**Title: Effect of antiplatelet agent number, types, and pre-endoscopic management on post-polypectomy bleeding: validation of endoscopy guidelines**

Short title: Post-polypectomy bleeding on antiplatelet

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**Abstract**

**Background:** It remains unclear whether type of antiplatelet (AP) therapy, AP combination therapy, and AP continuing or switching strategy affect the risk of post-polypectomy bleeding (PPB). In this study, we sought to elucidate this risk.

**Methods:** We analyzed 1050 patients who underwent colonoscopic polypectomy: 525 AP users and 525 controls matched for age, sex, comorbidities, concomitant non-steroidal anti-inflammatory drugs use, and polyp characteristics who did not receive antithrombotics. PPB risk was evaluated by AP number, type, and continuing or switching strategies during the peri-endoscopic period.

**Results:** In multivariate analysis, bleeding risk increased significantly as the number of AP agents used increased (monotherapy, adjusted odds ratio [aOR], 3.7; dual antiplatelet therapy (DAPT), 4.6; triple antiplatelet therapy (TAPT), 11.1) compared with controls. With monotherapy, significantly increased PPB risk was found for aspirin (aOR, 4.3), thienopyridine (aOR, 6.3), and cilostazol (aOR, 5.9), but not for eicosapentaenoic acid or other APs (beraprost, limaprost, sarpogrelate, dilazep, or dipyridamole). With DAPT, significantly increased PPB risk was found for combination aspirin plus cilostazol, but not aspirin plus other APs. Bleeding rates for continuing monotherapy were 4.3% for aspirin and 0% for thienopyridine, cilostazol, and other APs, respectively.

**Conclusions:** Analysis of this large polypectomy dataset showed that the use of low-dose aspirin, thienopyridine, or cilostazol and a combination of these is associated with increased PPB risk. Although PPB risk was high with DAPT or TAPT, PPB rate in any antiplatelet monotherapy even with a continuing strategy was low at < 5%.

**Key words:** dual antiplatelet therapy (DAPT), acetylsalicylic acid; delayed bleeding; ASGE guidelines; ESGE guidelines; JGES guidelines

## Introduction

Post-polypectomy bleeding (PPB) is a major adverse event, with an estimated incidence of 0.26-2.8% in the general population [1-5]. Owing to aging populations, the bleeding risk of antiplatelet (AP) therapy is increasingly a matter of concern [6-8]. Previous studies describing the impact of AP on PPB have focused on aspirin or thienopyridine, which are widely used in clinical practice. The reported PPB rate for aspirin is in the range of 3.2-8.8% [9-12], whereas that for thienopyridine is 0.85-13.4% [13-15].

However, these previous studies have not always distinguished between aspirin and NSAIDs [9-12], and the PPB rate for thienopyridine users ranged from 54.0% to 87.8% with concomitant use of aspirin [13-15]. Therefore, evidence for monotherapy with aspirin or thienopyridine is limited. In addition, data for other AP agents such as cilostazol, eicosapentaenoic acid, and dipyridamole is scarce. Nowadays, patients who undergo endoscopy sometimes receive a variety of AP agents not only as monotherapy, but also as combination therapy such as dual antiplatelet therapy (DAPT) [16] and even triple antiplatelet therapy (TAPT) [17]. Combined use of agents seems to increase the risk of bleeding, but there is no evidence as to whether a higher number of AP agents increases the risk of PPB or what type of combination increases the risk.

Based on previous studies revealing aspirin to be a low-risk medication and thienopyridine to be a high-risk medication, current guidelines [18-20] recommend that aspirin be continued and thienopyridine be either discontinued or switched to aspirin before polypectomy. However, to our knowledge, no studies have compared the risks and benefits of continuing, discontinuing, or switching strategies. If a continuing AP strategy is found to be associated with a low risk of developing PPB, then the strategy may be acceptable and pre-endoscopic management can be simplified for all physicians who perform endoscopy.

To examine these issues, in this study we evaluated the PPB risk according to single- and combined-use APs and compared such use with not receiving any antithrombotics. We

also assessed PPB risk according to pre-endoscopic management, namely, continuing or switching to another agent.

## Materials and Methods

### *Study design, setting, and subjects*

This retrospective cohort study was conducted at the Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine (NCGM), Japan. Among 7,985 patients who underwent colonoscopic polypectomy at our institution between August 2010 and May 2019, 4,329 provided responses to a questionnaire survey conducted during an interview in our previous study [21]. From these patients, we identified 686 who had received AP therapy (cases) and 3,578 patients who had not received any antithrombotic therapy (controls). Then, we excluded patients who underwent polypectomy with cold forceps or snare, hot biopsy, or endoscopic submucosal dissection, those who had concomitant colorectal disease including advanced colorectal cancer, active inflammatory bowel disease, diverticular bleeding, rectal ulcer, or radiation proctitis, those who had incomplete medical records, and those with long-term cessation of AP agent (> 14 days). Controls matched for decennial age, sex, metabolic disorders (diabetes mellitus, hypertension, or dyslipidemia), concomitant non-steroidal anti-inflammatory drug (NSAID) use, and characteristics of resected polyps (number, size, pathological findings, and location) were randomly selected at a ratio of 1:1. Finally, data from a total of 1050 subjects (525 cases, 525 controls) were analyzed (**Fig. 1**).

