

# Prophylactic clipping and post-polypectomy bleeding: a meta-analysis and systematic review

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## Abstract

**Background** Bleeding after polypectomy is a common issue associated with colonoscopy. To help prevent post-polypectomy bleeding, many endoscopists place clips at the site. However, this practice remains controversial. Therefore, we performed a meta-analysis of the efficacy of clip placement in the prevention of post-polypectomy bleeding.

**Methods** Multiple databases, including Embase, Scopus, MEDLINE/PubMed, CINAHL, Cochrane databases, and recent abstracts from major American meetings were searched in April 2016. Using the DerSimonian and Laird (random effects) model with odds ratio (OR), a meta-analysis was performed of post-polypectomy bleeding with prophylactic clip versus no prophylactic clip.

**Results** Five hundred and thirty potential articles and abstracts were discovered. Thirty-five articles were reviewed, with 12 studies satisfying the inclusion criteria. No statistically significant difference in prophylactic clipping versus no prophylactic clipping for post-polypectomy bleeding in all polyps was found when all studies (OR 1.49; 95% CI: 0.56–4.00; P=0.42), only peer-reviewed studies where abstracts were excluded (OR 0.84; 95% CI: 0.42–1.69; P=0.63), and only randomized controlled trials (OR 1.24; 95% CI: 0.69–2.24; P=0.47) were analyzed.

**Conclusions** The use of prophylactic clipping for all polypectomies does not seem to prevent post-polypectomy bleeding and should not be a routine practice. However, for large polyps (>2 cm), prophylactic clipping may or may not be beneficial in preventing post-polypectomy bleeding. Further studies are required to fully evaluate this subgroup.

**Keywords** Prophylactic, clip, polypectomy, bleeding

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## Introduction

Colorectal cancer is a common cancer in the United States, being the second leading cause of cancer death when genders are combined [1]. In 2016, the estimated number of new cases of

colon cancer is 134,490, potentially resulting in 49,910 deaths [1]. Screening for colon cancer with colonoscopy for early detection of polyps at a precancerous stage is extremely important in preventing these deaths. The death rates from colon cancer declined by on average 2.7% each year from 2004 to 2013, because of screening and removal of precancerous polyps [1]. However, polypectomies are associated with complications such as post-polypectomy bleeding, with the rate of bleeding varying from 0.4–10.2% [2–7]. Bleeding may occur immediately after polypectomy, usually being treated at that time, or it could be delayed. In the latter case, it may be more serious and require a second intervention. The incidence of delayed post-polypectomy bleeding ranges between 0.6–1.2% [8,9]. Multiple factors have been associated with an increased risk of post-polypectomy bleeding, including polyp size >10 mm, location (right colon), shape (pedunculated polyps have a higher risk of bleeding compared to sessile), body mass index, number of polyps removed, endoscopist's experience, pathology of polyps removed, and immediate post-polypectomy bleeding [8–10]. The use of aspirin and non-steroid anti-inflammatory drugs has not been associated with an increased risk of post-polypectomy bleeding [11]. Attempts to reduce

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the risk of post-polypectomy bleeding using various methods of prophylaxis have been described in multiple case series, retrospective, prospective, and a few randomized controlled studies. Among these methods, prophylactic clipping before or after polypectomy remains controversial, with conflicting results reported in different studies. Thus, this meta-analysis evaluated the role of prophylactic clipping in post-polypectomy bleeding.

