

Original Article

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

Nauzer Forbes MD, MS^{1,2}, Levi Frehlich², Matthew T. James MD, PhD^{1,2}, Robert J. Hilsden MD, PhD^{1,2}, Gilaad G. Kaplan MD, MPH^{1,2}, Todd A. Wilson MS², Diane L. Lorenzetti PhD², David J. Tate MBBS, MA^{3,4}, Michael J. Bourke MBBS^{3,4}, Steven J. Heitman MD, MS^{1,2}

¹Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ²Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ³Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, New South Wales, Australia; ⁴Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia

Correspondence: Dr. Steven J. Heitman MD, MS, FRCPC, Associate Professor of Medicine, TRW Building, 3280 Hospital Drive NW, Calgary, AB T2N 4Z6, Canada, e-mail steven.heitman@ucalgary.ca

Abstract

Background and Aims. Colorectal cancer (CRC) can be prevented through colonoscopic polypectomy, but this exposes patients to risks, including delayed post-polypectomy bleeding (DPPB). Endoscopists increasingly use clips prophylactically with the aim of preventing DPPB. However, clips are costly, and data to support their efficacy in this context are inconsistent. We performed a systematic review and meta-analysis of randomized controlled trials to assess the efficacy of prophylactic clipping for preventing DPPB.

Methods. We searched electronic databases and other relevant sources for randomized controlled trials assessing the efficacy of prophylactic clipping versus no clipping for the prevention of DPPB. Pooled relative risks were determined using a fixed-effects model. Subgroup analyses were also performed.

Results. A total of 2305 citations were initially screened. Seven randomized controlled trials satisfied all criteria for inclusion. The quality of included studies was generally low to moderate. A total of 2851 patients underwent 5405 polypectomies. Delayed post-polypectomy bleeding occurred at an overall pooled rate of 2.5%. No overall benefit of clipping for preventing DPPB was observed, with a pooled relative risk of 0.86 (95% confidence interval [CI], 0.55 to 1.36). No significant patient or polyp factors predicting DPPB were found through subgroup analyses. No publication bias was identified.

Conclusions. Randomized trials to date do not demonstrate a protective effect of prophylactic clipping for the prevention of DPPB, and therefore, the practice of routine prophylactic clipping appears unjustified. Additional high quality randomized trials are required to identify higher-risk groups that may benefit from prophylactic clipping.

Keywords: Colonoscopy; Hemorrhage; Polyps

Removal of precancerous adenomatous polyps during colonoscopy reduces the incidence and mortality associated with colorectal cancer (CRC) (1–4). However, polypectomy may be associated with adverse events, including sedation-related complications, pain, bleeding, bowel perforation and even death (5). Post-polypectomy bleeding can occur in the immediate setting (observed endoscopically at the time of polypectomy), but it can also be delayed. Delayed post-polypectomy bleeding (DPPB) is typically seen within 14 days (6) and is defined as luminal bleeding occurring up to 30 days following the procedure (7). Larger lesion size and proximal colonic location are among the well-established risk factors for DPPB (8).

Endoscopic clips are effective for the treatment of immediate post-polypectomy bleeding and small perforations recognized during colonoscopy (9). Increasingly, practitioners of colonoscopy are using endoscopic clips to prevent DPPB, yet data to support this practice are few and conflicting. A 2013 observational study included patients with polyps ≥ 20 mm; within this higher-risk group, full closure of polypectomy defects was associated with reduced frequency of DPPB (6). By virtue of its non-randomized design, this retrospective study was prone to bias. Among the few randomized controlled trials (RCTs) performed to date (10–16), only one has shown a beneficial effect of clipping (10). The remainder have failed to show a benefit of prophylactic clipping on DPPB, and in fact, observational studies have even shown trends toward increased risk when only partial defect closure is accomplished (17, 18). Previous meta-analyses studying this question have concluded no effect of prophylactic clipping in the prevention of DPPB (19–21). However, each of these reviews either 1) misses important studies (20), 2) combines clipping with other mechanical prophylaxis in their analysis (19), or 3) pools data from cases of polypectomy and endoscopic submucosal dissection (ESD) together (21).

