Surgical Endoscopy (2022) 36:1251–1262
https://doi.org/10.1007/s00464-021-08398-x

Prophylactic clipping to prevent delayed colonic post-polypectomy bleeding: meta-analysis of randomized and observational studies

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Received: 26 October 2020 / Accepted: 12 February 2021 / Published online: 9 March 2021

Abstract

Background and aims Delayed post-polypectomy bleeding (DPPB) is a commonly described adverse event following polypectomy. Prophylactic clipping may prevent DPPB in some patient subgroups. We performed a meta-analysis to assess both the efficacy and real-world effectiveness of prophylactic clipping.

Methods We performed a database search through March 2020 for clinical trials or observational studies assessing prophylactic clipping and DPPB. Pooled risk ratios (RR) were calculated using random effects models. Subgroup, sensitivity, and meta-regression analyses were performed to elucidate clinical or methodological factors associated with effects on outcomes.

Results A total of 2771 citations were screened, with 11 randomized controlled trials (RCTs) and 9 observational studies included, representing 24,670 colonoscopies. DPPB occurred in 2.0% of patients overall. The pooled RR of DPPB was 0.47 (95% CI 0.29–0.77) from RCTs enrolling only patients with polyps ≥ 20 mm. Remaining pooled RCT data did not demonstrate a benefit for clipping. The pooled RR of DPPB was 0.96 (95% CI 0.61–1.51) from observational studies including all polyp sizes. For patients with proximal polyps of any size, the RR was 0.73 (95% CI 0.33–1.62) from RCTs. Meta-regression confirmed that polyp size ≥ 20 mm significantly influenced the effect of clipping on DPPB.

Conclusion Pooled evidence demonstrates a benefit when clipping polyps measuring ≥ 20 mm, especially in the proximal colon. In lower-risk subgroups, prophylactic clipping likely results in little to no difference in DPPB.

Keywords Colonoscopy · Adenomas · Polypectomy · Adverse events · Bleeding · Clipping

Abbreviations

CENTRAL	Cochrane Central Registry of Controlled Trials
CI	Confidence interval
CRC	Colorectal cancer
DPPB	Delayed post-polypectomy bleeding
EMBASE	Excerpta Medica Database
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NOS	Newcastle-Ottawa scale
OR	Odds ratio
PRISMA	Referred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized control trial
ROB	Risk of bias
RR	Risk ratio

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Colorectal cancer (CRC) is the second leading cause of cancer death worldwide. In 2020, nearly 150,000 people will have been diagnosed with CRC in the USA alone [1]. Due to the highly prevalent and preventable nature of

CRC, systematic screening can reduce the overall burden of CRC by identifying higher-risk patients and removing adenomas endoscopically [2–5]. While safe overall, conventional polypectomy and endoscopic mucosal resection (EMR) can result in adverse events, with bleeding at the resection site being the most common [6]. Immediate bleeding can be treated at the time of polypectomy and is not generally considered a true adverse event; however, delayed post-polypectomy bleeding (DPPB) can occur up to 30 days following the procedure and often leads to unplanned healthcare resource utilization and the need for repeat endoscopic intervention(s).

The use of prophylactic endoscopic clipping to prevent DPPB varies among endoscopists, but is ultimately common [7]. This practice is costly [8], and previous evidence reviews have not supported its routine application. In 2018, we performed a meta-analysis of randomized control trials (RCTs) and failed to demonstrate a protective effect of routine prophylactic clipping for the prevention of DPPB in all-comers [9]. However, sufficient data were lacking at the time to evaluate its value in higher-risk subgroups. The results of several RCTs [10–12] and large observational studies [13] have since been published in which several clinically relevant subgroups have been considered. Moreover, a recent meta-analysis of RCTs concluded that prophylactic clipping prevents DPPB in large (≥ 20 mm) polyps and proximal polyps [14]. However, this study included pooled data from patients undergoing endoscopic submucosal dissection (ESD) [14], which is associated with a higher risk of adverse events compared to conventional polypectomy techniques [15]. In addition, observational data, which often conflict with RCT findings for complex interventions [16], were not considered. Though unquestionably providing the greatest internal validity among study designs, RCTs assessing prophylactic clipping may not be completely generalizable to real-world settings. This could be the result of including only expert endoscopists and employing ideal polyp selection in RCTs, both critical to achieving complete clip closure, which is associated with optimal clinical benefit [11]. Given the prevalence of newer literature on this topic and the potential discrepancies between randomized and observational data, we performed an updated systematic review and meta-analysis, including both RCT and observational studies assessing associations between prophylactic clipping and DPPB.