This study was approved by the Institutional Review Board of NCGM. Patient consent was waived because this was a retrospective study (approval number, 2176).

### *Data collection*

We collected clinical and endoscopic data from electronic medical records (MegaOak online imaging system, NEC, Japan) and an electronic endoscopic database

(SolemioEndo, Olympus, Japan), in which all clinical findings had been recorded immediately after clinical evaluation or endoscopy by physicians or nurses. We also collected data from patients using a detailed self-report questionnaire, which included items on medical information such as lifestyle, comorbidity, past history, and medication, and using a structured interview questionnaire completed by staff from the endoscopy unit on the day of colonoscopy [22]. Data on medication included NSAID use, oral anticoagulant use, heparin bridging, number of AP agents used (monotherapy, DAPT, or TAPT), and type of AP agents used (low-dose acetylsalicylic acid [aspirin], thienopyridines [clopidogrel, ticlopidine, or prasugrel], cilostazol, eicosapentaenoic acid, or other). Laboratory data included serum creatinine and blood platelet count before endoscopy.

***Endoscopy settings***

In all cases, colonoscopy was performed using the Olympus 240 or 260 series colonoscope (Olympus, Tokyo, Japan) with full oral bowel preparation. Polypectomy was performed using a polypectomy snare (SnareMaster; Olympus, Tokyo, Japan) and electrosurgical diathermy system (ERBE ICC-350, Somo Technology Inc., Tokyo, Japan or ESG-100, Olympus, Tokyo, Japan) with or without local saline injection. Routine prophylactic clip placement was performed in most cases. Physicians recorded data about polyps and procedures in the SolemioEndo electronic endoscopic database (Olympus) immediately after colonoscopy. Pathological evaluation of resected polyps was performed by a skilled pathologist using hematoxylin and eosin staining. We collected data on the number, size, and location of the polyps resected and the polypectomy technique from the electronic database. Pathological findings were assessed for the presence of adenocarcinoma.

***Management of antiplatelet agents during the peri-endoscopic period***

For patients who received AP monotherapy, we assessed the pre-procedural management of AP agents using the medical records. We evaluated whether the AP agent was continued or switched to low-dose aspirin or cilostazol a few days before polypectomy. Some patients had received unfractionated heparin during the peri-endoscopic period for bridging with AP or oral anticoagulant. Selection of these strategies was at the discretion of each attending physician. For patients who received DAPT or TAPT, we could not simply classify the management of AP agents because there were varying patterns of AP agent continuing or switching strategies. The pre-endoscopic management of DAPT or TAPT is described in detail in **Supplementary Table 1**.

***Clinical outcomes***

Primary outcomes of this study were post-polypectomy bleeding (PPB), thromboembolism, and death within 30 days of polypectomy. PPB was defined as delayed overt rectal bleeding after polypectomy [12-15, 23]. Thromboembolic events included acute coronary syndrome, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis, or arterial thromboembolism. All clinical outcomes were ascertained from the electronic medical records [24].

***Statistical analysis***

To minimize confounding, we matched controls to AP users at a ratio of 1:1 by age, sex, presence of metabolic disorders (diabetes mellitus, hypertension, or dyslipidemia), concomitant NSAID use, and characteristics of resected polyps (number, size, presence of adenocarcinoma, and location). Baseline characteristics were compared between controls and AP users, and the Chi-square test or Fisher's exact test was used, as appropriate, for categorical data. To determine PPB risk by the number of AP agents (monotherapy, DAPT, or TAPT) and type of AP agents (aspirin, thienopyridines, cilostazol, eicosapentaenoic acid, or other) used compared with controls, we performed

univariate and multivariate logistic regression analysis. In multivariate analysis, we developed multivariate models adjusting for age and sex of controls versus AP users (model 1) and including polyp size and location of resected polyps (model 2). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

We also examined PPB rate in users of AP monotherapy according to whether AP was continued or switched. Subgroup analysis was performed in 476 AP users with no anticoagulant use and 476 controls matched by age, sex, presence of metabolic disorders (diabetes mellitus, hypertension, or dyslipidemia), concomitant NSAID use, and characteristics of resected polyps (number, size, presence of adenocarcinoma, and location). A $P$ value < 0.05 was considered significant. All statistical analysis was performed using STATA version 14 software (StataCorp, College Station, TX).