## Materials and methods

A systematic and comprehensive literature search of Embase, Scopus, MEDLINE/PubMed, CINAHL, Cochrane databases, and recent abstracts (between 2010 and 2016) from major American meetings (Digestive Disease Week and the American College of Gastroenterology) were searched in April 2016. The references included in all articles were also searched. Search terms used were “prophylactic clip” and “post-polypectomy bleeding”. Two reviewers (CB and FM) independently reviewed all abstracts to be included in the study. A third reviewer (MLB) confirmed these results and mutual agreement was necessary in cases of discrepancy or disagreement. All studies in which clipping was the only prophylactic measure used were included. Studies that combined clipping with other measures, such as epinephrine injection or thermal coagulation, were excluded. Studies that had no control group were also excluded. The meta-analysis was conducted using the odds ratio (OR) with the DerSimonian and Laird (random effects) model examining post-polypectomy bleeding with or without a prophylactic clip. Three groups were analyzed: all studies, all peer-reviewed studies with abstracts excluded, and randomized controlled trials (RCTs). In addition, subgroup analysis was performed of those studies with prophylactic clipping performed after polypectomy. The  $I^2$  measure of inconsistency ( $P < 0.1$  or  $I^2 > 50\%$  was significant) was utilized to measure heterogeneity. If statistically significant heterogeneity was observed, a sensitivity analysis was performed, with the extraction of certain studies until heterogeneity was achieved. RevMan 5.3 (Review Manager, Version 5.3, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012) was used for statistical analysis. Quality assessment of the included studies was performed using the Cochrane’s Collaboration Risk of Bias Tool [12-14]. A GRADE was assigned to each outcome based on the quality of evidence. This GRADE is described as very low, low, moderate, or high quality based on variable quality parameters [12-14].

## Results

A total of 530 potential articles and abstracts were identified, from which 35 appropriate articles were reviewed. Once the comprehensive search was completed, 12 studies were included in the final analysis, including four RCTs, with the rest being retrospective [15-26] (Fig. 1). The characteristics of the 12 studies included are summarized in Table 1. In these studies, 13,009 patients were identified (although one study [25] did not

report the number of patients) comprising 18,416 polypectomies. The mean age ranged from 61.3-67.4 years (excluding four abstract studies with no available information about patients’ demographics). Nearly all studies utilized prophylactic clipping after polypectomy, while one study used clips on large pedunculated polyps prior to polypectomy [20] and one study used a combination of clipping before and after polypectomy [22]. A majority of studies used clips on all sizes of polyps, while a few studies used prophylactic clipping on only large polyps, such as  $>5$  mm [18],  $>1$  cm [20], or  $>2$  cm [15-17,19,22]. The quality of the studies ranged from low to moderate to high quality (Table 2).

## All studies

All 12 studies evaluated the use of prophylactic clipping in post-polypectomy bleeding ( $n=18,415$  polypectomies) [15-26]. Post-polypectomy bleeding was noted in 171 of 18,416 (0.9%) of all polypectomies. Post-polypectomy bleeding was found in 68 of 4175 (1.6%) polypectomies with prophylactic clipping and 103 of 14,241 (0.7%) polypectomies with no prophylactic clipping. On pooled analysis, no statistically significant difference was observed between prophylactic clipping versus no prophylactic clipping for post-polypectomy bleeding (OR 1.49; 95% CI: 0.56-4.00;  $P=0.42$ ) (Fig. 2). Significant heterogeneity was noted in this analysis ( $I^2=86\%$ ,  $P<0.01$ ). Based on this heterogeneity, a sensitivity analysis was performed and revealed similar results when two studies were excluded [15,23] with no significant heterogeneity (OR 1.24; 95% CI: 0.69-2.22;  $P=0.48$ ;  $I^2=35\%$ ,  $P=0.13$ ).

## All peer-reviewed studies (abstracts excluded)

Eight studies [15-22] were published in journals requiring extensive peer review while four were abstract publications [23-26] and were not peer-reviewed. In these peer-reviewed studies, post-polypectomy bleeding occurred in 121 polypectomies when abstracts were excluded. Of the remaining peer-reviewed studies, post-polypectomy bleeding was discovered in 50 of 3594 (1.4%) with prophylactic clipping