Methods

Overview

We conducted a systematic review and meta-analysis and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting standards (Supplementary Materials) [17, 18]. This study was an update of a previous meta-analysis [9] whose protocol was registered through PROSPERO (CRD42016039860). Our primary objective was to determine the efficacy (from RCTs) versus real-world effectiveness (from observational studies) of prophylactic endoscopic clipping for preventing DPPB. The secondary objectives were to assess whether the effect of prophylactic clipping on DPPB differs between clinically important study-, patient-, and polyp-related subgroups. Neither informed consent nor research ethics board approval were sought given our study's use of previously published material.

Search strategy and study selection

A comprehensive literature search was performed of the online databases MEDLINE, EMBASE (Excerpta Medica Database), CENTRAL (Cochrane Central Registry of Controlled Trials), and PubMed (Supplementary Materials). The search was executed from inception of the databases until 25 March 2020. Two reviewers (KB, ZWM) independently performed a title and abstract screen of citations identified through the search to identify potential articles for full-text review. Inter-reviewer discrepancies were resolved by consensus with a third author (NF).

Eligibility criteria

We included a study if it met all of the following criteria: (1) it reported on original data (i.e.: it was not a narrative or systematic review, though the references of these were searched for additional studies missed by our electronic strategy), (2) it was published in full manuscript form in any language (i.e.: no conference abstracts), (3) it was a RCT or an observational study (retrospective or prospective), (4) it was a study of adult patients undergoing colonoscopy with polypectomy, (5) it compared patients undergoing prophylactic clipping versus no clipping, and (6) it reported DPPB as a primary or secondary outcome. A study was excluded if: (1) there was no control group, (2) the control group received another hemostatic modality, as opposed to no intervention, (3) it was a study conducted among pediatric or non-human populations, or (4) it reported on prophylactic clipping following endoscopic submucosal dissection (ESD) exclusively. If a study reported combined data on polypectomy/EMR along with ESD, attempts were made to contact corresponding study authors to request original data that included polypectomy/EMR patients only.

Data extraction and study quality

A standardized data abstraction form was created to extract pre-specified data from each included study. Two reviewers (KB, ZWM) independently performed data extraction as well as assessments of bias and overall study quality. Individual components of study quality were assessed according to the Cochrane Risk of Bias Tool for randomized trials, version 2 (RoB 2) [19] and according to the ROBINS-I Tool for Assessing Risk of Bias in Non-randomized Studies of Interventions for observational studies [20]. Inter-reviewer discrepancies in bias and quality assessments were resolved by consensus (NF).

Outcomes

The primary outcome was clinically significant DPPB, defined as hematochezia or melena or drop in hemoglobin of ≥ 2 g occurring within 30 days of the index polypectomy [13, 21]. Secondary outcomes included DPPB in specific subgroups, such as after resection of polyps greater than 10 or 20 mm, resection of proximal polyps, and resection in patients on anticoagulation or antiplatelet therapy [13, 22–32].

Statistical analysis

Crude rates of DPPB were calculated by dividing the number of bleeding events by the total number of patients per relevant category. The effects of prophylactic clipping (compared to not clipping) were estimated using risk ratios (RR) calculated from pooled data from observational studies or RCTs separately and presented in forest plots along with corresponding 95% confidence intervals (CIs). In the case of any case–control observational studies, the odds ratio (OR) was calculated and compared to the RR, and the study was then included in the forest plot if the OR was within 5% of the RR, given the low overall DPPB event rate. A DerSimonian and Laird random effects model was used to carry out meta-analyses [19]. We used both χ^2 tests and I^2 statistics to detect heterogeneity. Publication bias was assessed using funnel plots in addition to Begg's and Egger's tests [33, 34]. Univariable meta-regression was also performed to examine potential mediators of heterogeneity.

