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Prophylactic Endoscopic Clipping Does Not Prevent Delayed Postpolypectomy Bleeding in Routine Clinical Practice: A Propensity Score–Matched Cohort Study

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INTRODUCTION: **Delayed postpolypectomy bleeding (DPPB) is a relatively common adverse event. Evidence is conflicting on the efficacy of prophylactic clipping to prevent DPPB, and real-world effectiveness data are lacking. We aimed to determine the effectiveness of prophylactic clipping in preventing DPPB in a large screening-related cohort.**

METHODS: **We manually reviewed records of patients who underwent polypectomy from 2008 to 2014 at a screening facility. Endoscopist-, patient- and polyp-related data were collected. The primary outcome was DPPB within 30 days. All unplanned healthcare visits were reviewed; DPPB cases were adjudicated by committee using a criterion-based lexicon. Multivariable logistic regression was performed, yielding adjusted odds ratios (AORs) for the association between clipping and DPPB. Secondary analyses were performed on procedures where one polyp was removed, in addition to propensity score–matched and subgroup analyses.**

RESULTS: **In total, 8,366 colonoscopies involving polypectomy were analyzed, yielding 95 DPPB events. Prophylactic clipping was not associated with reduced DPPB (AOR 1.27; 0.83–1.96). These findings were similar in the single-polyp cohort (n = 3,369, AOR 1.07; 0.50–2.31). In patients with one proximal polyp ≥20 mm removed, there was a nonsignificant AOR with clipping of 0.55 (0.10–2.66). Clipping was not associated with a protective benefit in the propensity score–matched or other subgroup analyses.**

DISCUSSION: **In this large cohort study, prophylactic clipping was not associated with lower DPPB rates. Endoscopists should not routinely use prophylactic clipping in most patients. Additional effectiveness and cost-effectiveness studies are required in patients with proximal lesions ≥20 mm, in whom there may be a role for prophylactic clipping.**

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INTRODUCTION

Endoscopic polypectomy reduces the incidence of and mortality from colorectal cancer (CRC) (1–3), and is safer and less costly than surgery (4–6). However, basic polypectomy and advanced endoscopic resection techniques such as endoscopic mucosal resection (EMR) are associated with several well-described adverse events (7). Postpolypectomy bleeding is the most common of these and can occur during the index procedure (immediate postpolypectomy bleeding [IPB]) or present in a delayed fashion. IPB is usually trivial and more often considered a technical interference rather than a true adverse event, as long as the patient's clinical course is unaffected (8,9).

Delayed postpolypectomy bleeding (DPPB) is broadly defined as any bleeding occurring up to 30 days after the index procedure that results in an unplanned presentation to a healthcare facility (10–14). For basic hot snare polypectomy among screening cohorts where most polyps are <10 mm, the incidence of DPPB is approximately 1%–2% (7,11). However, in the presence of high-risk predictors, including larger lesion size or proximal colon location, DPPB rates for EMR can exceed 15% (9,10,12,15–19). In

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contrast to IPB, DPPB events are often clinically significant, leading to readmissions, changes in medical management and/or reinterventions. Thus, effective interventions to prevent DPPB are desirable.

Endoscopic clipping is a well-established modality for treating IPB during polypectomy (14,20). Endoscopists also frequently use clips prophylactically to prevent DPPB, despite conflicting evidence to support this practice (21,22). Meta-analyses have failed to demonstrate any benefit of prophylactic clipping in the prevention of DPPB for basic low-risk polypectomy, particularly for polyps under 10 mm in size (23–27). For larger non-pedunculated lesions, some randomized studies have demonstrated the efficacy of prophylactic clip closure of polypectomy defects (28–30), whereas others have not (31).

Although the efficacy of prophylactic clipping remains controversial, even if the intervention is protective among high-risk subgroups, real-world data on the effectiveness of prophylactic clipping are required but are presently lacking. Thus, we conducted a propensity score–matched analysis of a large CRC screening-based cohort to determine the effectiveness of prophylactic clipping in the prevention of DPPB.

METHODS

Study design and setting

In this cohort study, records of polypectomy cases performed at the Forzani & MacPhail Colon Cancer Screening Centre (CCSC) in Calgary, Alberta, Canada, between 2008 and 2014 were manually reviewed. The CCSC is dedicated to the provision of CRC screening-related colonoscopies, including average-risk patients, patients with positive fecal occult blood testing (guaiac or immunochemical), patients with a family history of CRC or advanced polyps, and those undergoing CRC surveillance after previous colonoscopy. All referrals for symptomatic patients are redirected. Approximately 17,500 colonoscopies are performed annually by a group of over 40 gastroenterologists and colorectal surgeons with varying years of clinical practice and colonoscopy experience. To be eligible for colonoscopy at the CCSC, a patient must be between the ages of 18 and 75 years without significant medical comorbidities and asymptomatic at the time of referral. Patients are allocated from a common queue so that a similar case mix by indication and patient characteristics is achieved across endoscopists. No institutional policy regarding prophylactic clipping existed at the CCSC during the study time frame. Given the single payer healthcare system, there was no financial impact on patients from the use of clips. Furthermore, there was no financial incentive to the endoscopist from clip usage. The study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB14-2314).

Study patients

All patients who had endoscopic removal of at least one polyp between 2008 and 2014 were eligible to be included in the study cohort, regardless of polyp histology. Colonoscopies where a polypectomy was performed were initially identified from the CCSC's endoscopy reporting program endoPRO (Pentax Medical, Montvale, NJ), where either endoscopists reported finding a polyp and/or the endoscopy nurse reported a polyp specimen. EndoPRO was also used to identify whether at least one clip was used during the procedure. Finally, the CCSC's pathology database, which is a structured abstract of the final pathology report, was used to classify polyps as ≥10 mm or <10 mm. We manually reviewed the records of all cases where at least one endoscopic clip was deployed. To optimize the similarities between clipped and unclipped cohorts, we then manually reviewed the records of all unclipped cases where at least one polyp ≥ 10 mm was removed. A random sample of cases involving unclipped polypectomy <10 mm was also reviewed to maximize the chance of matching for the propensity score analysis. To ensure that the cohort included cases where clips were used exclusively for DPPB prophylaxis, cases where any degree of IPB was noted, even if only "oozing" or "trivial bleeding," were excluded, whether or not clips were used. Any cases performed by endoscopists performing fewer than 50 procedures in the study period were excluded.