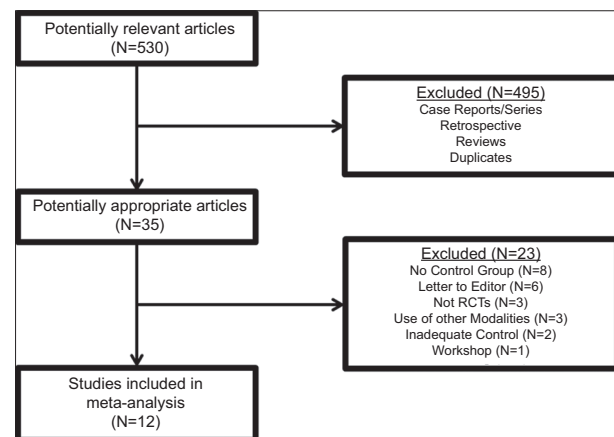
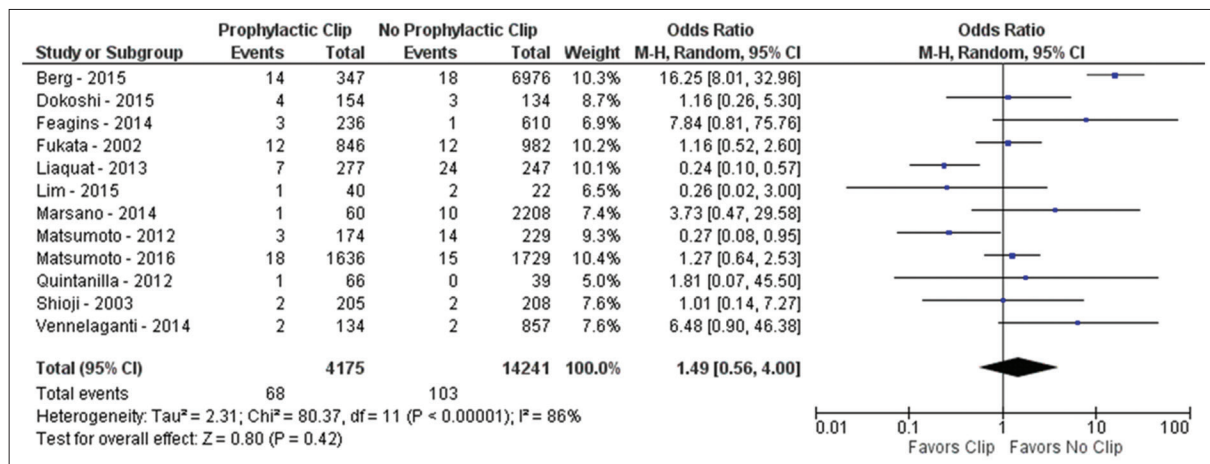


Figure 1 Details of article search and identification

**Table 1** Characteristics of the studies included in the meta-analysis

Author	Type of study	Country	Year	Number of patients/ polypectomies	Demographics	Groups	Number of polypectomies per group	Bleeding
Mastumoto <i>et al</i> [21]	Randomized controlled trial	Japan	2016	1499 patients 3365 polypectomies	M 1047 F 452 Median age 65-66*	Endoclip No Endoclip	1636 1729	18 15
Dokoshi <i>et al</i> [19]	Randomized controlled trial	Japan	2015	156 patients 288 polypectomies	M 208 F 80 Mean age 67.4	Endoclip No Endoclip	154 134	4 3
Berg <i>et al</i> [23] (Abstract)	Retrospective	United States	2015	7320 patients 7320 polypectomies	N/A	Endoclip No Endoclip	347 6976	14 18
Lim <i>et al</i> [25] (Abstract)	Retrospective	United States	2015	62 polypectomies	N/A	Endoclip No Endoclip	40 22	1 2
Marsano <i>et al</i> [26] (Abstract)	Retrospective	United States	2014	800 patients 2268 polypectomies	N/A	Endoclip No Endoclip	60 2208	1 10
Vennelaganti <i>et al</i> [24](Abstract)	Retrospective	United States	2014	696 patients 991 polypectomies	N/A	Endoclip No Endoclip	134 857	2 3
Feagins <i>et al</i> [17]	Retrospective	United States	2014	368 patients 1311 polypectomies	M 364 F 4 Mean age 63.7-64.9*	Endoclip No Endoclip	236 610	3 1
Liaquat <i>et al</i> [15]	Retrospective	United States	2013	463 patients 524 polypectomies	M 250 F 213 Mean age 67.1	Endoclip No Endoclip	277 247	7 24
Mastumoto <i>et al</i> [16]	Retrospective	Japan	2012	375 patients 403 polypectomies	M 240 F 135 Mean age 63.3	Endoclip No Endoclip	174 229	3 14
Quintanilla <i>et al</i> [20]	Randomized controlled trial	Spain	2012	98 patients 105 polypectomies	M 73 F 32 Mean age 64.05-65.55*	Endoclip No Endoclip	66 39	1 0
Shioji <i>et al</i> [18]	Randomized controlled trial	Japan	2003	323 patients 413 polypectomies	M 248 F 75 Mean age 63-63*	Endoclip No Endoclip	205 208	2 2
Fukata <i>et al</i> [22]	Retrospective	Japan	2002	911 patients 1828 polypectomies	M 618 F 293 Mean age 61.3-62.7*	Endoclip No Endoclip	846 982	12 12

