

Cold Snare Polypectomy in Patients Taking Dual Antiplatelet Therapy: A Randomized Trial of Discontinuation of Thienopyridines

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INTRODUCTION: Cold snare polypectomy (CSP) is a safe and effective method for removing polyps ≤ 10 mm. The aim of this study was to compare the risk of clinically significant bleeding and thromboembolic events after CSP between stopping and continuing thienopyridines in patients taking dual antiplatelet therapy (DAPT).

METHODS: The study was a single-center, noninferiority, and randomized controlled study involving patients who received colonoscopy from October 2015 to October 2016. Patients receiving DAPT with polyps ≤ 10 mm were randomly assigned to either the DAPT group (patients continued DAPT) or the aspirin group (patients discontinued thienopyridines for 1 week). Primary outcome was clinically significant bleeding. Secondary outcomes included intraprocedural bleeding, nonsignificant hematochezia, and occurrence of thromboembolic events.

RESULTS: Forty-two patients with 104 eligible polyps were allocated to the DAPT group, and 45 patients with 101 eligible polyps were allocated to the aspirin group. Patient demographic characteristics including size, location, shape, and pathology of the removed polyps were similar in the 2 groups. Intraprocedural bleeding and nonsignificant hematochezia rates were also similar between the 2 groups (4.8% vs 2.2%, $P = 0.608$; 19.0% vs 8.9%, $P = 0.170$). No thromboembolic event occurred in either group. Only 1 patient (2.4%) in the DAPT group showed clinically significant bleeding. No significant bleeding was found in the aspirin group.

DISCUSSION: Clinically significant bleeding rate after CSP for polyps ≤ 10 mm in patients continuing to take DAPT was 2.4%. Therefore, CSP is a safe method for removing small polyps even in patients taking DAPT (ClinicalTrials.gov number, NCT02865824).

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INTRODUCTION

Colorectal cancer is the third most common cancer type in humans and the fourth most common cause of cancer death (1). Polypectomy during colonoscopy can remove precursor lesions that may progress to cancer. Postpolypectomy bleeding defined as bleeding after polypectomy during the examination or after the examination is the major adverse event of polypectomy and occurs in approximately 1% of patients (2). With growing prevalence of cardiovascular diseases, antiplatelet agents have been increasingly used as part of medical therapy. In a registry of more than 68,000 outpatients with established atherosclerosis or multiple risk factors for atherosclerosis, 70% were on aspirin monotherapy, while 13% were on dual antiplatelet therapy (DAPT)

(aspirin and a thienopyridine antiplatelet agent) (3). Patients who receive coronary artery stenting are generally treated with DAPT of aspirin and clopidogrel for 12 months. Recent data suggest that certain patients may benefit from an extension of DAPT up to 30 months after the stenting procedure (4). It has been estimated that more than 40% of adults in the United States will have at least 1 form of cardiovascular disease by 2,030 (5). Thus, the number of patients needing antiplatelet therapy and DAPT is expected to grow in the coming years.

Gastroenterologists commonly encounter adverse effects of antiplatelet therapy in the form of gastrointestinal bleeding. A 2-fold increase in the risk of major gastrointestinal bleeding has been seen with aspirin monotherapy relative to aspirin nonuser

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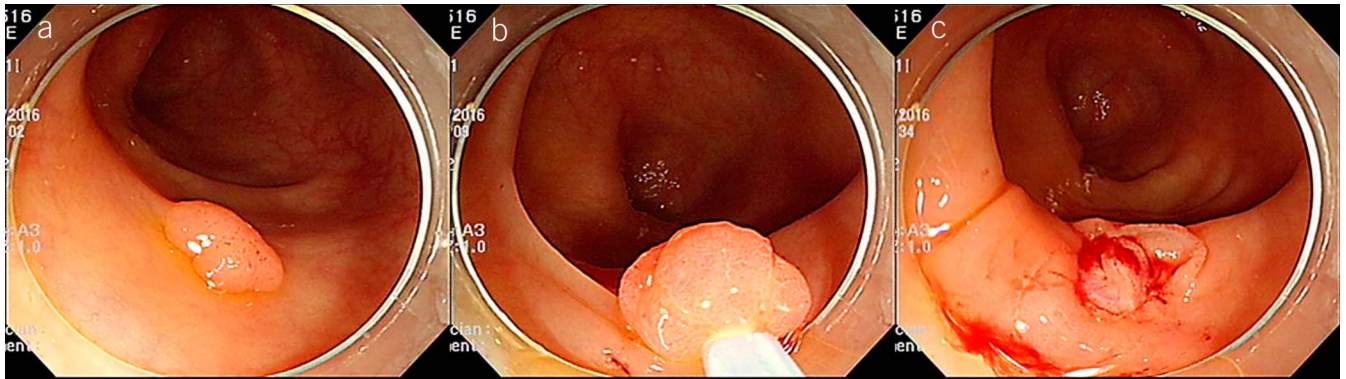