Demographic and clinical variables

Standardized data abstraction forms were used to collect all relevant endoscopist-, patient-, and polyp-level variables. Data elements were collated for each procedure after a thorough manual review of the endoscopist's procedure report, nursing charts, pathology requisition, and endoscopy images. Endoscopist-based variables included endoscopist specialty and endoscopist experience level when the index procedure was performed. Experience level was defined as the number of years spent performing colonoscopy during independent clinical practice and was determined using the public licensing registries and confirmed by direct inquiry. Patient-based variables included age, sex, relevant medications, procedural indication, and year of procedure.

Polyp-based variables included location, size, shape, use and type of submucosal injectate, device(s) used for polyp resection, presence or absence of cautery, presence or absence of piecemeal resection, use of any adjunctive hemostatic modalities (such as cauterization or injection of epinephrine), and presence or absence of prophylactic clipping. For polyp size, data values were populated using endoscopist and nursing notes at the time of the procedure, in which polyp sizes are reported as <10, 10–19, and ≥20 mm. For polyps ≥20 mm, free data entry of the endoscopist's estimate of polyp size was also performed. In polypectomies for which prophylactic clipping was used, variables included the number of clips fired, the number of clips successfully applied, the timing of the application (before polypectomy, after polypectomy, or both), and the presence or absence of closure of the entire defect (as opposed to partial closure only or targeted prophylactic clipping of a vessel). Variables were captured for a maximum of 15 polyps per procedure. In rare cases where a procedure contained details of more than 15 polypectomies, priority was given to (i) clipped polyps, (ii) polyps ≥10 mm, and (iii) all remaining polyps from proximal to distal location. Two reviewers were responsible for the manual data abstraction. Cohen kappa coefficient was calculated to determine their inter-rater agreement based on a sample of 50 cases, and following this, each reviewer extracted approximately equal numbers of cases independently.

Outcome measurements

The primary outcome was clinically significant DPPB, defined as any rectal bleeding resulting in a presentation to an emergency department or inpatient healthcare facility within 30 days of the index procedure that involved polypectomy.

The National Ambulatory Care Reporting System and Discharge Abstract Database are administrative databases used to capture all unplanned acute care visits across the province of

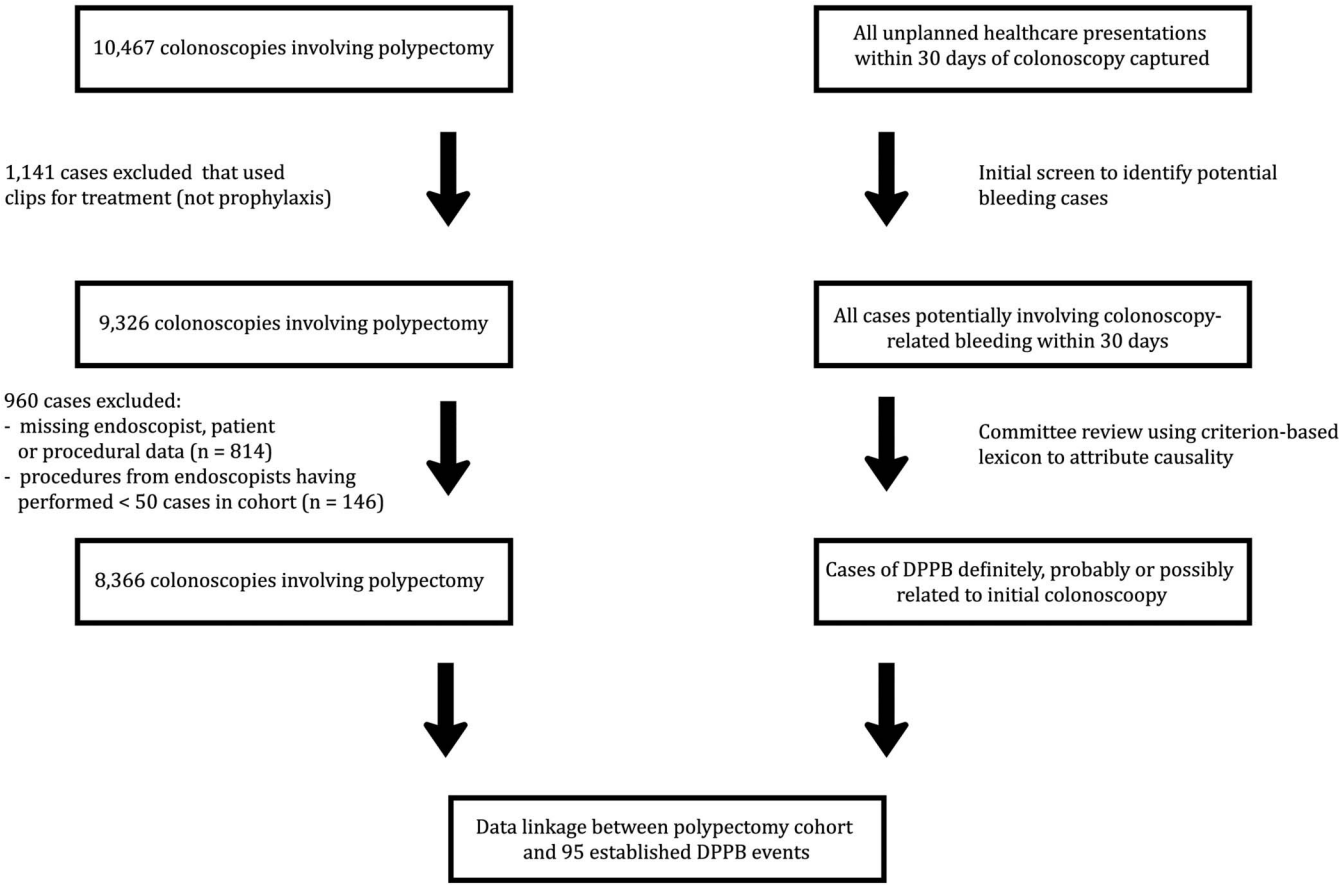

Figure 1. Study flow diagram outlining the process for determining the final polypectomy cohort and final set of DPPB events. DPPB, delayed post-polypectomy bleeding.