## Results

### *Characteristics and endoscopic data of AP users and controls*

Baseline characteristics are shown in **Table 1**. No significant differences were seen in age, sex, body mass index, alcohol consumption, smoking habit, comorbidities, platelet count, concomitant NSAID use, total number of polypectomies, polyp size, presence of adenocarcinoma, or location of polyps.

### *Odds ratios for PPB risk, thromboembolism, and death in AP users and controls*

The results of univariate and multivariate analysis are shown in **Table 2**. After adjustment for age ≥ 70 years, sex, polyp size ≥ 10 mm, and location of polyps (model 2), compared with controls, we found that users of AP monotherapy, DAPT, or TAPT were at increased risk of PPB in this order ($P$ for trend = 0.003) (**Table 2**). Users of AP monotherapy with aspirin, thienopyridine, or cilostazol were at increased risk of PPB (**Table 2**). This was not the case for users of eicosapentaenoic acid or other AP agents. Combined use of aspirin plus cilostazol significantly increased PPB risk, but aspirin plus thienopyridine,

eicosapentaenoic acid or other antiplatelet agents did not (**Table 2**). PPB was not observed with any other combination of DAPT, except in 1 patient using eicosapentaenoic acid with cilostazol. There were no thromboembolic events or deaths among any of the subjects. Subgroup analysis of 476 AP users with no anticoagulant use and 476 matched controls (**Supplementary Table 2**) showed similar results except for users of AP monotherapy vs controls (**Supplementary Table 3**). Major bleeding occurred in 8 cases (6 AP users and 2 controls), and this was not significantly different among the groups.

***Effect of continuing or switching AP strategy on PPB rate***

PPB rates for continuing and switching AP strategies were 3.2% and 0%, respectively (**Fig. 2A**). The PPB rate for continuing aspirin monotherapy was 4.3% (**Fig. 2B**). PPB rates for continuing and switching thienopyridine monotherapy were 0% and 0%, respectively (**Fig. 2C**). The PPB rate for continuing cilostazol monotherapy was 3.2% (**Fig. 2D**). Thus, the PPB rate associated with a continuing strategy was low at <5.0% irrespective of the type of AP agent used.

## Discussion

We focused on the risk of PPB in 525 AP users and 525 controls matched for age, sex, comorbidities, concomitant NSAID use, and polyp characteristics who were not using any antithrombotics. Our four main findings were as follows. First, as the number of AP agents used increased, the PPB rate increased. Second, monotherapy with aspirin, thienopyridine, or cilostazol, but not with eicosapentaenoic acid or other AP agents, had a higher risk of PPB. Third, combined use of aspirin plus cilostazol increased PPB risk. Fourth, the PPB rate was 0% with continuing use of thienopyridine and was low at < 5% with continuing use of aspirin or cilostazol. There were no thromboembolic events or deaths among any of the subjects.

No previous studies have compared PPB risk between non-AP users, single AP users, and

combination AP users. In this study, we showed that adjusted odds ratios for PPB in controls and patients receiving AP monotherapy, DAPT, and TAPT were 3.7, 4.6, and 11.1, respectively ($P$ for trend = 0.003). In a prospective study, Feagins et al. [15] showed an 11% delayed PPB rate in DAPT users (about 90% of cases were on DAPT with thienopyridine and aspirin), a rate that is a little higher than ours (7.1% [6/84]). Another retrospective cohort study by Singh et al. [13] demonstrated an increasing odds ratio of 3.7 for PPB in patients receiving DAPT (clopidogrel and aspirin/NSAIDs). These differences may be due to the definition of PPB, concomitant anticoagulant use, or the combination of agents. To our knowledge, no studies have reported on combinations other than aspirin plus thienopyridine. In this study, we additionally found an increased risk of PPB with aspirin plus cilostazol.

Limited data are available on PPB risk in non-aspirin AP users, and most previous studies evaluated the effect of using aspirin/NSAIDs or clopidogrel on PPB risk. Manocha et al. [12] showed that there was no significant increase in the delayed PPB rate in patients on aspirin or NSAIDs compared with controls (1.2% vs 0.9%). Other case-control studies have also shown no risk of PPB in aspirin users [10, 11, 25]. Conversely, Pan et al. reported an increased PPB rate in patients receiving aspirin compared with controls (5.5% vs 0.8%, $P < 0.05$) [26], which was similar to our results (5.2% [14/271] vs 1.3% [7/525], $P < 0.05$). These discrepant findings among studies could be due to differing definitions of PPB, as well as variations in the polypectomy setting such as the technique used (cold or hot), study sample size, and polyp characteristics. Racial differences may also pose diverse risks of bleeding [22]. To date, there have been no studies describing PPB risk with thienopyridine or cilostazol monotherapy. We found that PPB risk was higher in single thienopyridine and cilostazol users than in controls (aOR, 6.3 and 5.9). Consistent with our findings, a recent meta-analysis [27] reported that single clopidogrel use was a significant risk factor for delayed bleeding (OR, 9.7), although this included only two case-control studies.