Figure 1. Cold snare polypectomy. (a) A sessile polyp was detected, (b) the polyp was ensnared by a disposable snare, and (c) polypectomy was performed without acute adverse event.

(6, 7). The risk of bleeding for DAPT ranges from 38% to a nearly 2-fold increase compared with aspirin alone (8–10).

Aspirin monotherapy has been found to be safe in colonoscopic polypectomy. Therefore, it has been recommended to be continued in patients receiving most endoscopic procedures (11). Controversy exists on the management of DAPT before colonoscopy and polypectomy. Current guidelines recommend discontinuation of thienopyridines 5–7 days and continuation of aspirin before colonoscopy and polypectomy in patients treated with DAPT (11, 12). However, these recommendations do not have concrete evidence.

Recently, cold snare polypectomy (CSP) has been introduced as a safe and effective measure to remove polyps ≤ 1 cm (13). It is also safe in patients receiving anticoagulants such as warfarin (14). Therefore, we hypothesize that CSP for small polyps would also be safe in patients receiving DAPT. The aim of this study was to compare the risk of clinically significant bleeding after CSP between stopping and continuing thienopyridines in patients taking DAPT.

METHODS

Study design

This study was approved by the institutional review board at the Catholic University of Korea and registered with ClinicalTrials.gov (NCT02865824). Written informed consent was obtained from each patient. The study concept, hypothesis, and design were investigator-initiated. All authors had access to the study data and reviewed and approved the final manuscript.

Study population

This study was a single-center, noninferiority, and randomized controlled study involving patients who received colonoscopy from October 2015 to October 2016. Patients receiving DAPT

were subjects for inclusion. Patients were included if they were older than 20 years and were scheduled to undergo screening, surveillance, or diagnostic colonoscopy. Small colorectal polyps up to 10 mm in diameter were removed by CSP. Polyps larger than 10 mm were not removed. Patients receiving triple antithrombotic therapy (i.e., DAPT and an oral anticoagulant) and patients receiving 3 antiplatelet agents were excluded. Patients with pregnancy, history of colorectal surgery, or American Society of Anesthesiologists class III and IV, with inflammatory bowel disease, polyposis syndrome, or inability to provide informed consent were also excluded.

Randomization

Patients were randomly assigned into 2 groups (DAPT or aspirin) at 1:1 ratio through a computerized random number table prepared by an investigator without clinical involvement in the trial. Allocation was concealed in a sealed opaque envelope and provided to the physician by a research assistant. For the DAPT group, patients continued aspirin and thienopyridines before and after colonoscopy. For the aspirin group, patients discontinued thienopyridines (i.e., clopidogrel, prasugrel, and ticagrelor) at 1 week before their colonoscopy. Patients were advised to continue their thienopyridines at the following day after the procedure. If a patient had 1 or more polyps, all eligible polyps were removed using the CSP method. The endoscopist was blinded to the information on whether the patient continued or discontinued thienopyridines.

Colonoscopy and polypectomy

All procedures were performed by 1 experienced endoscopist who had performed $>5,000$ colonoscopies. Total colonoscopies were prospectively performed using high-definition colonoscopies (F-H260AL; Olympus, Tokyo, Japan). Bowel preparation consisted of patients drinking a total of 4 L of polyethylene glycol solution before their procedures. All polyps found during colonoscopy were photographed, and their characteristics including size and anatomical location were documented. Polyps deemed neoplastic (vessels surrounding oval, tubular, or branched pits under observation by high-definition white light endoscopy and narrow-band imaging endoscopy) were subjected to polypectomy. Polyp size was defined by using biopsy forceps with open width. If the size of the polyp was eligible for the study (≤ 10 mm), polypectomy was performed. CSP was performed by using a disposable braided oval snare with 10-mm diameter (SD-210U-10; Olympus) under gentle suction to reduce colonic wall tension, while the tip of the endoscope was deflected toward the