To attempt to clarify the efficacy of prophylactic endoscopic clips in the prevention of DPPB, we performed a systematic review and meta-analysis of all available RCTs. We also explored clinically relevant sources of heterogeneity in an effort to understand differences between studies and to focus the design of future clinical trials.

METHODS

Objectives and Study Protocol

The primary objective of this study was to determine the efficacy of endoscopic clipping for preventing DPPB. The secondary objective was to assess whether the effect of prophylactic clipping on DPPB differs among clinically important polyp characteristics.

The study protocol was registered through PROSPERO International Prospective Register of Systematic Reviews and assigned the identifier PROSPERO 2016: CRD42016039860.

The systematic review and meta-analysis were both conducted and reported according to the PRISMA statement recommendations (22), included in Appendix A. Two reviewers (NF, LF) searched the online databases MEDLINE, Pubmed, EMBASE (Excerpta Medica Database), and CENTRAL (Cochrane Central Registry of Controlled Trials). No date limits were applied from inception through March 2018. The same two reviewers also searched the references of all identified relevant published manuscripts, systematic reviews and abstracts of major North American gastroenterology meetings (American College of Gastroenterology, Digestive Diseases Week, Canadian Digestive Diseases Week) between January 1, 2014, and December 31, 2017. In addition, the tables of contents of major gastroenterology journals relevant to the field (Gastroenterology, American Journal of Gastroenterology, Gastrointestinal Endoscopy, Endoscopy and Surgical Endoscopy) were searched from January 1, 2013, to December 31, 2017. Experts in the field were contacted for any information or knowledge regarding ongoing or unpublished studies. In addition, study authors were contacted for any relevant information missing from publications. Finally, clinical trial registries were accessed to identify ongoing or unpublished trials, and these included clinicaltrials.gov, vascsp.gov, <http://www.cochranelibrary.com/about/central-landing-page.html>, controlled-trials.com/mrct, and isrctn.com.

Literature Search and Identification of Primary Studies

The search of online databases included all languages. Full details of the search strategy can be found in Appendix B. In summary, the search terms used were ‘endoscop-’, ‘polypect-’, ‘mucosal resect-’, ‘prophylac-’, ‘prevent-’, ‘clip-’, ‘hemoclip-’, ‘endoclip-’, ‘postpolypec-’, ‘post-polypect-’, ‘delay-’, ‘bleed-’, ‘hemmorha-’, ‘perforat-’, ‘complicat-’, and ‘adverse-’. An initial screen of abstracts identified was performed independently by two reviewers (NF and LF) to select articles eligible for further review. An article was considered eligible for inclusion if it met all of the following criteria: (1) it reported on original data from an original study (i.e., not a review article); (2) it had a randomized controlled trial design; (3) it was a study of adult patients undergoing colonoscopy and polypectomy; (4) it randomized patients to undergo prophylactic clipping versus no clipping following polypectomy; and (5) it reported outcomes including DPPB.

The initial screen was intentionally broad to encompass all potentially relevant literature. No RCT filter was applied such that relevant observational literature could also be extracted for perusal of articles and references. Agreement between reviewers was quantified using Cohen’s kappa coefficient. Any potential disagreement between reviewers was resolved by deciding vote (SJH). Articles were reviewed in full if either NF or LF felt it was warranted. Studies with observational designs, reviews,

nonhuman studies, pediatric studies and studies comparing clips to other modalities were excluded. This focused, stepwise strategy was designed to capture randomized trials that compared clipping to no clipping for meta-analysis.

Data Extraction

A data extraction form was created to collate information from each identified study and can be found in [Appendix C](#). Data elements were prespecified for extraction with the intent to include all relevant study details and potential predictors or modifiers of bleeding and other adverse event outcomes. The data elements included relevant citation and authorship data, study country and design, sample size, mean age, gender distribution, categories of polyp size (<5 mm, 5 to 9 mm, 10 to 14 mm, 15 to 19mm, ≥20 mm), location (proximal versus distal or colonic segment) and macroscopic classification (flat, sessile or pedunculated), along with patient use of medications of interest (anticoagulant and/or antiplatelet agents), endoscopist specialty and average number of clips used (10–14). Outcome data collected included duration of follow-up, number of cases in each group of bleeding, perforation, post-polypectomy syndrome and abdominal pain, in addition to mean procedural time and cost (10–14). One trial studied the effect of clipping on both postendoscopic mucosal resection (EMR) and postendoscopic submucosal dissection (ESD) adverse events (10). Our review focused on standard polypectomy techniques. As such, the corresponding author was contacted, who then provided data among the randomized EMR cases separately. We did not include the ESD cases in our analysis.