Alberta within 30 days of a colonoscopy performed at the CCSC, as previously described (11). Collectively, National Ambulatory Care Reporting System and Discharge Abstract Database capture all event records from hospitals, emergency departments, and urgent care centers across the province of Alberta, coded using the International Classification of Diseases v10. Linkage between CCSC colonoscopy records and event records was performed using a unique lifetime identifier common to all databases. Thus, all emergency department visits and inpatient stays that occurred from the day of the procedure up to 30 days after colonoscopy were captured. A manual medical record review of each of these healthcare encounters was then undertaken to exclude all nonbleeding events. After this, a committee of 6 gastroenterologists developed and validated a criteria-based lexicon for attribution of bleeding (32). Each remaining encounter was then reviewed using the lexicon to determine whether bleeding cases were unrelated, vs unlikely, possibly, probably, or definitely related to the index procedure (32). For the purposes of this study, only cases with definite, probable, or possible relatedness were included as delayed bleeding events.

Data analysis

For the primary analysis, we assumed an overall DPPB rate of 3% (given our overall healthy CRC screening-related cohort, but also taking into account a relatively large proportion of patients with polyps ≥10 mm). Assuming a 2-sided α of 0.05 and approximately 3,500 clipped cases, we estimated being capable of demonstrating odds ratios of 0.5 or less and 0.6 or less for clipping in preventing DPPB with 98.3% and 88.0% power, respectively. In anticipation of performing a propensity score–matched analysis, we aimed to review roughly 2 unclipped cases for each clipped case so that the likelihood of matching would be enhanced.

Demographic variables were compared using the Student *t* test for measured variables and χ^2 tests for categorical variables. 95% confidence intervals (CIs) were calculated. The primary outcome analysis was carried out in 3 stages. The first stage was a multivariable logistic regression with a binary indicator for the occurrence of a DPPB, adjusted for potential known confounding variables. Variables such as polypectomy technique, presence of injectate, and piecemeal resection were not included in the model as covariates, given that they are dependent on polyp size, shape, and location and are thus not truly independent.

The second stage of the analysis was restricted to only those procedures where a single polyp was removed per procedure; this was performed to ensure that DPPB could be directly attributed to the single clipped or unclipped lesion, eliminating the possibility that another (unclipped) lesion was responsible for the bleeding event in the clipped cohort. Subgroup analyses were also conducted in both the first and second stages for procedures with only removal of proximal polyps, those with polyps ≥10 mm, those with polyps ≥20 mm, those with pedunculated polyps, those with proximal polyps ≥20 mm, and those with pedunculated polyps ≥20 mm.

Table 1. **Demographics and procedural details of full, propensity-matched, and single-polyp cohorts**

	Full cohort (n = 8,366)			Propensity-matched cohort (n = 6,528)			Single-polyp cohort (n = 3,369)		
	Clipped (3,424)	Unclipped (4,942)	SMD	Clipped (3,264)	Unclipped (3,264)	SMD	Clipped (1,217)	Unclipped (2,152)	SMD
Sex (% male)	55.3 (1,894)	55.1 (2,721)	0.01	55.6 (1,816)	55.6 (1,816)	<0.01	47.7 (580)	46.3 (996)	0.03
Mean age, yr	59.4 (7.2)	58.6 (7.5)	0.11	59.5 (7.3)	59.3 (7.3)	0.02	58.3 (7.4)	57.6 (7.6)	0.10
Relevant peri-procedural medications									
Aspirin	5.5 (188)	7.6 (376)	0.09	5.6 (184)	7.2 (234)	0.06	5.3 (64)	5.9 (126)	0.03
Antiplatelets	1.1 (38)	0.4 (19)	0.08	1.2 (38)	0.4 (13)	0.09	1.4 (17)	0.3 (6)	0.12
Anticoagulants	0.3 (10)	0.1 (5)	0.04	0.3 (10)	0.1 (3)	0.05	0.1 (1)	0 (1)	0.01
Colonoscopy indication									
Average risk	42.4 (1,452)	44.4 (2,194)		42.8 (1,397)	46.3 (1,512)		44.9 (547)	45.8 (986)	
Family history	22.7 (776)	28.9 (1,429)		23.1 (754)	22.7 (742)		25.9 (315)	32.7 (704)	
FIT+	17.1 (587)	11.5 (570)	0.22	16.5 (539)	13.9 (453)	0.09	12.5 (152)	7.7 (166)	
<1 year repeat	8.3 (283)	5.6 (277)		8 (261)	7.3 (239)		8.6 (105)	5.3 (115)	0.24
1–3 year repeat	1.8 (60)	2.1 (106)		1.8 (58)	2.1 (68)		1.5 (18)	1.9 (40)	
>3 year repeat	5.5 (188)	5.0 (246)		5.5 (179)	5.4 (175)		4.8 (59)	4.5 (96)	
Other	2.3 (78)	2.4 (120)		2.3 (76)	2.3 (75)		1.7 (21)	2.1 (46)	
Endoscopist (% GI)	94.4 (3,232)	88.8 (4,389)	0.20	94.1 (3,073)	93.3 (3,044)	0.04	94.4 (1,149)	88.9 (1,914)	0.20
Endoscopist experience									
1–5 years	28.0 (958)	27.1 (1,341)		28.1 (916)	25.2 (822)	0.14	26.9 (327)	26.8 (578)	
6–10 years	29.3 (1,004)	21.8 (1,077)	0.19	29 (947)	25.2 (822)		31.1 (378)	20.6 (444)	0.26
11 or more years	42.7 (1,462)	51.1 (2,524)		42.9 (1,401)	49.6 (1,620)		42.1 (512)	52.5 (1,131)	
Mean no. of polyps	2.4 (1.5)	2.2 (1.3)	0.20	2.4 (1.5)	2.4 (1.4)	0.05	—	—	
Mean no. of clipped	1.1 (0.4)	0.0 (0.0)	—	1.1 (0.4)	0.0 (0.0)	—	1.0 (0.0)	0.0 (0.0)	—
Mean no. of clips applied per clipped polyp	1.8 (1.3)	0.0 (0.0)	—	1.7 (1.2)	0.0 (0.0)	—	1.6 (1.1)	0.0 (0.0)	—
At least 1 proximal polyp	64.7 (2,216)	47.2 (2,335)	0.36	63.7 (2,079)	58.9 (1,923)	0.10	48.6 (591)	30.2 (650)	0.38
Mean no. of proximal polyps	1.1 (1.1)	0.7 (1.0)	0.32	1 (1.1)	0.9 (1.0)	0.11	0.5 (0.5)	0.3 (0.5)	0.38
At least one polyp ≥10 mm	62.6 (2,144)	52.9 (2,616)	0.20	61.1 (1,993)	65 (2,121)	0.08	58.3 (710)	41.6 (895)	0.34
Mean no. of polyps ≥10 mm	0.8 (0.7)	0.6 (0.6)	0.24	0.7 (0.7)	0.7 (0.6)	0.00	0.6 (0.5)	0.4 (0.5)	0.34
At least one polyp ≥20 mm	19.6 (670)	7.8 (384)	0.35	16.4 (535)	11.2 (366)	0.15	18.6 (226)	8.7 (187)	0.29
Mean no. of polyps ≥20 mm	0.2 (0.4)	0.1 (0.3)	0.35	0.2 (0.4)	0.1 (0.3)	0.16	0.2 (0.4)	0.1 (0.3)	0.29
At least 1 proximal polyp ≥20 mm	7.0 (241)	3.5 (175)	0.16	5.2 (170)	5.3 (173)	0.00	7.2 (88)	4.3 (92)	0.13
Mean no. of proximal polyps ≥20 mm	0.1 (0.3)	0.0 (0.2)	0.16	0.1 (0.2)	0.1 (0.2)	0.00	0.1 (0.3)	0.0 (0.2)	0.13
At least one pedunculated polyp	33.8 (1,158)	27.3 (1,347)	0.14	33 (1,076)	31.1 (1,016)	0.04	29.4 (358)	21.5 (463)	0.18