Subgroup and sensitivity analyses

To address potential sources of inter-study heterogeneity, subgroup analyses were carried out to determine whether the effect of prophylactic clipping was dependent on the study population or characteristics of the polyps removed. Clinically relevant subgroups identified *a priori* included: proximal (versus distal) polyps, defined as those proximal to the transverse colon; moderate-sized and large (versus small) polyps, defined as those measuring ≥ 10 mm and ≥ 20 mm, respectively; large proximal polyps, pedunculated polyps (versus sessile or flat), and polyps removed in patients taking anticoagulant or antiplatelet medications (versus those not). Meta-regression was also performed to assess whether any of these variables in addition to patient sex and age were associated with the effect of the intervention on the outcome. We also considered study-specific methodologic details as subgroups, including separating single-center versus multi-center studies, North American versus European or Asian studies, and those published in or after 2016 versus before (to examine the potential effect of education on clipping and/or subsequently improved endoscopist technique). RCTs were separated according to their inclusion criteria, specifically, their minimum polyp size cut-offs (if any). We also conducted sensitivity analyses to evaluate the robustness of our results, as follows: (1) each study was removed individually, and (2) fixed effects models were used rather than random effects models. All statistical analyses were performed using Revman 5.3 (Cochrane Collaboration) or STATA version 16.1 (StataCorp, College Station, TX, USA).

Results

Study selection

A PRISMA flow diagram of the search results and study selection process is provided in the Supplementary Materials. The electronic search identified a total of 2769 citations. Two citations were identified through secondary methods. After the title and abstract screen, 160 full text articles were reviewed, and 20 studies were included in the meta-analysis.

Characteristics and quality of included studies

Baseline study characteristics of the 20 included studies are summarized in Table 1. All but two studies were published in 2012 or later. A total of 24,671 colonoscopies with polypectomy were included—11,609 with one or more clipped polyps and 13,062 with no clipping. A total of 18.2% of polyps were ≥ 20 mm, and 41.7% had a location proximal to the transverse colon. Six of the 11 RCTs were multi-centered, compared with 2 of the 9 observational studies.

A summary of patient and polyp characteristics is provided in Table 2. The study by Zhang et al. [35] included patients treated with both polypectomy/EMR and ESD. Data on polypectomy/EMR procedures only were included in the analysis after contacting the authors for additional data. The study by Chang et al. [36] included upper and lower gastrointestinal lesions; only the colonic polyp data were included for analysis. Proximal polyp

Table 1 Summary of baseline characteristics and study quality of studies included in the meta-analysis

Author	Year	Design	Country	Centers	Patients (clipped, unclipped)	Polyps (clipped, unclipped)	Bleeding events (clipped, unclipped)	Median/mean number of clips used per polyp (in clipping arm)	Risk of bias
Shioji [46]	2003	RCT	Japan	Single	323	413 (205, 208)	4 (2, 2)	1.7	Some concerns
Quintanilla [47]	2012	RCT	Spain	Single	98	105 (66, 39)	1 (1, 0)	N/R	Some concerns
Tominaga [38]	2014	RCT	Japan	Single	427 (211, 216)	801 (385, 416)	13 (4, 9)	N/R	Moderate
Zhang [35]	2015	RCT	China	Single	286 (141, 145)	286 (141, 145)	12 (2, 10)	N/R	Some concerns
Dokoshi [48]	2015	RCT	Japan	Single	156	288 (154, 134)	7 (4, 3)	2.2	Some concerns
Matsumoto [49]	2016	RCT	Japan	Multiple	1501 (752, 749)	3364 (1636, 1728)	33 (18, 15)	1.6	Some concerns
Albeniz [11]	2019	RCT	Spain	Multiple	235 (119, 116)	235 (119, 116)	20 (6, 14)	6.0	Some concerns
Feagins [10]	2019	RCT	USA	Multiple	1050 (530, 520)	1386 (680, 706)	27 (12, 15)	1.5	Some concerns
Pohl [12]	2019	RCT	USA	Multiple	919 (455, 464)	989 (490, 499)	49 (16, 33)	4.0	Low
Soh [43]	2020	RCT	South Korea	Multiple	116 (53, 63)	137 (67, 70)	10 (5, 5)	N/R	Some concerns
Inoue [42]	2020	RCT	Japan	Multiple	1039 (520, 519)	2960 (1449, 1511)	26 (12, 14)	4.0	Some concerns
Fukata [50]	2002	Observational	Japan	Single	911 (N/R)	1828 (846, 982)	24 (12, 12)	N/R	N/A*
Dior [51]	2013	Observational	France	Single	138 (110, 28)	139 (111, 28)	3 (2, 1)	N/R	Serious
Liaquat [39]	2013	Observational	USA	Single	463 (N/R)	524 (277, 247)	31 (7, 24)	3.7	Moderate
Feagins [52]	2014	Observational	USA	Single	368 (184, 184)	1311 (236, 1075)	4 (3,1)	N/R	Moderate
Albeniz [53]	2016	Observational	Spain	Multiple	1214 (N/R)	1255 (466, 775)	46 (30, 15)	3.0	Low
Tsuruta [54]	2019	Observational	Japan	Single	1660 (996, 664)	3844 (N/R)	46 (34, 12)	N/R	Low
Chang [36]	2020	Observational	USA	Multiple	(N/R)	485 (239, 246)	17 (7, 10)	1.4	Serious
Forbes [13]	2020	Observational	Canada	Single	8366 (3424, 4942)	19,129 (3869, 15,260)	95 (50, 45)	1.8	Low
Chen [55]	2020	Observational	Taiwan	Single	1424 (789, 635)	1925 (1037, 888)	17 (9, 8)	N/R	Low