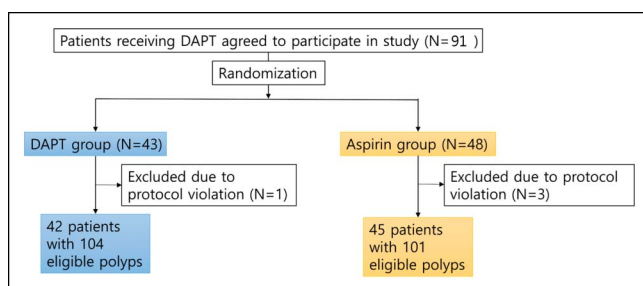


Figure 2. Flowchart of our study.

polyp base to ensnare 1–2 mm of normal mucosa around the polyp. Using a stopwatch, the time taken for polypectomy was measured from the emergence of endoscopic accessories (snare) from the colonoscope channel to the confirmation of tissue retrieval by an endoscopy nurse (Figure 1). After each procedure, the polypectomy site was observed for 60 seconds to confirm the presence of intraprocedural bleeding without any interventions. Hemoclips were applied when spurting or oozing persisted at the polypectomy site after 60 seconds. The patient returned 1 week later after each polypectomy to check hemoglobin level and be informed about their pathologic results. Patient was also assessed for postprocedural adverse events such as postpolypectomy bleeding or thromboembolic event. Clinically significant bleeding was defined as bleeding requiring endoscopic intervention within 2 weeks of endoscopic intervention. Bleeding that occurred without a decrease in hemoglobin and subsided naturally without endoscopic intervention was termed nonsignificant hematochezia. Composite outcomes were defined as any bleeding events occurring during or after the procedure.

Study outcomes

The primary study outcome was clinically significant bleeding. Secondary outcomes included rate of intraprocedural bleeding, nonsignificant hematochezia, and occurrence of thromboembolic events up to 1 month after the procedure. Thromboembolic event was defined as a formation in a blood vessel of a thrombus that broke loose and was carried by the blood stream to plug another vessel, e.g., lungs (pulmonary embolism), brain

(stroke), gastrointestinal tract (gastrointestinal infarction), kidneys (renal infarction), or leg (peripheral artery occlusive disease).

Sample size calculation and statistical analysis

A previous study showed major and minor bleeding events of 8%–9% after snare polypectomy (2). We assumed clinically significant bleeding rates of 8% for both groups. The sample size calculation was based on a noninferiority margin of 15%. A total of 40 subjects per group were required to detect noninferiority with at least 80% power and 1-sided type I error of 0.05.

The chi-squared test or Fisher exact test was used to compare categorical variables. *P* values of <0.05 were considered statistically significant. Continuous or discrete variables between the 2 groups were compared by using 2-sample *t* test. We also compared adverse events per polyps between 2 arms. Multivariate logistic regression analyses were performed for variables to assess factors affecting the composite outcome. All analyses were performed using SPSS for Windows version 21 (SPSS, Chicago, IL).

RESULTS

Ninety-one patients (54 men and 37 women) with mean age of 68.2 ± 8.5 years (range, 45–83 years) receiving DAPT agreed to participate in this study. After randomization, 43 patients were allocated to the DAPT group, while 48 were allocated to the aspirin group. We excluded 1 patient due to protocol violation in the DAPT group and 3 patients in the aspirin group. Finally, 42 patients with 104 eligible polyps (75.9% on clopidogrel, 21.2% on

Table 1. Baseline characteristics of patients in each group

Parameters	DAPT group (N = 42)	Aspirin group (N = 45)	Total (N = 87)	<i>P</i> value
Age (mean \pm SD, yr)	64.5 \pm 8.4	66.7 \pm 8.7	65.6 \pm 8.6	0.217
Male, n (%)	27 (64.3)	26 (57.8)	53 (60.9)	0.534
Height (mean \pm SD, cm)	163.2 \pm 8.5	161.6 \pm 8.8	162.4 \pm 8.6	0.394
Weight (mean \pm SD, kg)	66.8 \pm 11.1	64.9 \pm 10.6	65.8 \pm 10.8	0.418
Indication, n (%)				0.298
Screening	20 (47.6)	23 (51.1)	43 (49.4)	
Surveillance	4 (9.5)	6 (13.3)	10 (11.5)	
Functional disorders	9 (21.4)	10 (22.2)	19 (21.8)	
Anemia study	3 (7.1)	1 (2.2)	4 (4.6)	
Hematochezia	6 (14.3)	2 (4.4)	8 (9.2)	
For polypectomy	0	3 (6.7)	3 (3.4)	
Sedation, n (%)	38 (90.5)	43 (95.6)	81 (93.1)	0.423
Cecal intubation rate	42 (100)	45 (100)	87 (100)	>0.999
Withdrawal time (mean \pm SD, min)	9.5 \pm 3.8	8.9 \pm 4.5	9.2 \pm 4.2	0.518
Bowel preparation, n (%)				0.071
Excellent	12 (28.6)	6 (13.3)	18 (20.7)	
Good	18 (42.9)	27 (60.0)	45 (51.7)	
Fair	11 (26.2)	7 (15.6)	18 (20.7)	
Poor	1 (2.4)	5 (11.1)	6 (6.9)	