Table 1. (*continued*)

	Full cohort (n = 8,366)			Propensity-matched cohort (n = 6,528)			Single-polyp cohort (n = 3,369)		
	Clipped (3,424)	Unclipped (4,942)	SMD	Clipped (3,264)	Unclipped (3,264)	SMD	Clipped (1,217)	Unclipped (2,152)	SMD
Mean no. of pedunculated polyps	0.4 (0.7)	0.3 (0.6)	0.15	0.4 (0.7)	0.4 (0.6)	0.05	0.3 (0.5)	0.2 (0.4)	0.18
At least one polyp removed via hot snare	97.4 (3,335)	86.2 (4,260)	0.42	97.3 (3,175)	90.8 (2,963)	0.28	95.6 (1,164)	76.7 (1,650)	0.57
Mean no. of polyps removed via hot snare	2.1 (1.4)	1.7 (1.3)	0.29	2.1 (1.4)	1.9 (1.4)	0.14	1.0 (0.2)	0.8 (0.4)	0.57
At least one polyp removed piecemeal	24.9 (853)	14.6 (721)	0.26	23.4 (765)	19.1 (624)	0.11	22.4 (272)	13.4 (289)	0.23
Mean no. of polyps removed piecemeal	0.3 (0.5)	0.2 (0.4)	0.26	0.3 (0.5)	0.2 (0.4)	0.11	0.2 (0.4)	0.1 (0.3)	0.23
At least one polyp raised	46.1 (1,579)	15.7 (775)	0.70	45.3 (1,478)	20.7 (674)	0.54	46.8 (570)	14.8 (318)	0.74
Mean no. of polyps raised	0.5 (0.7)	0.2 (0.4)	0.64	0.5 (0.7)	0.2 (0.5)	0.50	0.5 (0.5)	0.1 (0.4)	0.74
Delayed bleeding event	1.5 (50)	0.9 (45)	0.05	1.3 (44)	1.1 (35)	0.03	1.2 (14)	0.7 (16)	0.04

Proximal polyp defined as polyp at or proximal to the hepatic flexure; raised polyps raised with one or more of saline, methylene blue or epinephrine.
FIT, fecal immunohistochemical testing; GI, gastroenterologist; and SMD, standard mean difference.

To further control for known confounders (including confounding by indication), propensity scores were then created for each procedure in the cohort. The propensity scores were computed from clinically relevant predictors of bleeding including sex, age, and polyp number and characteristics. Propensity score matching was then conducted to match procedures involving clipping and not involving clipping in a 1:1 ratio. Caliper matching without replacement was performed. The caliper size of the propensity matching was determined as a 0.25 factor of the propensity score SD (33). The third stage of the analysis was thus a propensity-matched analysis for all procedures using conditional logistic regression to account for correlation between matched pairs. Balance of covariates after matching was assessed using standardized mean differences (SMDs), as is standard for studies using propensity-matching methods. Any covariates whose SMD was greater than 10% were then adjusted for in the final propensity-matched model. All statistical analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Propensity score matching was performed using the *Matchlt* package in R (34).

RESULTS

We manually reviewed a total of 10,467 colonoscopies involving at least one polypectomy between January 1, 2008 and December 31, 2014. After applying our exclusion criteria, a total of 8,366 colonoscopies involving polypectomy were included in the final analysis, performed by 47 endoscopists. A study flow diagram is shown in Figure 1. Three thousand four hundred twenty-four of these procedures involved one or more clipped polyp(s), and 4,942 had no polyps clipped. Those in the clipped cohort had a higher mean number of polyps per procedure, were more likely to have at least one proximal polyp, were more likely to have a polyp ≥20 mm, and were more likely to have a pedunculated polyp compared with the unclipped cohort (Table 1). These trends were similar for the analysis of procedures in which only one polyp was removed per procedure.