RCT randomized controlled trial, *NOS* Newcastle–Ottawa scale, *ROB* cochrane risk of bias tool, *N/R* not reported

*Not in English

location varied slightly between studies (Table 2). Individual assessments of quality for RCTs according to RoB 2 revealed that there were some concerns mainly pertaining to outcome measurements, with otherwise low risks of bias [19]. For observational studies, there was moderate concern over the risk of bias in individual studies primarily due to confounding and outcome measurement, according to ROBINS-I [20]. Assessments of study quality are summarized in Table 1 [19, 20], with full assessments provided in the Supplementary Materials.

Clipping and overall DPPB

The effect of clipping on DPPB in all-comers separated by study type is reported in forest plots in Fig. 1. From observational studies, the DPPB rate was 1.8% (281 events

Table 2 Patient and polyp characteristics from studies included in the meta-analysis

Author	Year	Patients on antiplatelets or anticoagulants	Polyps with proximal location (%)	Polyps with size ≥ 10 mm (%)	Polyps with size ≥ 20 mm (%)	Proximal polyps with size ≥ 20 mm (%)	Pedunculated polyps (%)
Randomized controlled trials							
Shioji [46]	2003	N/R	187/413 (45.3)[a]	95/413 (23.0)	N/R	N/R	31/413 (7.5)
Quintanilla [47]	2012	16/98 (APLT) 8/98 (AC)	N/R	105/105 (100.0)	32/105 (30.5)	N/R	105/105 (100.0)
Tominaga [38]	2014	N/R	N/R	N/R	N/R	N/R	N/R
Zhang [35]	2015	N/R	N/R	286/286 (100.0)	N/R	N/R	N/R
Dokoshi [48]	2015	38/288 (APLT) 8/288 (AC)	N/R	104/288 (36.1)	14/288 (4.86)	N/R	41/288 (14.2)
Matsumoto [49]	2016	N/R	1668/3364 (49.6)[o]	339/3364 (10.1)	0	0	3062/3364 (91.0)[#]
Albeniz [11]	2019	84/235 (APLT) 61/235 (AC)	213/235 (90.6)[a] 178/235 (75.7)[b]	235/235 (100.0)	235/235 (100.0)	213/235 (90.6)[a] 178/235 (75.7)[b]	0
Feagins [10]	2019	557/1050 (APLT) 116/1,050 (AC)	536/1386 (47.5)[b]	1386/1386 (100.0)	222/1386 (16.0)	6/1386 (0.4)[b]	421/1386 (30.3)
Pohl [12]	2019	231/919 (APLT) 49/919 (AC)	658/989 (66.5)[b]	989/989 (100.0)	989/989 (100.0)	658/989 (66.5)[b]	0
Soh [43]	2020	20/116 (APLT)	52/137 (38.0)[a]	137/137 (100.0)	N/R	N/R	137/137 (100.0)
Inoue [42]	2020	161/1039 (APLT) 15/1039 (AC)	1680/2960 (56.8)[o]	1071/2960 (36.2)	0/2960 (0)	0/2960 (0)	157/2960 (5.3)
Observational studies							
Fukata [50]	2002	N/R	N/R	N/R	N/R	N/R	N/R
Dior [51]	2013	22/138 (APLT)	79/139 (56.8)[a] 63/139 (45.3)[b]	139/139 (100.0)	139/139 (100.0)	79/139 (56.8)[a] 63/139 (45.3)[b]	N/R
Liaquat [39]	2013	231/464 (AT)	393/524 (75.0)[a] 301/524 (57.4)[b]	524/524 (100.0)	524/524 (100.0)	393/524 (75.0)[a] 301/524 (57.4)[b]	0
Feagins [52]	2014	201/368 (APLT) 42/368 (AC)	602/1,311 (45.9)[o]	326/1311 (24.9)	100/1311 (7.6)	N/R	206/1311 (15.7)
Albeniz [53]	2016	519/1241 (AT)	643/1253 (51.3)[a] 501/1253 (40.0)[b]	1255/1255 (100.0)	1255/1255 (100.0)	643/1,253 (51.3)[a] 501/1253 (40.0)[b]	0
Tsuruta [54]	2018	0	1467/3844 (38.2)[c]	991/3844 (25.8)	N/R	N/R	433/3844 (11.3)
Chang [36]	2020	N/R	347/485 (71.5)[a] 279/485 (57.5)[b]	(N/R)	N/R	N/R	N/R
Forbes [13]	2020	621/8,366 (APLT) 15/8366 (AC)	4,551/8366 (54.5)[b]	4,760/8366 (56.9)	1054/8366 (12.6)	416/8366 (5.0)[b]	2505/8366 (29.9)
Chen [55]	2020	74/1424 (APLT) 15/1424 (AC)	838/1925 (43.5)[o]	N/R	0/1925 (0)	0/1925 (0)	268/1925 (13.9)