\*Median or mean age represents the median or mean age of each group (control and variable)



**Figure 2** Forest plot showing the comparison between prophylactic clipping and no prophylactic clipping for polypectomies in all studies

and 71 of 4178 (1.7%) with no prophylactic clipping. No statistically significant difference was noted between the two groups for post-polypectomy bleeding when abstracts were excluded (OR 0.84; 95% CI: 0.42-1.69; P=0.63). Heterogeneity was statistically significant ( $I^2=60\%$ ,  $P=0.01$ ) (Fig. 3). On sensitivity analysis, when one study was removed [15], the results were similar with no significant heterogeneity (OR 1.07; 95% CI: 0.61-1.88;  $P=0.8$ ;  $I^2=25\%$ ,  $P=0.24$ ).

noted in 25 of 2061 (1.2%) polypectomies in the prophylactic clip group and 20 of 2110 (0.9%) polypectomies in the no prophylactic clip group. In pooled analysis, no statistically significant difference was noted in RCTs between prophylactic clipping versus no prophylactic clipping for post-polypectomy bleeding (OR 1.24; 95% CI: 0.69-2.24;  $P=0.47$ ) (Fig. 4). No publication bias or heterogeneity was noted ( $I^2=0\%$ ,  $P=0.99$ ).

**RCTs**

Four RCTs (4171 polypectomies in 2076 patients) were analyzed separately [18-21]. In these RCTs, 45 episodes of post-polypectomy bleeding were noted. Delayed bleeding was