A total of 96 delayed bleeding events were initially captured for the study cohort, following manual medical record reviews of all unplanned healthcare events within 30 days of the index colonoscopy. After a detailed committee-based review of these events and application of a criterion-based lexicon, 95 were deemed to be definitely, probably, or possibly related to the index procedure (Figure 1), with one case being excluded from the analysis because of being deemed unlikely to be related to the index procedure. This patient had mild rectal bleeding with a normal hemoglobin count 19 days after the index procedure, during which 8 low-risk subcentimeter polyps were removed. No follow-up colonoscopy was performed, and the patient was discharged home from the emergency department. The total DPPB event rate was 1.1%. There were 50 DPPB events in the clipped group and 45 DPPB events in the unclipped group. After adjusting for clinically relevant covariates, the adjusted odds ratio (AOR) of DPPB between the clipped and unclipped groups was not statistically significant, at 1.27 (95% CI, 0.83–1.96). There was no evidence of effect modification based on the polyp size after testing for interactions in the multivariable logistic regression model. The overall results from unmatched logistic regression of the entire study cohort are shown in Table 2.

Table 2. Odds ratios of delayed bleeding from the multivariable logistic regression models

	Full cohort (n = 8,366)		Single-polyp cohort (n = 3,369)	
	AOR of DPPB (95% CI)	*P* value	AOR of DPPB (95% CI)	*P* value
Male sex (relative to female sex)	1.60 (1.04–2.51)	0.04[a]	1.28 (0.61–2.71)	0.51
Age (per additional year)	1.01 (0.98–1.04)	0.47	0.99 (0.94–1.04)	0.70
Total no. of polyps (per additional polyp)	0.97 (0.83–1.13)	0.73	—	—
Presence of antiplatelet or anticoagulant medications	0.97 (0.40–1.99)	0.94	1.19 (0.19–4.29)	0.82
Surgeon performing polypectomy (with gastroenterologist as reference)	1.02 (0.45–2.01)	0.96	1.90 (0.54–5.16)	0.26
At least 1 proximal polyp	2.91 (1.76–4.99)	<0.01[a]	5.88 (2.31–17.52)	<0.01[a]
At least 1 polyp ≥20 mm	1.68 (0.98–2.75)	0.05	3.07 (1.34–6.63)	<0.01[a]
At least 1 pedunculated polyp	1.00 (0.61–1.58)	0.99	0.89 (0.24–2.65)	0.85
Prophylactic clipping employed (versus no clipping)	1.27 (0.83–1.96)	0.26	1.07 (0.50–2.31)	0.85

Proximal polyp defined as polyp at or proximal to the hepatic flexure.
AOR, adjusted odds ratio; CI, confidence intervals; DPPB, delayed postpolypectomy bleeding.
[a]Statistically significant.

A separate analysis was performed on procedures where only one polyp was removed. After adjusting for covariates, the odds ratio of DPPB between the clipped and unclipped groups was 1.07 (95% CI, 0.50–2.31). Table 2 shows the unmatched logistic regression results for the subset of procedures where only one polyp was removed.

Analyses were also performed on clinically relevant subgroups to determine whether there was any protective effect of prophylactic clipping (Table 3). No protective effect of clipping was seen in any subgroup analyzed. However, the point estimates for AOR of DPPB after clipping were less than 1 for polyps ≥20 mm and for proximal polyps ≥20 mm in the single-polyp cohort (AORs 0.64 [0.14–2.79] and 0.55 [0.10–2.66] respectively). These failed to reach statistical significance, given the limited power for this subgroup analysis.

After 1:1 propensity score matching, there were 3,264 matched pairs of clipped and unclipped procedures (6,528 total procedures). This matching was successful in achieving a greater balance across covariates, as evidenced by the SMDs in Table 1. After removing any covariates whose SMDs were less than 10%, the AOR of DPPB between the clipped and unclipped groups was 1.20 (95% CI, 0.73–1.97). Table 4 shows the propensity-matched conditional logistic regression results for all procedures.

DISCUSSION

We demonstrated in this large-scale propensity score–matched cohort study that prophylactic endoscopic clipping is not associated with decreased DPPB rates after polypectomy. Prophylactic clipping was not associated with a protective benefit against DPPB in the overall cohort, nor in any of the subgroups analyzed, either by traditional logistic regression or propensity score matching. There were 95 delayed bleeding events in our cohort, more than any other study specifically examining DPPB outcomes.

Several smaller studies have evaluated the effect of prophylactic clipping for polyps of all sizes (35–42), with each failing to show a protective effect of clipping on delayed bleeding, especially among lesions <20 mm. Retrospective study designs, lack of clear outcome definitions, and, in the case of randomized trials, small sample sizes are among the limitations associated with these previous studies. Although our study was a historical cohort, we used a variety of approaches to address confounding, with all approaches showing consistent findings in over 8,300 procedures. In our overall cohort, the delayed bleeding rate was 1.1%. Although our overall DPPB rate falls within those reported in the literature (7,11), it was lower than anticipated, given our generally healthy screening-related cohort. Under these real-world clinical practice terms, the bleeding rates associated with prophylactic clipping were not lower than in cases without clipping. Thus, we believe that this new evidence adds to the existing body of literature, which together with our study indicates that there is unlikely to be any benefit associated with the routine use of clips to prevent DPPB in patients undergoing resection of polyps <20 mm.