DAPT, dual antiplatelet agent.

Table 2. Characteristics of polyps in each group

Parameters	DAPT group (N = 104)	Aspirin group (N = 101)	Total (N = 205)	P value
Gross diameter (mean ± SD, mm)	5.4 ± 2.2	4.8 ± 2.4	5.1 ± 2.3	0.077
Gross size (mm; n [%])				0.299
≤5	66 (63.5)	71 (70.3)	137 (66.8)	
6–10	38 (36.5)	30 (29.7)	68 (33.2)	
Location, n (%)				0.543
Cecum/ascending colon	32 (30.8)	26 (25.7)	58 (28.3)	
Transverse colon	30 (28.8)	25 (24.8)	55 (26.8)	
Descending/sigmoid colon	38 (36.5)	47 (46.5)	85 (41.5)	
Rectum	4 (3.8)	3 (3.0)	7 (3.4)	
Shape, n (%)				>0.999
Flat	35 (33.7)	35 (34.7)	70 (34.1)	
Sessile	63 (60.6)	61 (60.4)	124 (60.5)	
Pedunculated	6 (5.8)	5 (5.0)	11 (5.4)	
Time for polypectomy (median [IQR], s)	40 (28–53)	35 (22–55)	38 (26–54)	0.217
Number of polyps per patient	2.5	2.2	2.4	
Polyp retrieval, n (%)	103 (99.0)	99 (98.0)	202 (98.5)	0.618
Resected specimen diameter (mean ± SD, mm)	5.8 ± 3.6	5.5 ± 4.0	5.7 ± 3.8	0.599
Size of resected specimen (mm; n [%])				0.217
≤5	60 (58.3)	66 (66.7)	126 (62.4)	
6–10	43 (41.7)	33 (33.3)	76 (37.6)	
Pathology, n (%)				0.857
Tubular adenoma	91 (87.5)	89 (88.1)	180 (87.8)	
Hyperplastic polyp	7 (6.7)	7 (6.9)	14 (6.8)	
Inflammation	5 (3.8)	3 (3.0)	8 (3.9)	
Unknown	1 (1.0)	2 (2.0)	3 (1.5)	

DAPT, dual antiplatelet agent; IQR, interquartile range.

ticagleror, and 2.9% on prasugrel) were allocated to the DAPT group, and 45 patients with 101 eligible polyps were allocated to the aspirin group (Figure 2).

Table 3. Comparison of bleeding in patients between the DAPT group and the aspirin group

Parameters	DAPT group (N = 42)	Aspirin group (N = 45)	Total (N = 87)	P value
Intraprocedural bleeding, n (%)	2 (4.8)	1 (2.2)	3 (3.4)	0.608
Nonsignificant hematochezia, n (%)	8 (19.0)	4 (8.9)	12 (13.8)	0.170
Clinically significant bleeding, n (%)	1 (2.4)	0	1 (1.1)	0.483
Perforation, n (%)	0	0	0	—
Thromboembolic event, n (%)	0	0	0	—

DAPT, dual antiplatelet agent.

Patients and polyp characteristics

Baseline characteristics and clinical features of patients enrolled in this study are shown in Table 1. There were no significant differences in indication of colonoscopy, rate of sedation, cecal intubation rate, mean withdrawal time, or bowel preparation between the DAPT group and the aspirin group. The DAPT group had more patients with coronary artery disease than the aspirin group (83% vs 49%, $P = 0.001$).