Trials then underwent an assessment of quality by both reviewers, including a final rating (23). Discrepancies between the reviewers were resolved by consensus (SJH). The elements of the quality and bias assessments were designed to meet the Cochrane standards for reporting of meta-analyses (23).

Statistical Analysis

Relative risks were calculated from available study data if not explicitly reported. The primary outcome of the pooled relative risk of DPPB following clipping compared with no clipping was then calculated from the meta-analysis of RCTs. Analyses were conducted using a fixed-effects model in anticipation of the ability to conclude a common effect of the intervention across randomized controlled studies with common populations. Heterogeneity was assessed using the I^2 statistic.

Univariate metaregression analyses were considered but ultimately not reported, in compliance with the Cochrane Handbook for Systematic Reviews of Interventions, which states that metaregression should not generally be performed in reviews with fewer than 10 studies (23). Subgroup analyses were performed according to prespecified variables associated with an increased risk of delayed bleeding; specifically, polyp size, shape, location and anticoagulant status were selected. Publication bias was assessed by applying Egger and Begg tests and creating funnel plots. All statistical analyses were performed using STATA version 14 (StataCorp, College Station, TX, USA).

RESULTS

Identification of Studies for Meta-Analysis

The overall search and study selection results are displayed in [Figure 1](#) (22). The search identified 2304 citations (after removing duplicates). No citations were identified through searches among the other sources. The initial title and abstract screen resulted in the exclusion of 2166 articles, with an overall inter-rater agreement (for article selection) of 0.73 (Cohen's kappa). Any article that was selected for full-text review by either reviewer underwent full-text screening by both reviewers. The next round of full-text screening excluded a further 132 articles, with seven randomized controlled

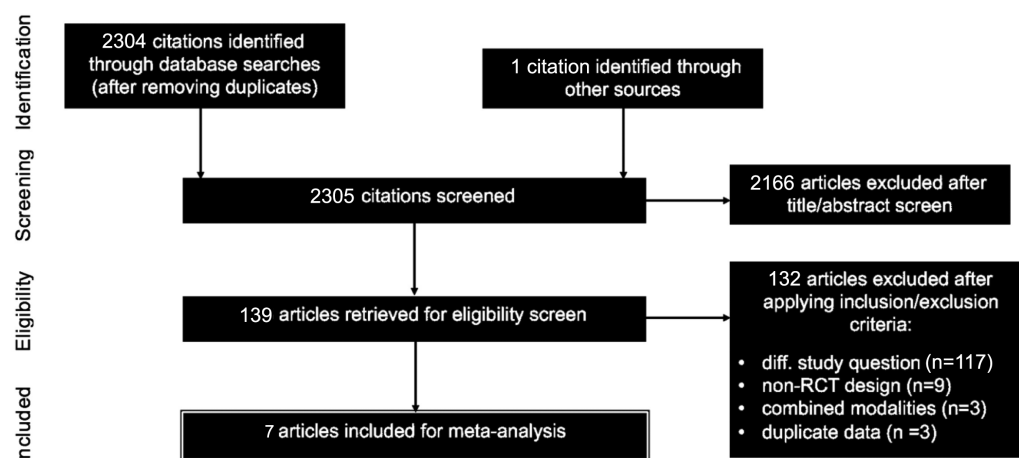


Figure 1. Study flow diagram (22) detailing methodology for initial study identification, screening, eligibility and final inclusion for analysis.

trials ultimately identified for inclusion in the meta-analysis. Cohen's kappa coefficient for inter-rater agreement was 1.00 for the second screen. Reasons for exclusion following full-text review included the following: the manuscript posed a different study question than that prespecified (117 studies), the study was not an RCT design (nine studies), the study combined multiple endoscopic prevention modalities (three studies), or the publication presented duplicate data from a previously reviewed trial (three studies).