Although pooled data from randomized trials (25) together with this large propensity score–matched cohort study suggest no benefit of routine prophylactic clipping in preventing DPPB among polyps <20 mm, there may yet be a role for clipping larger resection defects. A recent randomized controlled trial (RCT) demonstrated a statistically significant benefit of clipping polyps ≥20 mm, with the biggest benefit observed among proximal lesions (28). A second recent randomized trial, however, showed no protective effect of clipping polyps ≥10 mm or within subgroup analyses of polyps ≥20 mm (31). Among procedures with one or more proximal polyp(s) ≥20 mm removed, the DPPB rate in our study was 3.4%, which is significantly lower than that reported in RCTs. This demonstrates important differences between our healthy screening-related cohort and more comorbid populations undergoing dedicated complex polypectomy or EMR. We contend that our cohort is more representative of routine polypectomy practice, wherein prophylactic clipping is commonly considered by colonoscopy practitioners. Despite reviewing over 10,000 colonoscopies, our study was ultimately underpowered to demonstrate a difference in DPPB in procedures with a single proximal polyp ≥20 mm, although we did observe an odds ratio of 0.55 (95% CI, 0.10–2.66). Although entirely statistically nonsignificant with

Table 3. Subgroup analyses—odds ratios of delayed bleeding for clipping, vs no clipping, from the multivariable logistic regression models

	Full cohort (n = 8,366)			Single-polyp cohort (n = 3,369)		
	Procedures in subgroup, (n clipped, n unclipped)	AOR of DPPB, (95% CI)	*P* value	Procedures in subgroup, (n clipped, n unclipped)	AOR of DPPB (95% CI)	*P* value
At least one proximal polyp	4,551, (2,216, 2,335)	1.14 (0.71–1.85)	0.58	1,306, (614, 692)	0.84 (0.36–2.00)	0.69
At least one polyp ≥10 mm	4,760, (2,144, 2,616)	1.45 (0.91–2.32)	0.12	1,605, (710, 895)	1.20 (0.50–2.92)	0.68
At least one polyp ≥20 mm	1,054, (670, 384)	1.50 (0.56–4.31)	0.43	413, (226, 187)	0.64 (0.14–2.79)	0.55
At least one proximal polyp ≥20 mm	416, (241, 175)	1.22 (0.37–4.30)	0.74	180, (88, 92)	0.55 (0.10–2.66)	0.46

Proximal polyp defined as polyp at or proximal to the hepatic flexure.
AOR, adjusted odds ratio; CI, confidence intervals; DPPB, delayed postpolypectomy bleeding.

a wide CI, this point estimate was nevertheless below 1.0 in a direction indicating a lower odds of bleeding, and thus quite different than the odds ratios seen for other subgroups. Ultimately, we would have had to capture over 1,400 procedures with proximal polyps ≥20 mm in our study to show a statistically significant protective benefit of clipping.

Aside from different patient populations, the conditions of a RCT also differ from those in a real-world cohort. In our study, 47 endoscopists with variable training backgrounds and experience performed polypectomy as compared to the clinical trials where the procedures were completed by a smaller number of experts in the field. It is likely that "real-world" clipping techniques are highly variable, which may affect outcomes. General endoscopists may not have the technical skillset to close larger defects. This is relevant because complete defect closure was recently shown to be important for the efficacy of clips in reducing the risk of DPPB among polyps ≥20 mm; even among a group of expert endoscopists, this was not possible in 43% of cases (30). Furthermore, nonspecialized endoscopists may be less likely to perform effective targeted therapy of an at-risk vessel (43).

The overwhelming majority of patients undergoing polypectomy never develop DPPB. Furthermore, of those who present with delayed bleeding, over 50% can be conservatively managed without any intervention (44). Those who go on to require reintervention generally respond well to endoscopic therapy, with only a minority ever requiring angiography or surgery (19,44). Thus, it may be more efficient to apply widespread efforts towards optimizing periendoscopic conditions including antiplatelet/anticoagulant management and application of evidence-based polypectomy techniques to reduce the risk of DPPB while dealing with relatively rare and treatable bleeding events when they present. The corresponding cost effectiveness of prophylactic clipping in this context should be formally determined. However, the combined results of previous RCTs and the observational findings that we report here suggest that an economic evaluation would reveal clipping to be an entirely nonviable strategy economically, with increased costs without improvement in outcomes. Indeed, earlier economic analyses have made the conclusion that prophylactic clipping in moderate-high risk patients is not justified (45–47).

Table 4. Odds ratios of delayed bleeding from the propensity score–matched conditional logistic regression model

	Full cohort (n = 6,532)	
	AOR for DPPB[a] (95% CI)	*P* value
At least 1 proximal polyp	3.64 (1.39–9.53)	<0.01[a]
At least 1 polyp ≥ 20 mm	4.33 (1.01–18.55)	0.05[a]
Prophylactic clipping employed (versus no clipping)	1.20 (0.73–1.97)	0.46

Proximal polyp defined as polyp at or proximal to the hepatic flexure.
AOR, adjusted odds ratio; CI, confidence intervals; DPPB, delayed postpolypectomy bleeding.
[a]Statistically significant.

Our study has several strengths. We manually reviewed over 10,000 cases involving polypectomy, resulting in the largest cohort assembled to study the effect of clipping on DPPB. The manual nature of our review ensured the collection of all clinically relevant variables, and the inter-rater agreement was high between data abstracters. The criteria for inclusion in the final analysis were rigorous, whereby any procedure with borderline or trivial intraprocedural bleeding was excluded, thus ensuring a robust and unbiased cohort. We also used rigorous methodology to review each event by committee, ensuring at least a possible, probable or definite relatedness of the delayed bleeding to the initial procedure. Finally, a propensity score–matched analysis was used to achieve a balance of known potential confounders between clipped and unclipped groups before assessing for bleeding.

Some important limitations to the study also need to be acknowledged. Despite detailed manual review of each procedure in addition to committee-based consensus for each postcolonoscopy bleeding event, it can be difficult to attribute causality of DPPB to an initial polypectomy unless a follow-up colonoscopy is performed confirming a site of recent or active bleeding. This issue is compounded in cases where more than one polyp was removed, with individual sites clipped or left unclipped, a problem also present within RCTs. To address this issue, we performed subgroup analyses of procedures where only one polyp was removed, and the results from these analyses were no different than our overall results. In an effort to obtain a pure cohort of prophylactic clipping cases, we elected to exclude all cases of IPB, even if bleeding was trivial. However, IPB is an established predictor of DPPB (9,48), and thus, our conservative approach lowered the rate of DPPB observed in our cohort. The observed DPPB rate in our study was also lower than anticipated because of the underestimation of the healthy cohort effect. In addition, given our generally healthy study cohort, meaningful conclusions regarding DPPB risk in patients on antiplatelet or anticoagulant medications

could not be reached, in contrast to other recent studies (31). Furthermore, our study period predates the widespread use of cold snare polypectomy (CSP), and therefore, data on CSP are limited from this cohort. However, given that CSP drastically reduces the rates of DPPB (49–51), we feel even more strongly that routine clipping should not be used in today's practice environment. The fact that our study was single center may also be seen as a limitation, but data from 47 endoscopists with various backgrounds were available during the study period. Finally, although propensity score matching attempts to reduce bias from confounding, it is still incapable of controlling for unknown confounders.