Characteristics of size, location, shape, and pathology of polyps between the 2 groups were similar to each other (Table 2). Adenoma was the most common pathology in both groups. The mean number of resected polyps per patient was 2.5 in the DAPT group and 2.2 in the aspirin group. Retrieval rates of polyps were similar between the 2 groups (99% [103/104] vs 98% [99/101], $P = 0.618$) (Table 2). There was no significant difference in time for polypectomy between the 2 groups (Table 2).

Postpolypectomy adverse events

Intraprocedural bleeding rate was similar between the 2 groups as shown in Tables 3 and 4 (DAPT group: 4.8% [2/42] vs aspirin group: 2.2% [1/45], $P = 0.608$). Endoscopic hemostasis with

Table 4. Per-polyp comparison of bleeding between the DAPT group and the aspirin group

Parameters	DAPT group (N = 104)	Aspirin group (N = 101)	Total (N = 205)	P value
Intraprocedural bleeding, n (%)	2 (1.9)	4 (4.0)	6 (2.9)	0.441
Nonsignificant hematochezia, n (%)	27 (26.0)	8 (7.9)	35 (17.1)	0.001
Clinically significant bleeding, n (%)	3 (2.9)	0	3 (1.5)	0.246
Composite outcomes, n (%)	29 (27.9)	12 (11.9)	41 (20.0)	0.005

DAPT, dual antiplatelet agent.

hemoclips was successful for all cases of intraprocedural bleeding. Nonsignificant hematochezia was seen in 19% (8/42) in the DAPT group and 8.9% (4/45) in the aspirin group ($P = 0.170$). Clinically significant bleeding requiring endoscopic intervention occurred in 2.4% (1/42) of patients in the DAPT group. It occurred within 2 days after polypectomy, and endoscopic hemostasis with hemoclips was successful in this case. In case of per-polyp comparison, there was a significant increase in nonsignificant hematochezia after polypectomy in the DAPT group compared with that in the aspirin group (26% [27/104] vs 7.9% [8/101], $P = 0.001$). Also, composite outcomes in the DAPT group were higher than in the aspirin group (27.9% [29/104] vs 11.9% [12/101], $P = 0.005$). However, per-polyp clinically significant bleeding was only seen in the DAPT group

(2.9% [3/104]). Neither perforation nor thromboembolic event was observed in either group during this study.

Predictor of composite outcomes

Based on univariate analysis, composite outcomes were significantly more frequent in patients who continued DAPT compared with that in patients who discontinued thienopyridine (Table 5). In multivariate analysis, the independent predictive factor for composite outcomes was larger tumors (≥ 6 mm) and the DAPT group (odds ratio [OR] 2.40, 95% confidence interval [CI] 1.17–4.91, $P = 0.016$, OR 2.54, 95% CI 1.20–5.40, $P = 0.015$, respectively).

DISCUSSION

American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy guidelines recommend temporary discontinuation of antithrombotics for colonoscopy before CSP (11, 12). Recent studies have shown that CSP is a very safe and effective method for removing polyps ≤ 1 cm, even in patients receiving anticoagulants (13, 14). This study hypothesized that CSP would be safe in patients receiving DAPT. Therefore, we compared the risk of clinically significant bleeding between patients who followed current guidelines and discontinued thienopyridine and those who did not discontinue DAPT before CSP. Clinically significant bleeding occurred in 2.4% (1/42) of patients in the DAPT group, which was not considerably different from results of previous reports (2, 13). No thromboembolic event was observed in either group during the study period. Therefore, colorectal polyps ≤ 10 mm in size can be removed by CSP without increasing the risk of significant bleeding, even in patients who are continuing DAPT.

Table 5. Univariate and multivariate analysis for predictors of composite outcome

Variable		Univariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% CI)	P value
Age					
<65 yr	15/63 (23.8%)	1 (reference)	0.365		
≥ 65 yr	26/142 (18.3%)	0.72 (0.35–1.48)			
Medication			0.005		0.015
Aspirin group	12/101 (11.9%)	1 (reference)		1 (reference)	
DAPT group	29/104 (27.9%)	2.87 (1.37–6.01)		2.54 (1.20–5.40)	
Tumor location			0.400		
Left colon ^a	16/92 (17.4%)	1 (reference)			
Right colon ^a	25/113 (22.1%)	1.35 (0.67–2.71)			
Tumor size			0.005		0.016
<6 mm	17/125 (13.6%)	1 (reference)		1 (reference)	
≥ 6 mm	24/80 (30.0%)	2.72 (1.35–5.48)		2.40 (1.17–4.91)	
Histology					
Nonadenoma	4/23 (17.4%)	1 (reference)	0.740		
Adenoma	37/182 (20.3%)	1.21 (0.39–3.78)			

CI, confidence interval; DAPT, dual antiplatelet agent; OR, odds ratio.