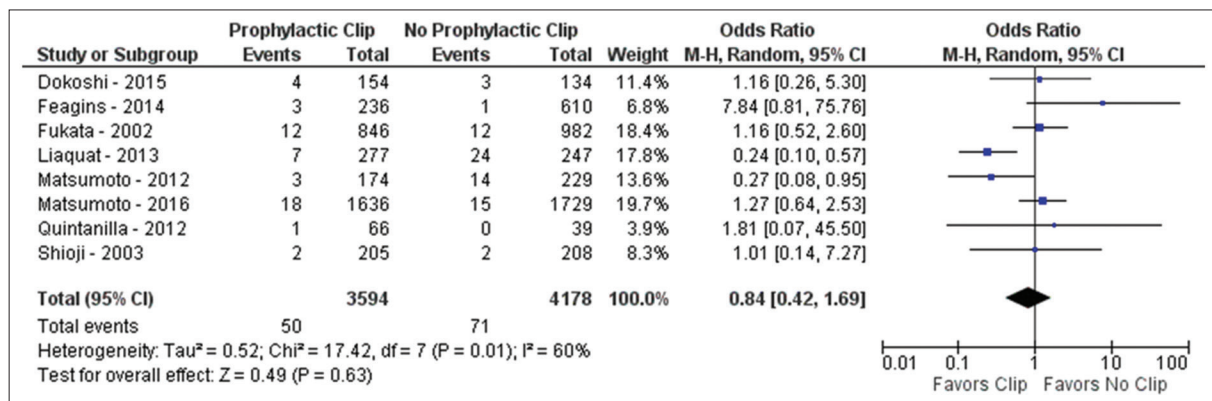
**Subgroup analysis**

The use of prophylactic clipping only after polypectomy was evaluated by 10 studies (16,483 polypectomies) [15-19,21,23-26]. Two studies were excluded from this subgroup analysis because of clipping before the polypectomy [20,22]. In this subgroup

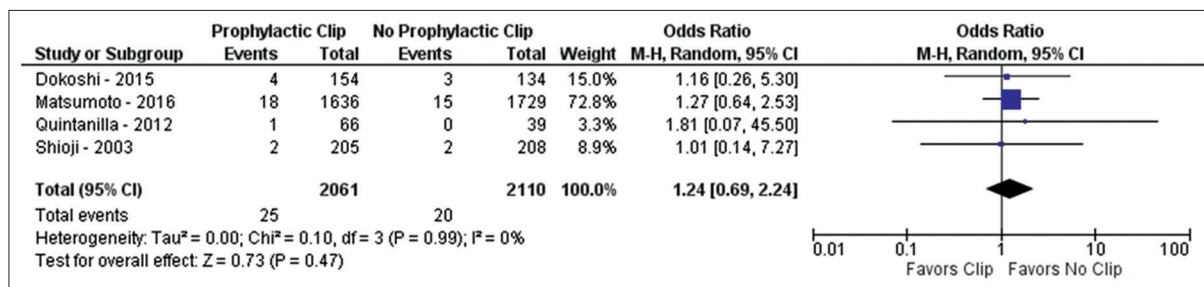
**Table 2** Assessment of quality of included studies using Cochrane’s collaboration risk of bias tool

Study	Study design	Random sequence generation	Allocation concealment	Blinding	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Quality assessment
Dokoshi <i>et al</i> [19] 2015	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Quintanilla <i>et al</i> [20] 2012	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	None	High
Shioji <i>et al</i> [18] 2003	RCT	Inadequate	Adequate	Single-blinded	Adequate	None	None	None	High
Matsumoto <i>et al</i> [21] 2016	RCT	Adequate	Adequate	Single-blinded	Adequate	None	None	Mild	Moderate-to-high
Feagins <i>et al</i> [17] 2014	Retrospective	None	None	None	None	None	None	None	Moderate
Liaquat <i>et al</i> [15] 2013	Retrospective	None	None	None	None	None	None	None	Moderate
Matsumoto <i>et al</i> [16] 2012	Retrospective	None	None	None	None	None	None	None	Moderate
Fukata <i>et al</i> [22] 2002	Retrospective	None	None	None	None	None	None	None	Moderate
Berg <i>et al</i> [23] 2015-Abstract	Retrospective	None	None	None	None	None	None	None	Low-to-moderate
Lim <i>et al</i> [25] 2015-Abstract	Retrospective	None	None	None	None	None	None	None	Low-to-moderate
Vennelaganti <i>et al</i> [24] 2014-Abstract	Retrospective	None	None	None	None	None	None	None	Low-to-moderate
Marsano <i>et al</i> [26] 2014-Abstract	Retrospective	None	None	None	None	None	None	None	Low-to-moderate

RCT, randomized controlled trial



**Figure 3** Forest plot showing the comparison between prophylactic clipping and no prophylactic clipping for polypectomies in only peer-reviewed studies (no abstracts)



**Figure 4** Forest plot showing the comparison between prophylactic clipping and no prophylactic clipping for polypectomies in only randomized controlled trials

analysis, prophylactic clipping demonstrated no difference from no clipping for post-polypectomy bleeding (OR 1.53; 95% CI: 0.46-5.03; P=0.49).