Few studies reported to date have examined the validity of the continuing strategy. Here, we found that continuing aspirin monotherapy had a higher PPB rate compared with controls (4.3% vs 1.3%, $P < 0.05$), but the rate was low at < 5%. We presume that a 3-5% PPB rate in patients who continued AP is not extremely high compared with our controls (1.3%) or with the reported PPB rate in general populations (0.26-2.8%) [1-5]. Singh et al. [13] reported a delayed PPB rate of 3.5% in patients who continued clopidogrel before polypectomy versus 1.0% in controls and concluded that continuing clopidogrel before polypectomy is acceptable. Consistent with Singh et al., we believe continuing single AP before polypectomy may be acceptable. In this study, there were no occurrences of PPB with continuing thienopyridine monotherapy. In a recent randomized controlled study, Chan et al. [23] found no significant difference in PPB rate between thienopyridine continuing and discontinuing groups regardless of monotherapy (0% vs 0%) and DAPT (4.8% vs 4.7%). Considering the low risk of PPB in their study and ours, it is acceptable that single-use thienopyridine be continued before polypectomy, which then simplifies the management of AP therapy during the peri-endoscopic period. However, the decision on whether to continue or discontinue AP agents requires weighing the risks of bleeding and thromboembolism, and all physicians should recognize the high risk of thromboembolism unless AP therapy is resumed [28].

This study has some limitations. First, this was a single-center retrospective study. However, we used prospectively collected data comprising lifestyle factors and medication. Second, the management strategy of discontinuing AP, DAPT, or TAPT before polypectomy could not be evaluated in detail because complete information about when and how the AP agents had been discontinued was not available from the electronic medical records in many cases, and there were varying patterns of management in DAPT or TAPT. Third, we used a 1:1 matching ratio to balance the characteristics between cases and controls because the number of controls was too small to conduct 1:3 or 1:4 matching. Fourth, despite the relatively large number of AP users and controls, the number of

bleeding events were relatively small, which may have resulted in the wide confidence intervals of the odds ratios. Fifth, although previous studies have shown the non-significant effect of prophylactic clip placement on PPB risk, especially for patients with relatively small polyps (< 20 mm) [29, 30], prophylactic clip placement after polypectomy in our study was different from that in the Western countries and this may have influenced the PPB risk. Sixth, polyp size was recorded as categorical data (< 10 mm or ≥ 10 mm) in our electronic endoscopic database, and so we could not report detailed data on polyp size as mean or range. Nevertheless, one of the strengths of this study is our analysis of a relatively large sample of polypectomy data (N = 1050) and the collection of detailed information on the clinical course and background of the patients. Lastly, we evaluated PPB risk by dividing AP drugs into single- and combined-use categories.

In conclusion, analysis of this large polypectomy dataset showed that the use of low-dose aspirin, thienopyridine, or cilostazol and the combination of these are associated with increased PPB risk. Although PPB risk was high with DAPT or TAPT, PPB rate in any antiplatelet monotherapy even with a continuing strategy was low at < 5%.