^aLeft colon: descending colon to rectum; right colon: cecum to transverse colon.

It was well known that aspirin monotherapy is safe in colonoscopic polypectomy (15–17). In a randomized controlled study, 220 high-risk patients undergoing noncardiac surgery were randomized to 2 groups: continuing aspirin or temporary replacement of aspirin by placebo (18). There was no significant difference in bleeding rate between the 2 groups, with a low risk of major cardiac events in the aspirin continuation group (18). On the other hand, there are conflicting results regarding delayed bleeding on uninterrupted clopidogrel therapy (19–23). One meta-analysis has assessed postpolypectomy bleeding in patients on continued clopidogrel therapy (574 patients vs 6,169 controls) (22). Delayed bleeding was observed in 15 (2.7%) of 565 patients who continued clopidogrel therapy and 37 (0.6%) of 6,158 controls. The pooled relative ratio for delayed bleeding on continued clopidogrel therapy was 4.66 (95% CI: 2.37–9.17, $P < 0.001$), suggesting an increased risk in delayed bleeding. Because these studies included patients with polyp size ≥ 10 mm and the proportion of patients on DAPT ranged from 54% to 88%, no conclusion could be drawn for DAPT.

Current guidelines recommend discontinuation of thienopyridines 5–7 days before polypectomy, but no definitive evidence from clinical trials or large observation studies support this practice (11). Although the incidence is low, stent thrombosis may occur in 2% of patients within 5 days of discontinuing clopidogrel (24).

To the best of our knowledge, this is the first randomized controlled trial that compares clinically significant bleeding risk between DAPT and aspirin without thienopyridine. Results of this study suggest that colorectal polyps ≤ 10 mm can be removed by CSP without increasing the risk of delayed bleeding even in patients who are continuing thienopyridines.

Interestingly, per-polyp nonsignificant hematochezia after polypectomy was different between the 2 groups (26% [27/104] vs 7.9% [8/101], $P = 0.001$). In addition, larger polyps and continuation of DAPT were independent risk factors for composite outcomes after CSP (OR 2.40, 95% CI 1.17–4.91, $P = 0.016$, OR 2.54, 95% CI 1.20–5.40, $P = 0.015$, respectively). Based on these results, a more meticulous observation might be required for patients continuing DAPT and with larger polyps. Although hematochezia occurred more often in the DAPT group, most of them subsided naturally without endoscopic hemostasis. Clinically significant bleeding was not different between the 2 groups.

Our study has few limitations. We originally assumed clinically significant bleeding rates of 8%. However, clinically significant bleeding rates were actually much lower in our study, and our small sample size may have led to type II errors. All the procedures were performed by 1 experienced endoscopist in a tertiary referral center and therefore do not reflect the daily endoscopic practice. Also, a small number of sample size may be a limitation of our study. A multicenter trial with a larger sample size is needed to confirm the safety of CSP while continuing thienopyridine.

Nevertheless, this is the first randomized study that compares clinically significant bleeding rates between patients with and without continuation of DAPT. All enrolled patients returned to our outpatient clinic at 1 week after CSP to assess bleeding which is a major strength of our study. This protocol diminishes unintended underestimation of clinically significant bleeding due to loss of follow-up. Moreover, the endoscopist was blinded to interruption of thienopyridines during procedure to minimize bias as much as possible.

In conclusion, results of our randomized study showed that clinically significant bleeding rate after CSP for polyps ≤ 10 mm in patients continuing to take DAPT was 2.4%. Therefore, CSP might be a safe and effective method for removing small polyps even in patients who are taking DAPT.

CONFLICTS OF INTEREST

Guarantor of the article: Joon Sung Kim, MD, PhD.

Specific author contributions: D.W.M. and J.S.K.: study conception, study design, data collection, statistical analysis, data interpretation, drafting of the article, and critical revision of the manuscript; J.-S.J., B.-W.K., and H.C.: critical revision of the manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Thienopyridine should be stopped 5–7 days before colonoscopy and polypectomy.

WHAT IS NEW HERE

- ✓ Thienopyridines can be continued without risk of postpolypectomy bleeding.

TRANSLATIONAL IMPACT

- ✓ Management of DAPT before colonoscopy and polypectomy.

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