APLT antiplatelet agents including aspirin and thienopyridines, *AC* anticoagulant agents including vitamin K antagonists, direct oral anticoagulants, and therapeutic doses of intravenous or subcutaneous anticoagulant agents, *AT* use of either APLTs or ACs

[a]Proximal defined as cecum to transverse colon

[b]Proximal defined as cecum to hepatic flexure

[c]Proximal defined as cecum to mid transverse colon

[o]Proximal location not defined

[#]Reported as protruded, not pedunculated

among 16,034 patients), while from RCTs, the DPPB rate was 2.3% (202 events among 8637 patients). The RR was 0.96 (95% CI 0.61 to 1.51) from 8 observational studies including 14,609 patients. Heterogeneity was considerable for observational studies ($I^2 = 62\%$).

The pooled RR for clipping as derived from all RCTs was significant at 0.70 (95% CI 0.53 to 0.94; $I^2 = 2\%$); however, given the breakdowns below, this finding was clearly driven by the results from RCTs enrolling only patients with larger polyps. Five RCTs including 5905 patients with polyps of

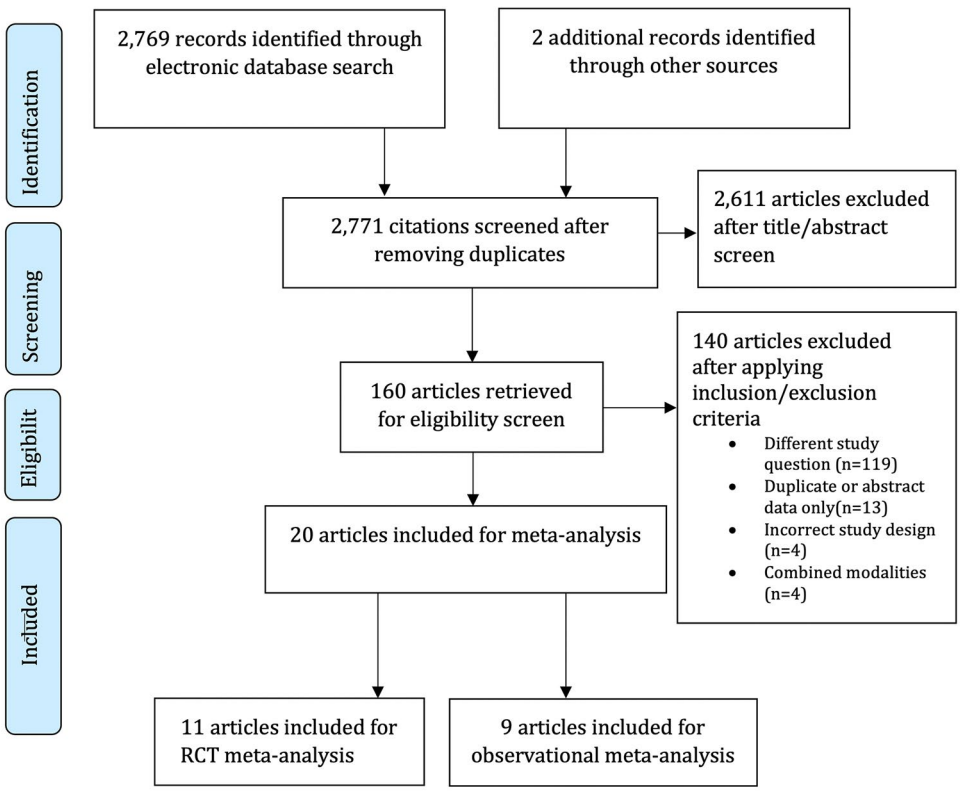

Fig. 1 PRISMA flow diagram of the search results and study selection process [18]