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## Figure legends

**Figure 1.** Patient selection and study flow

Abbreviations: ESD, endoscopic submucosal dissection

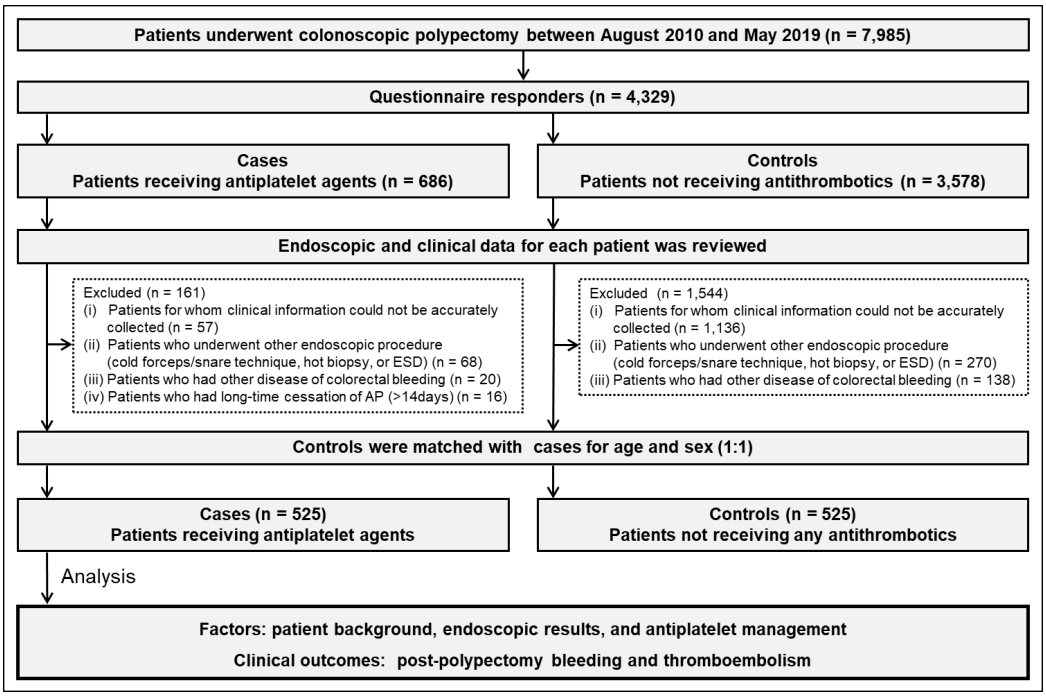


**Figure 2.** Post-polypectomy bleeding rate by each pre-procedural management strategy in patients receiving antiplatelet monotherapy.

A. PPB rate in controls and the AP monotherapy continuing and switching groups

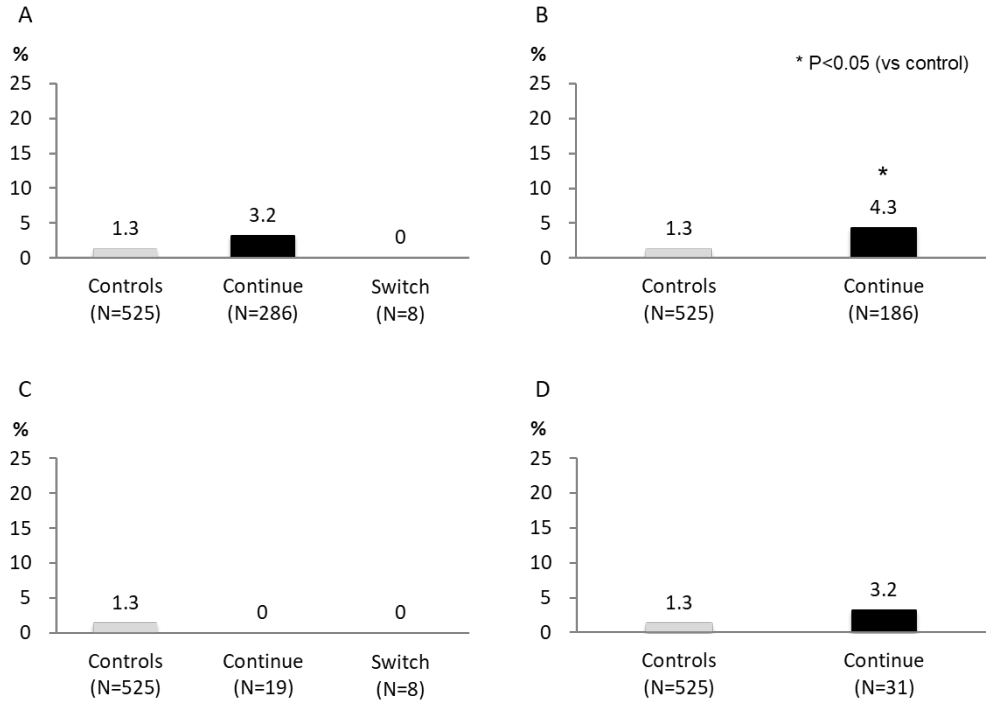
B. PPB rate in controls and the aspirin monotherapy continuing groups

C. PPB rate in controls and the thienopyridine monotherapy continuing and switching groups

D. PPB rate in controls and the cilostazol monotherapy continuing groups

**Note**: Thienopyridines included clopidogrel, ticlopidine, and prasugrel.

**Abbreviations**: PPB, post-polypectomy bleeding; AP, antiplatelet.



**Tables**

**Table 1.** Characteristics of antiplatelet users and baseline-matched controls who were not using any antithrombotics (N = 1050).

