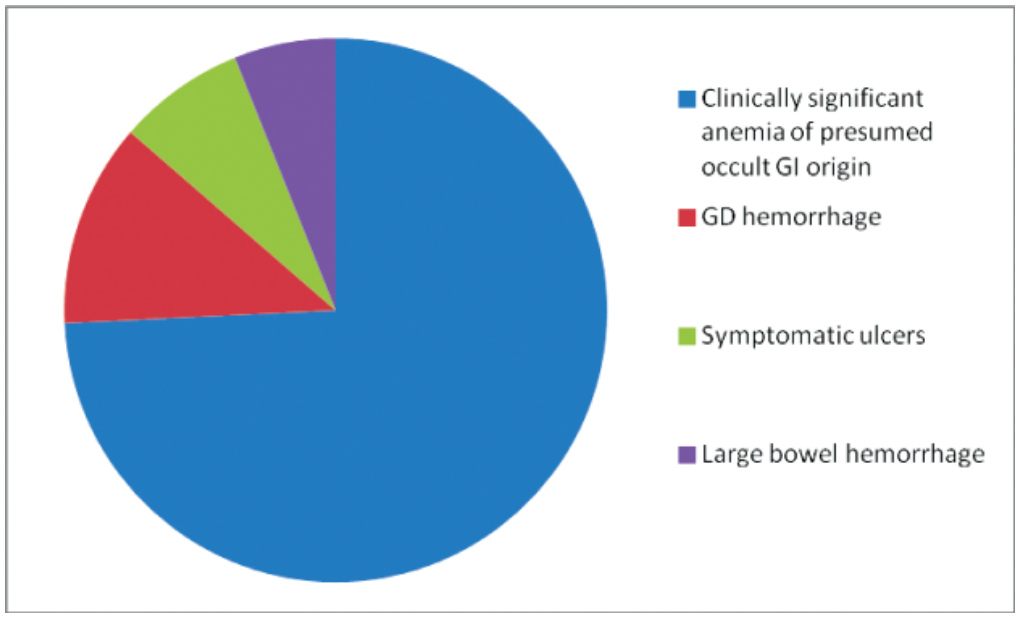

Figure 2. Characteristics of the GI events.

Table 2. Adjusted Odds Ratio (95% confidence interval) for GI events.

	Adjusted Odds Ratio (95% confidence interval)	***p*-value**
Age ≥ 60	1.512 (0.875-2.615)	0.139
ASA+Clopidogrel	1.202 (0.278-5.202)	0.806
NSAIDs	2.929 (0.596-14.394)	0.186
Warfarin	1.059 (0.241-4.651)	0.939
PPIs	1.520 (0.910-2.542)	0.110
Follow up time	0.983 (0.949-1.019)	0.361

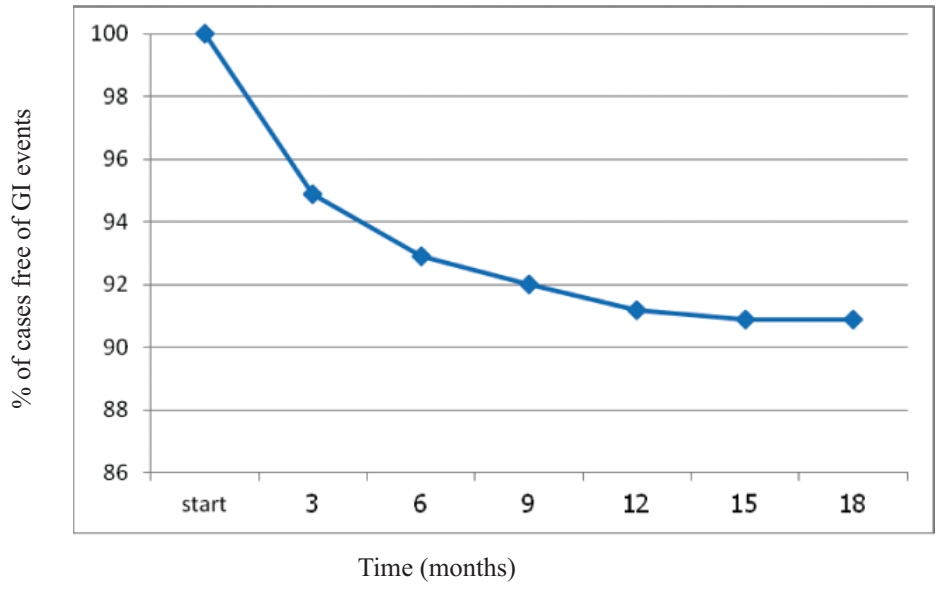

Figure 3. Time trends of GI events in the study population.