any size did not demonstrate a statistically significant benefit of clipping, with a pooled RR of 0.96 (95% CI 0.62 to 1.48; $I^2 = 0\%$). Four RCTs including 1578 patients with polyps ≥ 10 mm also did not demonstrate a benefit, with a pooled RR of 0.69 (95% CI 0.36 to 1.34; $I^2 = 14\%$). Only two RCTs including 1,154 patients with polyps ≥ 20 mm demonstrated a significant benefit of clipping, with a pooled RR of 0.47 (95% CI 0.29 to 0.77; $I^2 = 0\%$). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [37] was also employed to prepare formal assessments of the certainty of evidence, provided in the Supplementary Materials.

Subgroup, meta-regression and sensitivity analyses

For patients with one or more polyp(s) ≥ 20 mm, the RR of DPPB with clipping was 0.55 (95% CI 0.35 to 0.85) using data from 5 RCTs on 1422 patients, and 0.72 (95% CI 0.35 to 1.46) using data from 5 observational studies on 3053 patients (Fig. 2). Heterogeneity was moderate for observational studies ($I^2 = 51\%$) and low for RCTs ($I^2 = 0\%$). For patients with one or more proximal polyp(s), the RR of DPPB was 0.73 (95% CI 0.33 to 1.62; $I^2 = 71\%$) from RCTs and 1.17 (95% CI 0.75 to 1.85) from the only observational study that captured data on polyp location. These results are summarized in Fig. 3. For patients with one or more proximal polyp(s) ≥ 20 mm, the RR of DPPB with clipping was 0.47 (95% CI 0.24 to 0.95) using data from 3 RCTs on 910 patients. Data from observational studies were again limited in this subgroup, but the results from one study demonstrated a non-significant RR of 0.97 (95% CI 0.34 to 2.74). These results are summarized in Figure 4, 5.

A summary of the findings of all *a priori* subgroup and meta-regression analyses is provided in Table 3. Due to the presence of varying types of antiplatelet and/or anticoagulant medications and inconsistent or unclear manners in which these patient-level data were presented across studies, meaningful subgroup analyses could not be conducted in this group. All results were robust to a sensitivity analysis where fixed effects models were used rather than random effects models. For overall pooled data, exclusion of each study in turn did not significantly alter the effect on the primary outcome. However, when considering only RCT data, exclusion of any of the studies by Albeniz [11], Feagins [10], Pohl [12], Tominaga [38] or Zhang [35] resulted in the upper bound of the 95% confidence interval crossing 1.00. Meta-regression demonstrated that clipping was associated with significant benefit in RCT patients with one or more polyp(s) ≥ 20 mm and that clipping was associated with significant harm in RCT patients with one or more pedunculated polyp (p values of 0.04 and 0.006, respectively). Egger's test demonstrated no significant evidence