## Discussion

Polypectomy during colonoscopy is considered safe and well tolerated by patients. However, since post-polypectomy bleeding has a significant impact on both patients and healthcare costs, it would be desirable to decrease its incidence. Endoscopists have used clips in an attempt to decrease the rate of post-polypectomy bleeding, although the overall benefit of this method remains controversial. Some retrospective studies have demonstrated a benefit from prophylactic clip application to decrease the risk of post-polypectomy bleeding. Liaquat *et al* found that the delayed hemorrhage rate was 9.7% in the non-clipping group versus 1.8% in the clipping group; however, all endoscopic mucosal resections were performed on lesions larger than 2 cm, and multivariate analysis showed that polyp size was associated with delayed bleeding [15]. Mastumoto *et al* showed that delayed bleeding after endoscopic resection of colorectal lesions larger than 2 cm was more prevalent in patients who did not undergo prophylactic clip placement [16]. Feagins *et al* reported no benefit from prophylactic clipping, with bleeding rates of 1.6% in the prophylactic hemoclipping group and 0.5% in the matched control group, a difference without statistical significance [17].

In contrast, all RCTs to-date have failed to show a beneficial effect of prophylactic clipping. In 2003, Shioji *et al* evaluated 413 post-polypectomy ulcers treated by the endoscopic mucosal resection technique, with a mean polyp size of 7.8 mm, and found no decrease in delayed bleeding after polypectomy with prophylactic clip placement [18]. In another RCT, Dokoshi *et al* showed that there was no difference in bleeding between patients who received clips and those who did not [19]. Although the rate of bleeding was significantly higher in lesions 2 cm or larger in size, there was no significant difference in the bleeding rate between the clipping and non-clipping groups, regardless of the size of the lesions [19]. In 2012, another RCT showed no beneficial effects of clipping for preventing delayed bleeding [20]. However, this study was somewhat different and included only pedunculated polyps larger than 10 mm, in which prophylactic clipping was performed before

the endoscopic resection, and the study was suspended early because of the increase risk of morbidity in the clipping group, with high rates of mucosal burns and perforation exceeding that of post-polypectomy bleeding [20]. In all three of these RCTs, patients on anticoagulation were asked to discontinue their medications up to 7 days prior to the procedure, according to the guidelines. In the most recent RCT, Mastumoto *et al* demonstrated the non-inferiority of no clipping by analyzing 3365 polyps less than 2 cm in diameter [21]. The rates of post-polypectomy bleeding were 1.1% in the clipping group versus 0.9% in the non-clipping group, with a difference of -0.2% (95% CI: -0.96-0.53) [21]. In this RCT, polypectomies were performed using either endoscopic mucosal resection or snare polypectomies with electrosurgical current. Antithrombotic medication, including antiplatelet agents, was interrupted before the procedure in accordance with the relevant guidelines. The investigators' univariate analysis revealed that polyp size, additional coagulation, and the endoscopist's experience were risk factors for post-polypectomy bleeding; however, multivariate analysis showed that only additional coagulation for oozing vessels after resection and polyp size were significant risk factors.

Our meta-analysis, considering all polypectomies performed by endoscopic mucosal resection or snare polypectomy, when all polyp sizes were pooled together, found that prophylactic clip placement was not associated with any difference in post-polypectomy bleeding. This result was consistent across multiple analyses of all studies in the literature, of only peer-reviewed studies, and of only RCTs. Given the consistency of results across all levels of the literature, prophylactic clipping does not appear to be beneficial in preventing post-polypectomy bleeding for all polyps.