DISCUSSION

The efficacy of antiplatelet therapy after coronary revascularization for the prevention of new events is well established. However, antiplatelet therapy may be injurious to the gastrointestinal mucosa can and cause complications throughout the GI tract.

Gastrointestinal complications frequently occur in patients receiving antiplatelet therapy. The prevalence varies, and is related to the patient characteristics as well as the definition used. Most previous studies focused primarily on the damages to the upper GI tract, and often neglected the lower GI tract. In this study, we chose to use the CSULGIE endpoint[15], which extends the traditional assessment of upper GI complications by including also events in the lower GI tract (small/large bowel) such as perforation, bleeding, and clinically significant anemia.

Our cohort comprised 729 patients with coronary artery disease receiving antiplatelet therapy. The incidence of GI complications was 6.03 events per 100 patient-years, with a comparable occurrence in the upper and the lower GI tract. These data are in agreement with a recent epidemiological study[13] which showed a time trend decrease in the number of hospitalizations due to upper GI bleeding and an increased number of hospitalizations due to lower GI bleeding, a trend that was attributed to an increase in the implementation of prevention strategies in NSAID/ASA-associated upper GI complications. The explanation for the relatively large proportion of lower GI events in this population may vary, considering that low-dose ASA may induce damages in the lower GI tract while PPIs have no therapeutic effect beyond the duodenum.

Clinically significant anemia of presumed occult GI origin was the most common complication, the incidence in our study being comparable to a previous study by Anker et al.[18] There are many possible causes of anemia, including an inflammatory reaction in response to tissue injury, hemodilution occurring in heart failure, and the use of blockers of the rennin-angiotensin system. In the study by Anker etal[18], iron deficiency appeared to be the main determinant associated with a lower hemoglobin. Endoscopy capsule studies[14] have shown that ASA can induce erosions and ulcers in the small bowel. Thus the cause of anemia in our study could have been a consequence of chronic occult blood loss from mucosal damage in the small bowel.

PPIs were recommended for use to prevent gastroduodenal complications and resulted in a decrease UGIB in many studies[19,20,21]. On the other hand, PPIs can evidently increase small bowel injury due to development of SIBO, which may enhance the effect of ASA-induced small bowel mucosal damage leading to a high incidence of clinically significant anemia.

History of peptic ulcer disease, advanced age, concomitant use of NSAIDs, steroid, anticoagulants, and dual antiplatelet therapy, are known risk factors for GI complications[22,23]. In this study, we could not identify any significant correlation between such risk factors and the occurrence of GI complication and clinically significant anemia. Smecoul et al.[14] demonstrated that short-term administration of cardiovascular doses of ASA can damage the small bowel mucosa in some people. On the basis of video capsule endoscopy (VCE), examination, they observed that half of the study population receiving low-dose ASA had macroscopic damage. Not all such small bowel lesions are clinically significant. The risk factors for the progression of these lesions to clinical significance are unclear and require further study.

One strength of our study was that by reporting all GI events, we had addressed a more comprehensive picture linked to GI complications associated with dual antiplatelet therapy in real life clinical practice. The management of our patients had followed current recommendations in the prevention of UGIB. There were limitations also. First, the adjudication of presumed occult GI bleeding was a diagnosis by exclusion rather than by direct confirmation of the source of blood loss. Thus we could not state with certainty that the bleeding site was within the GI tract. Second, there was no protocol for monitoring the hemoglobin, and for taking history of GI symptoms. I should be pointed out also that our analysis was based on medical and prescription records, and that a systematic assessment of medication compliance or other drugs used was not possible due to the study design. These could have underestimated the incidence of occult bleeding and GI events or altered the risk factor analysis.

CONCLUSION

The incidence of GI complications in patients receiving antiplatelet therapy in Maharaj Nakorn Chiang Mai Hospital was 6.03 events per 100 patient-years. Clinically significant anemia of presumed oc-

cult GI origin was the most common complication. PPIs may not have adequate efficacy to prevent this complication. Further study and new drugs with better protective effect throughout the GI tract are needed.

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