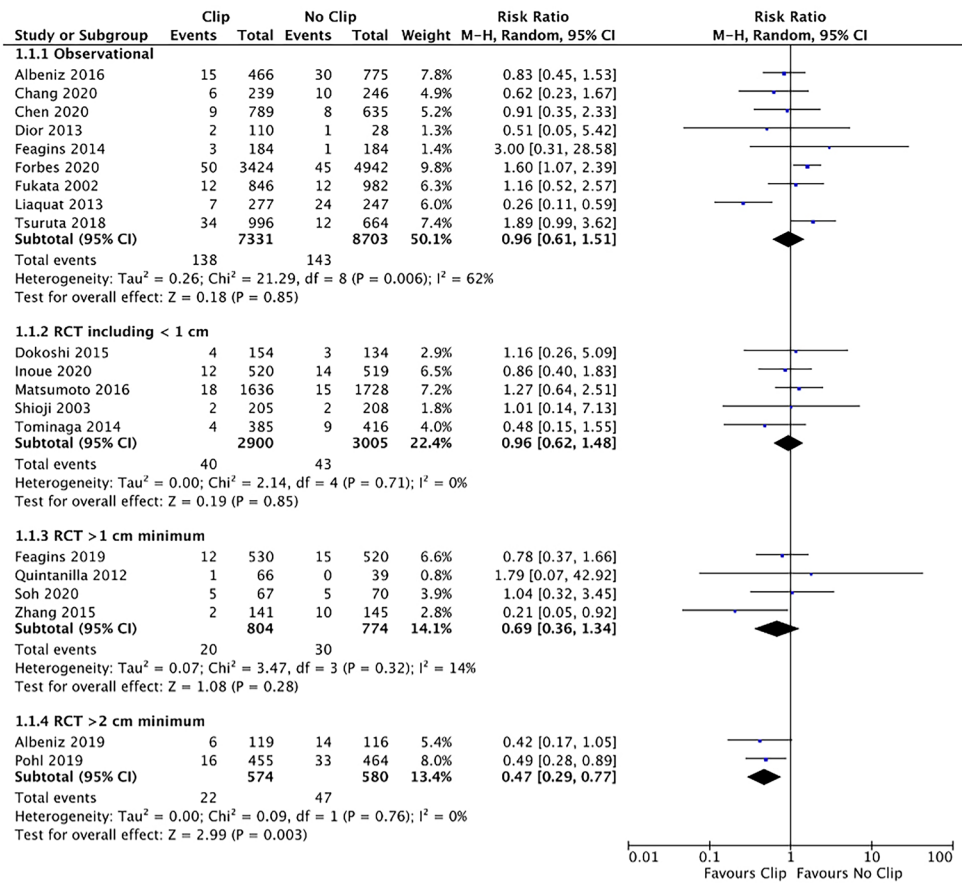

Fig. 2 Forest plot comparing clipping and non-clipping for prevention of delayed post-polypectomy bleeding in all-comers, divided by study type (observational, RCT including polyps of all sizes, RCT including polyps ≥ 10 mm, RCT including only polyps ≥ 20 mm)

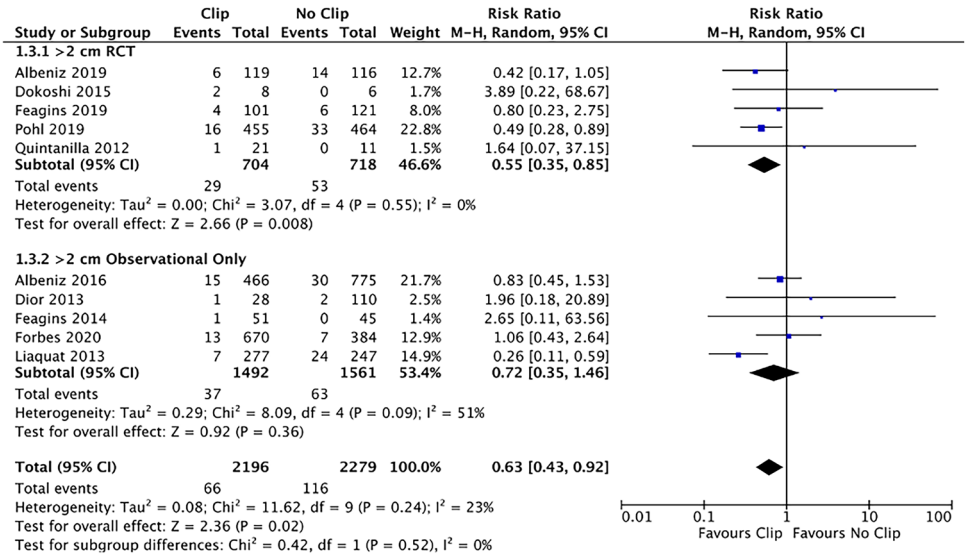

Fig. 3 Forest plot comparing clipping and non-clipping for prevention of delayed post-polypectomy bleeding—all polyps measuring ≥ 20 mm

of publication bias, with *p* values of 0.52 and 0.78 for RCTs and observational studies, respectively. Visual examination of a funnel plot demonstrated no evidence of small study effects (Supplementary Materials).