All studies, including meta-analyses, have strengths and weaknesses. In this meta-analysis, the strengths include the following. First, an extensive three-stage literature search was performed of the databases most commonly used in meta-analyses. Second, studies in various locations were analyzed, including Japan, the United States, and Spain. Third, three separate analyses were performed, based on the level of evidence in the literature: all studies, only peer-reviewed studies, and only RCTs. This validated the same result across the levels of evidence. However, the limitations of this study must also be acknowledged. First, heterogeneity was considered significant in two of the three outcomes (all studies and only peer-reviewed studies). Based on this, a random effects model

was used for analysis and sensitivity analyses were performed on these two outcomes, showing no difference in the results. Furthermore, when RCTs were analyzed no heterogeneity was observed, with similar results to the other two outcomes. Second, anticoagulation/antiplatelet therapy was interrupted in accordance with the guidelines. Therefore, the benefit of prophylactic clipping was not assessed in patients who were taking anticoagulation or antiplatelet medications and the results in those patients might be different. Some authors reported a benefit from clipping in patients on antithrombotic drugs [27-29]. Borodyansky *et al* suggested that polyps larger than 2 cm in patients not receiving antithrombotic therapy and larger than 1 cm in patients receiving antithrombotic treatment be clipped [29]. Further studies of prophylactic clipping should be performed that include patients on these medications. Third, despite the pooling of all available data, the rate of post-polypectomy bleeding is very low and may be subject to type II statistical bias with a lack of overall power. This may be seen from the large confidence intervals. However, this meta-analysis included 171 cases of post-polypectomy bleeding in 18,416 polypectomies, which represent all the available literature. In addition, the confidence intervals for the peer-reviewed studies and RCTs were not large, suggesting that type II error had only a minimal effect. Fourth, the method of closure of the post-polypectomy defect was not fully analyzed, since the closure method was not consistently reported across all the studies. Further studies are necessary to evaluate the effect of closure method on post-polypectomy bleeding. Fifth, given the limited number of studies performing prophylactic clipping on only pedunculated polyps, further studies are required for analysis of the use of prophylactic clipping in these polyps. Finally, all polypectomies were included in this meta-analysis, with no distinction between large polyps (>2 cm) and other smaller polyps. Since the majority of research articles did not discriminate between large and small polyps, reporting a fraction of the data from those that did would have introduced bias. In addition, in those studies from which we were able to extract data specifically for large polyps (>2 cm) [15-17,19,22], prophylactic clipping demonstrated a trend toward less post-polypectomy bleeding, but the difference did not reach statistical significance (OR 0.42; 95% CI: 0.14-1.23; P=0.11). However, this pooling of data may not be accurate given that one of the studies [17] had zero post-polypectomy bleeding in both groups, resulting in a non-estimable analysis. Furthermore, these five studies used different techniques for prophylactic clipping, with one study [22] using clips before and after polypectomy, while the others used clips after polypectomy. Therefore, prophylactic clipping, although not beneficial across all polypectomies, may or may not be beneficial in the treatment of large polyps. Further studies are required to elucidate this matter.

In conclusion, prophylactic clipping with polypectomy does not appear to be beneficial in preventing post-polypectomy bleeding in all polyps. Given the increased procedure-related costs (higher in the United States than in other countries) and the time required to perform a procedure with prophylactic clipping, without any obvious benefit, prophylactic clipping should not be routinely used during

### Summary Box

#### What is already known:

- Post-polypectomy bleeding is a complication endoscopists' would prefer to prevent
- Prophylactic clipping before and after polypectomy has become widely used, although the literature is lacking regarding the efficacy of such a practice
- Prophylactic clipping before or after polypectomy remains controversial

#### What the new findings are:

- Prophylactic clipping does not appear to affect the rates of post-polypectomy bleeding for all polypectomies
- Given the cost and lack of efficacy, prophylactic clipping should not be routinely used in all polypectomies
- In polyps >2 cm, prophylactic clipping may or may not be beneficial in preventing post-polypectomy bleeding and further studies are required to fully assess this population

colonoscopy. Further studies are required to assess the benefit of prophylactic clipping after polypectomy in patients who are taking anticoagulant or antiplatelet medications and in those with large polyps (>2 cm).

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