Characteristics of Included Studies

Pertinent characteristics of the seven studies included in the meta-analysis are summarized in Table 1. A total of 5405 polyps were analyzed (2660 clipped and 2745 unclipped); 24.0% of the polyps were ≥ 10 mm, and 49.1% had a proximal location (transverse colon or more proximal). Of the seven studies, six were performed in Asia (five in Japan). Most studies were recent, with only one (Shioji et al. [12]) performed over five years ago. All but one study (Matsumoto et al. [13], also the largest) was single-centred. The event rate was low overall, with delayed bleeding occurring in 1.0% to 4.0% of patients across all seven studies. The study by Zhang et al. (10) included patients treated by either EMR or ESD; data on EMR procedures only are presented (and were analyzed accordingly) after contacting the authors for study data.

Assessment of Study Quality

Individual components of trial quality for each RCT, as assessed according to the Cochrane Risk of Bias Tool (23), are summarized in Table 2. Study quality was generally low-moderate, with two studies lacking reporting of allocation concealment and only one trial specifying blinding of outcome assessors.

Effect of Clipping on Delayed Bleeding

There was no overall difference in the pooled relative risk (RR) of DPPB in the clipping group compared with the nonclipping group (RR = 0.86; 95% CI, 0.55 to 1.36) using a fixed effects model (Figure 2). There was a low degree of heterogeneity between the seven studies, indicated by an I^2 value of 19.1%. Subgroup analyses failed to show a statistically significant effect of prophylactic clipping among any of the following groups: pedunculated versus nonpedunculated polyps, polyps ≥ 5 mm versus < 5 mm, polyps ≥ 10 mm versus < 10 mm, polyps ≥ 20 mm versus < 20 mm, right-sided versus left-sided polyps, and patients on versus off anticoagulant/antiplatelet medications (Table 3). Overall, no protective effect of clipping was seen across all polyp characteristics, though a trend was seen toward a protective effect with polyp size ≥ 10 mm, with an RR of 0.65 (95% CI, 0.31 to 1.36). The subgroup with polyps ≥ 20 mm had a limited sample size of 122. Begg and Egger tests yielded no significant evidence of small study bias, with P values of 0.76

and 0.54, respectively. A funnel plot (Figure 3) also yielded no clear visual evidence of small study effects.

DISCUSSION

This systematic review and meta-analysis examining the efficacy of prophylactic endoscopic clipping for prevention of DPPB identified seven RCTs that included a total of 5405 polypectomies among 2851 patients. The overall delayed bleeding rate was 2.5% (72 patients), consistent with previous reports where DPPB ranged from 0.5% to 7.2% (18, 24–31). We found no overall effect of prophylactic clipping on the risk of DPPB, with a pooled RR of 0.86 for clipping compared with no clipping (95% CI, 0.55 to 1.36).

The overall heterogeneity was low, as suggested by the I^2 value of 19.1% (23). However, this assessment was limited by low power, given the small number of included studies. We did not find statistically significant factors in the subgroup analyses associated with a lower relative risk of DPPB following prophylactic clipping. Larger polyps (≥ 10 mm) were associated with a nonstatistically significant reduction in DPPB (RR = 0.65, 95% CI, 0.31 to 1.36). The wide confidence intervals suggest our study was underpowered to detect a significant difference. This lack of power is further supported by the small overall number of polyps measuring ≥ 20 mm and the small number of associated bleeding events. Thus, additional RCT-level evidence focused on larger polyps and other higher-risk settings (e.g., right-sided lesions or among patients exposed to anticoagulants or antiplatelet agents) is warranted.

This meta-analysis has several important strengths. The broad search strategy provides a thorough and up-to-date review of the current state of evidence regarding the efficacy of prophylactic endoscopic clips for prevention of DPPB. By limiting the analysis to RCTs, our findings are less prone to bias than previous reviews that pooled results from both experimental and observational study designs (20). Nevertheless, our objective assessment of the literature revealed low-moderate overall quality among the included studies (Table 2). Significant study limitations were identified, including lack of blinding of outcome assessors and inconsistent allocation concealment.