| | Antiplatelet users (n = 525) | Matched controls (n = 525) | *P*-value |
|---|---|---|---|
| Age ≥ 70 years | 364 (69.3) | 351 (66.9) | 0.39 |
| Men | 387 (73.7) | 370 (70.5) | 0.24 |
| BMI ≥ 25 | 200 (38.1) | 196 (37.3) | 0.80 |
| Current alcohol drinker | 280 (57.1) | 296 (57.3) | 0.97 |
| Current smoker | 80 (16.0) | 79 (15.3) | 0.72 |
| Comorbidity | | | |
| Diabetes mellitus | 187 (35.6) | 170 (32.4) | 0.27 |
| Hypertension | 402 (76.6) | 381 (72.6) | 0.14 |
| Dyslipidemia | 297 (56.6) | 278 (53.0) | 0.24 |
| Platelet count < $10 \times 10^4/\mu L$ | 11 (2.2) | 12 (2.7) | 0.61 |
| Concomitant NSAID use | 16 (3.1) | 15 (2.9) | 0.86 |
| Concomitant anticoagulant use | 49 (9.3) | 0 | NA |
| Heparin bridging | 36 (6.9) | 0 | NA |
| Number of antiplatelet agents | | | |
| Monotherapy | 432 (91.1) | 0 | NA |
| DAPT | 84 (8.0) | 0 | NA |
| TAPT | 9 (0.9) | 0 | NA |
| Total number of polyps excised ≥ 3 | 168 (32.0) | 159 (30.3) | 0.55 |
| Size of largest polyp ≥ 10 mm | 155 (29.5) | 139 (26.5) | 0.27 |

| | | | |
|---|---|---|---|
| Adenocarcinoma | 54 (10.3) | 59 (11.2) | 0.62 |
| Location of polyps | | | 0.46 |
| Right side | 214 (40.8) | 203 (38.7) | |
| Right and left sides | 144 (27.4) | 136 (25.9) | |
| Left side | 167 (31.8) | 186 (35.4) | |

**Note**: Values in parentheses are percentages.

**Abbreviations**: BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; DAPT, dual antiplatelet therapy; TAPT, triple antiplatelet therapy; NA, not applicable.

**Table 2.** Post-polypectomy bleeding risk by number and type of antiplatelet agents used compared with controls (N = 1050).

| | | Univariate analysis | | Multivariate analysis (model 1) | | Multivariate analysis (model 2) | |
|---|---|---|---|---|---|---|---|
| | No. of patients with bleeding /All subjects | Crude odds ratio (95% CI) | *P* value | Age (≥ 70 years) and sex adjusted odds ratio (95% CI) | *P* value | Age (≥ 70 years), sex, polyp size (≥ 10 mm), and polyp location adjusted odds ratio (95% CI) | *P* value |
| Controls | 7/525 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Antiplatelet users | 27/525 | 4.0 (1.7-9.3) | 0.001 | 4.1 (1.8-9.5) | 0.001 | 4.0 (1.7-9.3) | 0.001 |
| Number of antiplatelets used | | | | | | | |
| Controls | 7/525 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Monotherapy | 20/432 | 3.6 (1.5-8.6) | 0.004 | 3.7 (1.5-8.8) | 0.004 | 3.7 (1.6-9.0) | 0.003 |
| DAPT | 6/84 | 5.7 (1.9-17.4) | 0.002 | 5.9 (1.9-18.4) | 0.002 | 4.6 (1.4-14.4) | 0.010 |
| TAPT | 1/9 | 9.3 (1.0-84.2) | 0.048 | 10.2 (1.1-95.8) | 0.041 | 11.1 (1.2-105.8) | 0.037 |
| Type of antiplatelet monotherapy | | | | | | | |
| Controls | 7/525 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Low-dose aspirin | 14/271 | 4.0 (1.6-10.1) | 0.003 | 4.1 (1.6-10.4) | 0.003 | 4.3 (1.7-11.0) | 0.002 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Thienopyridines | 3/45 | 5.3 (1.3-21.2) | 0.019 | 5.8 (1.4-24.2) | 0.016 | 6.3 (1.4-27.5) | 0.015 |
| Cilostazol | 3/52 | 4.5 (1.1-18.1) | 0.032 | 4.8 (1.2-19.2) | 0.028 | 5.9 (1.3-25.6) | 0.018 |
| Eicosapentaenoic acid | 0/33 | 1.7 (0-11.4) | 1.000 | 1.7 (0-11.8) | 1.000 | 2.3 (0-17.5) | 1.000 |
| Other antiplatelet | 0/31 | 1.8 (0-12.1) | 1.000 | 2.0 (0-14.1) | 1.000 | 1.7 (0-12.8) | 1.000 |
| Type of DAPT | | | | | | | |
| Controls | 7/525 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Low-dose aspirin + thienopyridine | 3/50 | 4.7 (1.2-19.0) | 0.028 | 4.0 (1.0-16.2) | 0.056 | 2.9 (0.7-12.3) | 0.156 |
| Low-dose aspirin + cilostazol | 2/8 | 22.6 (3.9-132.2) | 0.001 | 24.1 (4.0-144.2) | < 0.001 | 29.7 (4.2-211.3) | 0.001 |
| Low-dose aspirin + eicosapentaenoic acid | 0/7 | 8.7 (0-69.4) | 1.000 | 8.3 (0-63.9) | 1.000 | 4.7 (0-41.4) | 1.000 |
| Low-dose aspirin + other antiplatelet | 0/5 | 13.3 (0-119.0) | 1.000 | 12.5 (0-116.6) | 1.000 | 10.1 (0-102.6) | 1.000 |
| Thienopyridine + any other antiplatelet | 0/4 | 13.3 (0-119.0) | 1.000 | 14.2 (0-124.0) | 1.00 | 26.2 (0-254.7) | 1.000 |
| Any other combination | 1/10 | 9.6 (0.2-94.0) | 0.124 | 8.8 (0.9-83.2) | 0.058 | 6.8 (0.6-84.0) | 0.133 |