In conclusion, routine prophylactic clipping during polypectomy of lesions <20 mm is not associated with a reduced rate of DPPB, based on the results from a very large real-world screening-related cohort involving 47 accredited colonoscopists with various backgrounds and experience. Our study should alert all practitioners of colonoscopy and polypectomy to the probable ineffectiveness of this costly practice, in an attempt to preserve valuable health resources.

CONFLICTS OF INTEREST

Guarantor of the article: Steven J. Heitman, MD, MSc.

Specific author contributions: N.F., R.J.H., L.C.H., W.A.G., M.J.B., S.J.H.: conception and design. All authors: analysis and interpretation of the data. N.F.: drafting of the article. All authors: critical revision of the article for important intellectual content: all authors. All authors: final approval of the article.

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Study Highlights

WHAT IS KNOWN

- ✓ Routine polypectomy can result in DPPB.
- ✓ Randomized controlled trials demonstrate a lack of efficacy of prophylactic endoscopic clipping for prevention of DPPB after routine polypectomy.
- ✓ Despite a lack of evidence showing benefit, many endoscopists use prophylactic clipping during low-risk polypectomy to prevent DPPB.

WHAT IS NEW HERE

- ✓ The overall DPPB rate in a healthy cohort of over 8,300 screening-related colonoscopies involving polypectomy was 1.1%.
- ✓ In procedures where one or more proximal polyp ≥20 mm was removed, the DPPB rate was 3.4%, which is lower than previous randomized studies.
- ✓ Analysis of a large real-world healthy cohort undergoing screening-related colonoscopies with polypectomy by a diverse group of endoscopists shows no benefit of prophylactic clipping in preventing DPPB in all-comers or in any clinically relevant subgroup.
- ✓ Although prophylactic clipping with a complete defect closure of proximal lesions ≥20 mm has been shown to be efficacious, it is unclear whether meaningful reductions in DPPB can be achieved in routine practice.

REFERENCES

1. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525–32.
2. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–105.
3. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: A multicentre randomised controlled trial. Lancet 2010;375:1624–33.
4. Peery AF, Shaheen NJ, Cools KS, et al. Morbidity and mortality after surgery for nonmalignant colorectal polyps. Gastrointest Endosc 2018;87:243–50.e2.
5. Hassan C, Repici A, Sharma P, et al. Efficacy and safety of endoscopic resection of large colorectal polyps: A systematic review and meta-analysis. Gut 2016;65:806–20.
6. Jayanna M, Burgess NG, Singh R, et al. Cost analysis of endoscopic mucosal resection vs surgery for large laterally spreading colorectal lesions. Clin Gastroenterol Hepatol 2016;14:271–8.
7. Rabeneck L, Paszat LF, Hilsden RJ, et al. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. Gastroenterology 2008;135:1899–906, 1906.e1.
8. Heitman SJ, Tate DJ, Bourke MJ. Optimizing resection of large colorectal polyps. Curr Treat Options Gastroenterol 2017;15:213–29.
9. Burgess NG, Metz AJ, Williams SJ, et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014;12:651–61.e1-3.
10. Liaquat H, Rohn E, Rex DK. Prophylactic clip closure reduced the risk of delayed postpolypectomy hemorrhage: Experience in 277 clipped large sessile or flat colorectal lesions and 247 control lesions. Gastrointest Endosc 2013;77:401–7.
11. Hilsden RJ, Dube C, Heitman SJ, et al. The association of colonoscopy quality indicators with the detection of screen-relevant lesions, adverse events, and postcolonoscopy cancers in an asymptomatic Canadian colorectal cancer screening population. Gastrointest Endosc 2015;82:887–94.
12. Bahin FF, Rasouli KN, Byth K, et al. Prediction of clinically significant bleeding following wide-field endoscopic resection of large sessile and laterally spreading colorectal lesions: A clinical risk score. Am J Gastroenterol 2016;111:1115–22.
13. Metz AJ, Bourke MJ, Moss A, et al. Factors that predict bleeding following endoscopic mucosal resection of large colonic lesions. Endoscopy 2011;43:506–11.
14. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017;49:270–97.
15. Buchner AM, Guarner-Argente C, Ginsberg GG. Outcomes of EMR of defiant colorectal lesions directed to an endoscopy referral center. Gastrointest Endosc 2012;76:255–63.
16. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 2011;140:1908–18.
17. Albeniz E, Fraile M, Ibanez B, et al. A scoring system to determine risk of delayed bleeding after endoscopic mucosal resection of large colorectal lesions. Clin Gastroenterol Hepatol 2016;14:1140–7.
18. Buddingh KT, Herngreen T, Haringsma J, et al. Location in the right hemi-colon is an independent risk factor for delayed post-polypectomy hemorrhage: A multi-center case-control study. Am J Gastroenterol 2011;106:1119–24.
19. Sawhney MS, Salfiti N, Nelson DB, et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008;40:115–9.
20. Anastassiades CP, Baron TH, Wong Kee Song LM. Endoscopic clipping for the management of gastrointestinal bleeding. Nat Clin Pract Gastroenterol Hepatol 2008;5:559–68.
21. Nelson M, Komanduri S, Nimmagadda K, et al. Endoscopic clips are frequently used for ineffective indications after routine ambulatory colonoscopy. Gastrointest Endosc 2018;87:AB372–3.
22. Forbes N, Hilsden RJ, Kaplan GG, et al. Practice patterns and predictors of prophylactic endoscopic clip usage during polypectomy. Endosc Int Open 2019;7:E1051–60.
23. Park CH, Jung YS, Nam E, et al. Comparison of efficacy of prophylactic endoscopic therapies for postpolypectomy bleeding in the colorectum: A systematic review and network meta-analysis. Am J Gastroenterol 2016;14:1140–7.