A recent network meta-analysis evaluating multiple prophylactic endoscopic modalities (including clipping) concluded that none were effective in the prevention of DPPB (19). In addition, a second meta-analysis that focused solely on clipping drew similar conclusions (20). Our meta-analysis adds to the existing literature by including the one trial that showed a benefit of clipping in the prevention of DPPB (10). Zhang et al. (10) enrolled patients who underwent both EMR and ESD, but we were able to select the EMR data alone in our meta-analysis, rather than pooling these clinically heterogeneous groups (21). The inclusion of this study

Table 1. Summary of characteristics of RCTs included in the meta-analysis

First Author	Year	Country	Centres	Patients (clipped, unclipped)	Polyps (clipped, unclipped)	Bleeding events (clipped, unclipped)	Polyps with proximal location* (%)	Polyps with size ≥ 1 cm (%)
Matsumoto	2016	Japan	Multiple	1499 (752, 749)	3364 (1636, 1728)	33 (18, 15)	1668/3364 (49.6)	339/3364 (10.1)
Zhang	2015	China	Single	286 (141, 145)	286 (141, 145)	12 (2, 10)	N/R	286/286 (100.0)
Mori	2015	Japan	Single	62 (N/R)	148 (73, 75)	2 (2, 0)	N/R	146/146 (100.0)
Tominaga	2014	Japan	Single	427 (211, 216)	801 (385, 416)	13 (4, 9)	N/R	N/R
Dokoshi	2015	Japan	Single	156	288 (154, 134)	7 (4, 3)	N/R	104/288 (36.1)
Quintanilla	2012	Spain	Single	98	105 (66, 39)	1 (1, 0)	N/R	105/105 (100.0) [†]
Shioji	2003	Japan	Single	323	413 (205, 208)	4 (2, 2)	187/413 (45.3)	N/R

*Proximal location represents cecum, ascending colon, hepatic flexure or transverse colon.

[†]All polyps in this study were pedunculated.

N/R = not reported

Table 2. Measures of quality of RCTs included in the meta-analysis

	Matsumoto	Zhang	Mori	Tominaga	Dokoshi	Quintanilla	Shioji
<i>Selection bias</i>							
Random sequence generation	present	absent	present	present	absent	present	absent
Allocation concealment	absent	present	present	present	present	absent	present
<i>Performance bias</i>							
Blinding of participants and personnel	absent	absent	absent	absent	absent	absent	absent
<i>Detection bias</i>							
Blinding of outcome assessment	absent	present	absent	absent	absent	absent	absent
<i>Attrition bias</i>							
Incomplete outcome data	none	none	none	none	none	some	none
<i>Reporting bias</i>							
Selective reporting	none	none	none	none	none	none	none
<i>Other bias</i>							
Other sources of bias	none	none	none	none	none	none	none
<i>Overall assessment of quality</i>							
Overall quality	Moderate	Moderate-high	Moderate	Moderate	Low	Low-moderate	Moderate