**Note**. In risk analysis, we adjusted for age (≥ 70 years) and sex between controls and antiplatelet users in model 1, and we adjusted for age (≥ 70 years), sex, and polyp size (≥ 10 mm), polyp location (right or only left) and the presence of adenocarcinoma in model 2. Thienopyridines included clopidogrel, ticlopidine, and prasugrel. Other antiplatelet agents included beraprost, limaprost, sarpogrelate, dilazep, and dipyridamole.

**Abbreviations**: CI, confidence interval; DAPT, dual antiplatelet therapy; TAPT, triple antiplatelet therapy

## Supplementary Tables

**Supplementary Table1.** Pre-endoscopic management of each antiplatelet agents.

| Agent | Pre-endoscopic management |
|---|---|
| Antiplatelet monotherapy (n=432) | |
| Low-dose aspirin (n=271) | Aspirin was continued in 186 cases.<br>Aspirin was discontinued in 85 cases. |
| Thienopyridines (n=45) | Thienopyridines was continued in 19 cases.<br>Thienopyridines was discontinued in 18 cases.<br>Thienopyridines was switched to aspirin in 8 cases. |
| Cilostazol (n=52) | Cilostazol was continued in 31 cases.<br>Cilostazol was discontinued in 21 cases. |
| Eicosapentaenoic acid (n=33) | Eicosapentaenoic acid was continued in 29 cases.<br>Eicosapentaenoic acid was discontinued in 4 cases. |
| Other antiplatelet (n=31) | Agent was continued in 21 cases.<br>Agent was discontinued in 10 cases. |
| DAPT (n=84) | |
| Low-dose aspirin + thienopyridine (n=50) | Aspirin and thienopyridine were both continued in 19 cases.<br>Aspirin and thienopyridine were both discontinued in 11 cases.<br>Only aspirin was discontinued in 1 cases.<br>Only thienopyridine was discontinued in 19 cases. |
| Low-dose aspirin + cilostazol (n=8) | Aspirin and cilostazol were both continued in 3 cases.<br>Aspirin and cilostazol were both discontinued in 1 case.<br>Only aspirin was discontinued in 1 case.<br>Only cilostazol was discontinued in 3 cases. |
| Low-dose aspirin + eicosapentaenoic acid (n=7) | Aspirin and cilostazol were both continued in 5 cases.<br>Aspirin and eicosapentaenoic acid were both discontinued in 1 case.<br>Only aspirin was discontinued in 1 case. |

| | |
|---|---|
| Low-dose aspirin + other antiplatelet agent (n=5) | Aspirin and other antiplatelet were both continued in 4 cases.<br>Only aspirin was discontinued in 1 cases. |
| Thienopyridine + any other antiplatelet agent (n=4) | Thienopyridines was discontinued and cilostazol was continued in 1 case.<br>Thienopyridines and cilostazol were both discontinued in 1 case.<br>Thienopyridine was switched to aspirin and eicosapentaenoic acid was continued in 1 cases.<br>Thienopyridine was switched to cilostazol and eicosapentaenoic acid was continued in 1 cases. |
| Any other combination (n=10) | Agents were both continued in 3 cases.<br>Agents were both discontinued in 4 cases.<br>Either one was discontinued in 3 cases. |
| TAPT (n=9) | |
| Low-dose aspirin + thienopyridine + cilostazol (n=1) | All agents were discontinued. |
| Low-dose aspirin + thienopyridine + eicosapentaenoic acid (n=3) | All agents were discontinued in 1 case.<br>Only thienopyridine was discontinued in 1 case.<br>All agents were continued in 1 case. |
| Low-dose aspirin + cilostazol + eicosapentaenoic acid (n=1) | Only cilostazol was discontinued. |
| Low-dose aspirin + cilostazol + other antiplatelet (n=3) | All agents were discontinued. |
| Thienopyridine + cilostazol + eicosapentaenoic acid (n=1) | Thienopyridine and eicosapentaenoic acid were discontinued and cilostazol was continued. |

**Note**. Thienopyridines included clopidogrel, ticlopidine, and prasugrel. Other antiplatelet agents included beraprost, limaprost, sarpogrelate, dilazep, and dipyridamole.