24. Boumitri C, Mir FA, Ashraf I, et al. Prophylactic clipping and post-polypectomy bleeding: A meta-analysis and systematic review. Ann Gastroenterol 2016;29:502–8.
25. Forbes N, Frehlich L, James M, et al. Routine prophylactic endoscopic clipping is not efficacious in the prevention of delayed post-polypectomy bleeding: A systematic review and meta-analysis of randomized controlled trials. J Can Assoc Gastroenterol 2019;2:105–17.
26. Nishizawa T, Suzuki H, Goto O, et al. Effect of prophylactic clipping in colorectal endoscopic resection: A meta-analysis of randomized controlled studies. United Eur Gastroent 2017;5:859–67.
27. Mangira D, Ket SN, Majeed A, et al. Postpolypectomy prophylactic clip closure for the prevention of delayed postpolypectomy bleeding: A systematic review. JGH Open 2018;2:105–10.
28. Pohl H, Grimm IS, Moyer MT, et al. Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology 2019;157:977–84.
29. Zhang QS, Han B, Xu JH, et al. Clip closure of defect after endoscopic resection in patients with larger colorectal tumors decreased the adverse events. Gastrointest Endosc 2015;82:904–9.
30. Albéniz E, Álvarez MA, Espinós JC, et al. Clip closure after resection of large colorectal lesions with Substantial risk of bleeding. Gastroenterol 2019;157:1213–21.
31. Feagins LA, Smith AD, Kim D, et al. Efficacy of prophylactic hemoclips in prevention of delayed post-polypectomy bleeding in patients with large colonic polyps. Gastroenterology 2019;157:967–76.
32. Maxwell CM, Rostom A, Dube C, et al. Development of a definition and rules for causal attribution of post-colonoscopy bleeding (PCB). J Can Assoc Gastroenterol 2019;S2:59–60.
33. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med 2014;33:1057–69.
34. Ho D, Imai K, King G, et al. MatchIt: Nonparametric preprocessing for parametric causal inference. J Stat Softw 2011;42:1–28.
35. Fukata M, Kijima H, Sanjo A, et al. Prophylactic clipping may not eliminate delayed hemorrhage in colonoscopic polypectomies. Jikeikai Med J 2002;39:133–42.
36. Shioji K, Suzuki Y, Kobayashi M, et al. Prophylactic clip application does not decrease delayed bleeding after colonoscopic polypectomy. Gastrointest Endosc 2003;57:691–4.
37. Feagins LA, Nguyen AD, Iqbal R, et al. The prophylactic placement of hemoclips to prevent delayed post-polypectomy bleeding: An unnecessary practice? A case control study. Dig Dis Sci 2014;59:823–8.
38. Dokoshi T, Fujiya M, Tanaka K, et al. A randomized study on the effectiveness of prophylactic clipping during endoscopic resection of colon polyps for the prevention of delayed bleeding. Biomed Res Int 2015; 2015:490272.
39. Matsumoto M, Kato M, Oba K, et al. Multicenter randomized controlled study to assess the effect of prophylactic clipping on post-polypectomy delayed bleeding. Dig Endosc 2016;28:570–6.
40. Quintanilla E, Castro JL, Rabago LR, et al. Is the use of prophylactic hemoclips in the endoscopic resection of large pedunculated polyps useful? A prospective and randomized study. J Interv Gastroenterol 2012;2:183–8.
41. Sobrino-Faya M, Martinez S, Gomez Balado M, et al. Clips for the prevention and treatment of postpolypectomy bleeding (hemoclips in polypectomy). Rev Esp Enferm Dig 2002;94:457–62.
42. Inoue T, Ishihara R, Nishida T, et al. Prophylactic clipping does not decrease post-polypectomy bleeding for colon polyps: A multicenter, open labelled randomized controlled trial. Gastrointest Endosc 2018;87:AB97.
43. Jensen DM, Jutabha R, Sul J, et al. A targetted approach to risk Stratification and prevention of delayed post-polypectomy hemorrhage in high risk patients after removal of benign colon polyps. Gastrointest Endosc 2019;89:AB121.
44. Burgess NG, Williams SJ, Hourigan LF, et al. A management algorithm based on delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014;12: 1525–33.
45. Bahin FF, Rasouli KN, Williams SJ, et al. Prophylactic clipping for the prevention of bleeding following wide-field endoscopic mucosal resection of laterally spreading colorectal lesions: An economic modeling study. Endoscopy 2016;48:754–61.
46. Parikh ND, Zanocco K, Keswani RN, et al. A cost-efficacy decision analysis of prophylactic clip placement after endoscopic removal of large polyps. Clin Gastroenterol Hepatol 2013;11:1319–24.
47. Albeniz E, Gonzalez MF, Martínez-Ares D, et al. Cost-effectiveness of prophylactic clipping after colorectal endoscopic mucosal resection and economic impact according to a bleeding risk score. Gastrointest Endosc 2016;83:377–8.
48. Zhang Q, An S, Chen Z, et al. Assessment of risk factors for delayed colonic post-polypectomy hemorrhage: A study of 15553 polypectomies from 2005 to 2013. PLoS One 2014;9:e108290.
49. Chang LC, Shun CT, Hsu WF, et al. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. Endosc Int Open 2019;7:E232–8.
50. Arimoto J, Chiba H, Ashikari K, et al. Safety of cold snare polypectomy in patients receiving treatment with antithrombotic agents. Dig Dis Sci 2019; 64:3247–55.
51. Thoguluva Chandrasekar V, Spadaccini M, Aziz M, et al. Cold snare endoscopic resection of nonpedunculated colorectal polyps larger than 10 mm: A systematic review and pooled-analysis. Gastrointest Endosc 2019;89:929–36.e3.