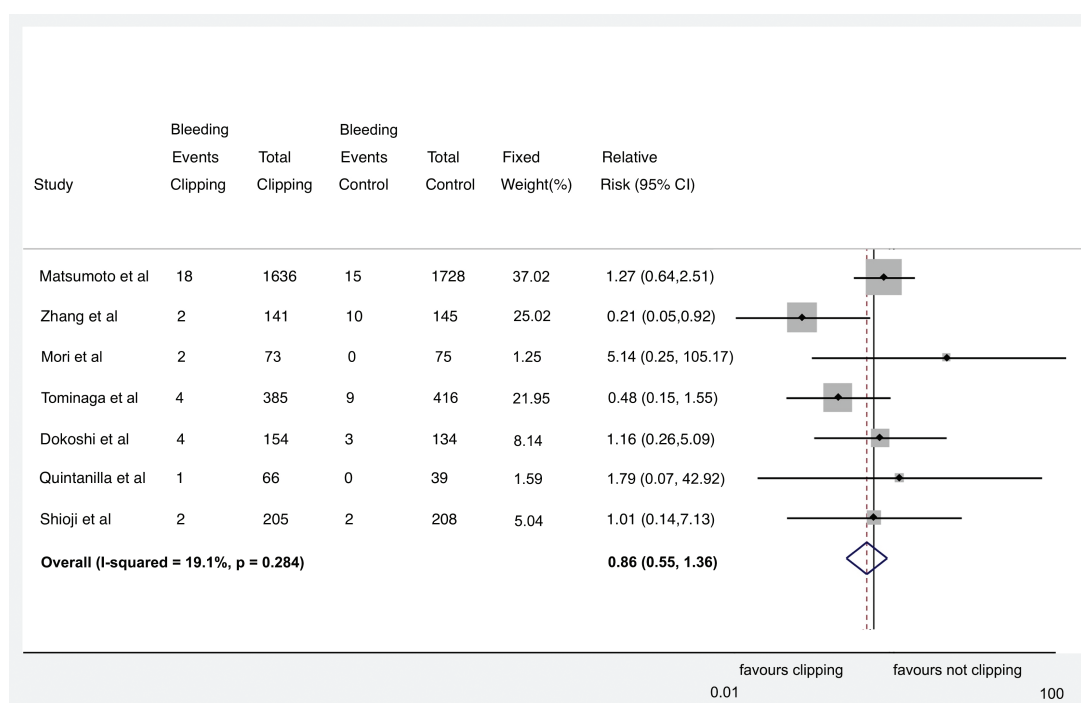
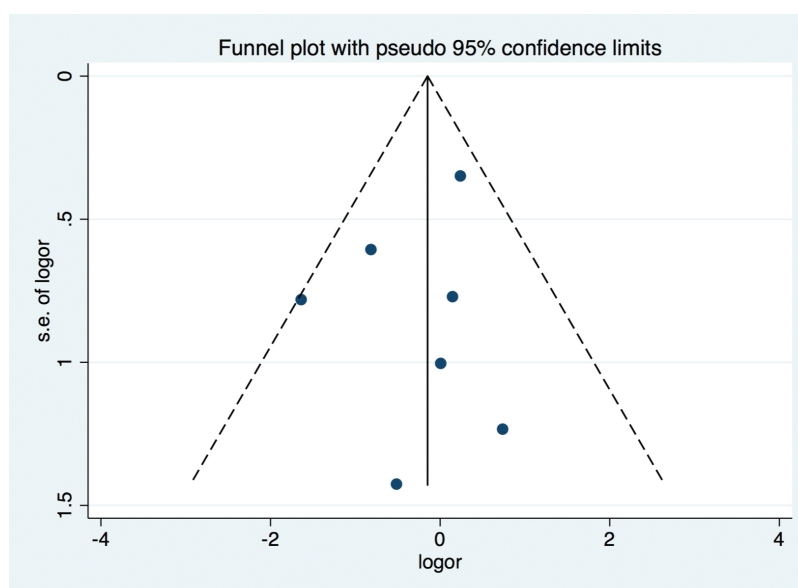
**Figure 2.** Forest plot comparing clipping and nonclipping for prevention of delayed post-polypectomy bleeding.

Table 3. Subgroup analyses performed to assess effect of prophylactic clipping on various clinically relevant subgroups (fixed effects models applied)

Variable	Relative risk	95% CI	Heterogeneity (I^2)	Number of trials	Polyps (clipped, unclipped)	Bleeding events (clipped, unclipped)
Pedunculated polyps	1.20	0.63–2.28	Low (0.0%)	4	3239 (1575, 1664)	33 (18, 15)
Patients on anticoagulant/antiplatelet medications	0.87	0.32–2.36	Low (7.8%)	3	889 (444, 445)	13 (6, 7)
Polyp size ≥ 5 mm	0.88	0.47–1.65	Moderate-high (63.3%)	3	2094 (1064, 1030)	38 (18, 20)
Polyp size ≥ 10 mm	0.65	0.31–1.36	Low-moderate (36.0%)	4	876 (488, 388)	27 (12, 15)
Polyp size ≥ 20 mm	1.11	0.31–3.99	Low (0.0%)	3	122 (82, 40)	7 (5, 2)
Proximal polyp location*	2.18	0.76–6.26	Low (0.0%)	1	1668 (823, 845)	16 (11, 5)