**Supplementary Table 2.** Characteristics of antiplatelet users and baseline-matched controls who were not using any antithrombotics (N = 952).

| | Antiplatelet users (n = 476) | Matched controls (n = 476) | *P*-value |
|---|---|---|---|
| Age (years) ≥70 | 330 (69.3) | 317 (66.6) | 0.37 |
| Men | 347 (72.9) | 336 (70.6) | 0.43 |
| BMI ≥25 | 181 (38.0) | 183 (38.5) | 0.89 |
| Current alcohol drinker | 255 (57.4) | 267 (57.1) | 0.91 |
| Current smoker | 71 (15.8) | 72 (15.4) | 0.87 |
| Comorbidity | | | |
| Diabetes mellitus | 167 (35.1) | 155 (32.6) | 0.41 |
| Hypertension | 368 (77.3) | 355 (74.6) | 0.32 |
| Dyslipidemia | 267 (56.1) | 265 (55.7) | 0.90 |
| Platelet count < $10 \times 10^4/\mu L$ | 8 (1.8) | 7 (1.8) | 0.99 |
| Concomitant NSAID use | 15 (3.2) | 13 (2.7) | 0.70 |
| Heparin bridging | 18 (3.8) | 0 | NA |
| Number of antiplatelet agents | | | |
| Monotherapy | 387 (81.3) | 0 | NA |
| DAPT | 80 (16.8) | 0 | NA |
| TAPT | 9 (1.9) | 0 | NA |
| Total number of polyps excised ≥ 3 | 153 (32.1) | 144 (30.3) | 0.53 |
| Size of largest polyp ≥ 10 mm | 141 (29.6) | 127 (26.7) | 0.31 |
| Adenocarcinoma | 47 (9.9) | 53 (11.1) | 0.53 |
| Location of polyps | | | 0.52 |

| | | | |
|---|---|---|---|
| Right side | 191 (40.1) | 176 (37.0) | |
| Right and left sides | 128 (26.9) | 128 (26.9) | |
| Left side | 157 (33.0) | 172 (36.1) | |

**Note**: Values in parentheses are percentages.

**Abbreviations**: BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; DAPT, dual antiplatelet therapy; TAPT, triple antiplatelet therapy; NA, not applicable.

**Supplementary Table 3.** Post-polypectomy bleeding risk by number and type of antiplatelet agents used compared with controls (N = 952).

| | | Univariate analysis | | Multivariate analysis (model 1) | | Multivariate analysis (model 2) | |
|---|---|---|---|---|---|---|---|
| | No. of patients with bleeding /All subjects | Crude odds ratio (95% CI) | *P* value | Age (≥ 70 years) and sex adjusted odds ratio (95% CI) | *P* value | Age (≥ 70 years), sex, polyp size (≥ 10 mm), and polyp location adjusted odds ratio (95% CI) | *P* value |
| Controls | 6/476 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Antiplatelet users | 16/476 | 2.7 (1.1-7.0) | 0.038 | 2.7 (1.1-7.1) | 0.037 | 2.6 (1.0-6.8) | 0.048 |
| Number of antiplatelets used | | | | | | | |
| Controls | 6/476 | 1 (referent) | | 1 (referent) | | 1 (referent) | |
| Monotherapy | 9/387 | 1.9 (0.7-5.3) | 0.241 | 1.9 (0.7-5.3) | 0.370 | 1.9 (0.7-5.5) | 0.310 |
| DAPT | 6/80 | 6.4 (1.8-16.6) | 0.002 | 6.7 (2.1-21.7) | 0.001 | 4.8 (1.4-15.8) | 0.011 |
| TAPT | 1/9 | 9.8 (1.1-91.0) | 0.045 | 10.9 (1.1-104.6) | 0.038 | 12.4 (1.2-123.2) | 0.033 |

**Note**. In risk analysis, we adjusted for age (≥ 70 years) and sex between controls and antiplatelet users in model 1, and we adjusted for age (≥ 70 years), sex, and polyp size (≥ 10 mm), polyp location (only right or left) and the presence of adenocarcinoma in model 2. Thienopyridines included clopidogrel, ticlopidine, and prasugrel. Other antiplatelet agents included beraprost, limaprost, sarpogrelate,

dilazep, and dipyridamole.

**Abbreviations**: CI, confidence interval; DAPT, dual antiplatelet therapy; TAPT, triple antiplatelet therapy.