*Proximal location represents cecum, ascending colon, hepatic flexure or transverse colon

**Figure 3.** Funnel plot assessing small study effects with regard to the protective effect of clipping (versus no clipping).

and isolation of EMR data are important, since it showed a benefit of prophylactic clipping with an RR of 0.21 among EMR cases (95% CI, 0.05 to 0.92) (10). This is the only RCT to date that has shown a benefit of prophylactic clipping, possibly as a result of limiting their enrollment to lesions ≥ 10 mm or sessile morphology. Thus, the results of our systematic review and meta-analysis highlight not only the need for additional high quality RCTs but also trials focused on higher-risk lesions or among patient populations at higher risk of bleeding who are more likely to benefit from prophylactic endoscopic clipping.

There are clinical scenarios for which prophylactic clipping is currently recommended based on available evidence. Mechanical hemostatic prophylaxis, which can include placement of prophylactic endoscopic clips, may be efficacious in preventing bleeding following removal of large pedunculated polyps. In this scenario, and in contrast to sessile or flat lesions, where vascular supply is usually broad and multifocal, the blood supply in large pedunculated lesions is generally limited to a few or one larger blood vessel(s) within the stalk, and hemostasis by conventional electrosurgical means cannot be assured (32). Mechanical prophylaxis, using a detachable loop or a snare with

clip(s), has been shown to decrease post-polypectomy bleeding from pedunculated polyps ≥ 20 mm (33, 34). The efficacy of clipping alone in this context has not been studied, and thus, our meta-analysis does not address this question. Nevertheless, European guidelines currently recommend pretreatment of pedunculated polyps with heads ≥ 20 mm or stalks ≥ 10 mm using either mechanical prophylactic measures or injection of dilute epinephrine (35). Deploying a clip or multiple clips across a thick stalk to achieve tissue ischemia can be technically challenging, and the use of a detachable loop also has its limitations; hence, feasibility and cost should also be considered in future studies and clinical guidelines.

Despite its strengths, this study has limitations. The included trials were generally small and underpowered to demonstrate treatment effects within important subgroups. Small sample size and insufficient reporting of data also limited our ability to pool within strata (e.g., increasing polyp size, polyp location) or to evaluate the effect of prophylactic clipping on other adverse events and procedure-related outcomes, such as delayed perforation; however, this is uncommon with modern electrosurgical techniques. This limitation was most evident in the analysis of lesions ≥ 20 mm. In addition, most of the included studies followed evidence-based guidelines, and thus, anticoagulant and antiplatelet medications were typically held preprocedure (36). The potential for clips to lower the risk of DPPB among patients at potentially greater risk of bleeding remains unknown. Finally, the included trials were conducted in a relatively small number of countries; most originated from Japan, and six out of seven were conducted in Asia. With a paucity of Western clinical trials addressing this important question, the generalizability of our findings may be less certain.

The results of this meta-analysis can help inform clinical practice. At the present time, despite the widespread use of prophylactic endoscopic clipping, there is little if any evidence to support this approach in any therapeutic environment. Endoscopic clips are also costly (37). Furthermore, clipping is not always a benign intervention, with uncommon reports of complications following their deployment (11). These factors, when combined with our pooled results demonstrating a lack of clinical efficacy of prophylactic clips, ought to make practitioners take pause. Nonjudicious use of these devices as a means to help the endoscopist 'sleep better at night' cannot be justified. More appropriate practice necessitates a careful case-by-case consideration of all relevant patient-, endoscopist-, polyp- and procedure-related factors before making the decision on whether or not to prophylactically clip a polypectomy site. In particular, use of prophylactic clips for small polyps < 10 mm appears ineffective, outside of their potential usefulness in selected higher-risk circumstances (i.e., among patients with recent exposure or immediate need of anticoagulants or antiplatelet agents). More data are urgently needed to better

serve our patients and rationalize health care costs. Ultimately, additional high-quality and adequately powered randomized trials are needed to determine whether prophylactic clips are efficacious in preventing DPPB following removal of large pedunculated and larger nonpedunculated lesions.

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All authors critically revised the article for important intellectual content and gave final approval.

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APPENDIX A: PRISMA Checklist (20)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1,2,4
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4,5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5,25
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5,6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6,7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6,7,26–28
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8,9,17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,18

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12,13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13,14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

APPENDIX B: Search Strategy

The search of online databases initially included all languages. The first Boolean search (addressing the population of interest) was performed by using the term 'or' to explode and map the terms 'endoscop*.tw', 'polypect*.tw', 'mucosal resect*.tw' (with the asterisks representing words truncated at that point, and the '.tw' confining searches to titles and abstracts only) and the MeSH heading 'Endoscopy'. The second Boolean search (addressing the intervention and comparison of interest) was performed using the term 'or' to explode and map the terms 'prophylac*.tw', 'prevent*.tw', 'clip.tw', 'hemoclip.tw', 'endoclip.tw' and the MeSH heading 'Prophylactic Surgical Procedures'. The third Boolean search (addressing the outcome of interest) was performed by using the term 'or' to explode and map the terms 'postpolypec*.tw', 'post-polypect*.tw', 'delay*.tw' and the MeSH heading 'Postoperative Complications'. The fourth and final Boolean search (also addressing the outcome of interest) was performed by using the term 'or' to map and explode the terms 'bleed*.tw', 'hemmorha*.tw', 'perforat*.tw', 'complicat*.tw', 'adverse*.tw' and the MeSH headings 'Intestinal Perforation' and 'Hemorrhage'. The four Boolean searches were then combined by using the Boolean term 'and'.

APPENDIX C: Data Extraction Form

1. Reviewer: _____
2. Study ID #: _____
3. Lead author name: _____
4. Title: _____
5. Journal: _____
6. Publication year: _____
7. Volume and issue: _____
8. Pages: _____

ELIGIBILITY CRITERIA

- | | | | |
|---|-----|----|---------|
| 9. Reports on original data? | Yes | No | Unclear |
| 10. Endoscopic clips used for prevention? | Yes | No | Unclear |

DATA

11. Baseline data

	Clipped Group	Non-clipped Group
Sample size (n)		
Mean age (SD)		
Male # (%)		
Polyp size in mm # (%)		
<5		
6–10		
11–20		
20+		
Macroscopic polyp type # (%)		
Sessile		
Flat		
Pedunculated		
Diminutive		
Polyp location # (%)		
Rectum		
Sigmoid		
Descending		
Transverse		
Ascending		
Cecum		
Antiplatelet drug use # (%)		
ASA		
Clopidogrel		
Other		
Anticoagulant drug use # (%)		
Warfarin		
Novel		
Endoscopist specialty # (%)		
Gastroenterology		
Surgery		
Other		
Average number of clips		

12. Duration of Follow-up _____

13. Outcomes/Results

	Clipped Group	Non-clipped Group
Bleeding Cases # (%)		
Perforation Cases # (%)		
Coagulation syndrome cases # (%)		
Abdominal pain cases # (%)		
Mean procedure time		
Mean case cost (USD)		
Mean follow-up		

STUDY QUALITY

14. Inclusion/exclusion criteria specified?	Yes	No	Unclear
15. Randomization process described?	Yes	No	Unclear
16. Allocation concealment used?	Yes	No	Unclear
17. Blinding of study participants undertaken?	Yes	No	Unclear
18. Blinding of outcome assessors undertaken?	Yes	No	Unclear
19. Control/comparison used?	Yes	No	Unclear
20. Attrition reported?	Yes	No	Unclear
21. Intention to treat analysis used?	Yes	No	Unclear
22. Important baseline differences exist?	Yes	No	Unclear
23. Power calculation/sample size reported?	Yes	No	Unclear
24. Cross over occurred/reported?	Yes	No	Unclear