Discussion

This meta-analysis assessed the efficacy of prophylactic clipping in preventing DPPB from 11 RCTs as well as the real-world effectiveness of clipping from 9 observational

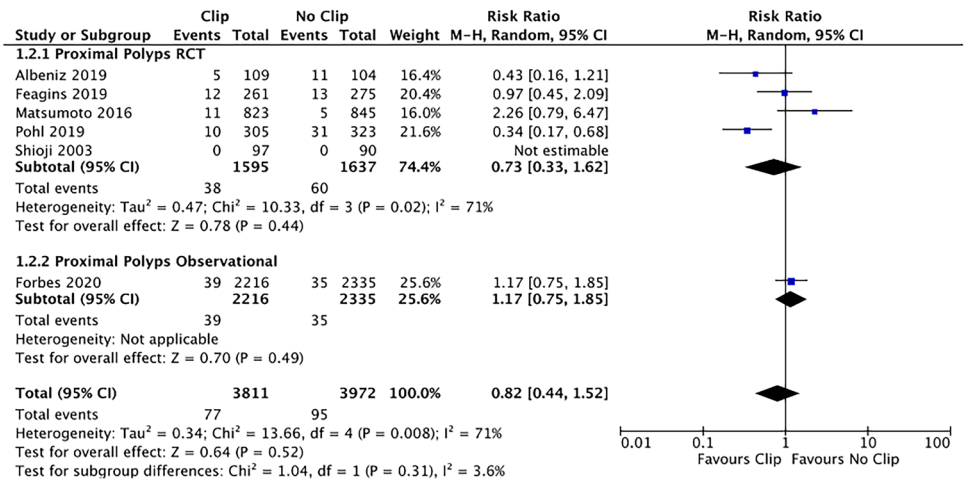

Fig. 4 Forest plot comparing clipping and non-clipping for prevention of delayed post-polypectomy bleeding—all proximal polyps

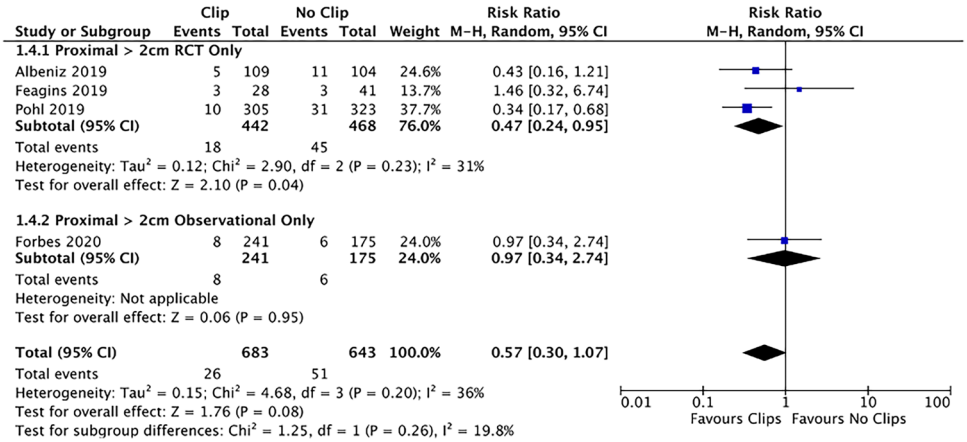

Fig. 5 Forest plot comparing clipping and non-clipping for prevention of delayed post-polypectomy bleeding—all proximal polyps measuring ≥ 20 mm

studies. The efficacy of prophylactic clipping was demonstrated in RCTs enrolling patients with large polyps but not from pooled data on remaining RCTs or observational studies; therefore, the benefits of this practice likely do not extend to all-comers. Furthermore, our finding that the clinical efficacy of prophylactic clipping among large and large proximal polyps does not appear to translate into real-world clinical effectiveness has important implications for endoscopic practice.

Given the absence of benefit among lower-risk polyps, the field has shifted to determining whether higher-risk polyps may benefit from prophylactic clipping. Larger polyp size and proximal colonic location are established predictors of DPPB [13, 22–32], and thus, recent trials have focused on these lesions [10–12]. The study by Pohl et al. [12] reported that prophylactically clipped patients with proximal polyps ≥ 20 mm experienced DPPB at a significantly lower rate than unclipped patients. In contrast, two additional RCTs assessing this polyp subgroup failed to demonstrate statistically significant differences in DPPB between clipped and unclipped patients [10, 11]. The resultant pooled RCT data nevertheless reveal a risk ratio of 0.47 (95% CI 0.24 to 0.95) for DPPB with clipping in this high-risk subgroup. Thus, clipping appears to be modestly effective at reducing DPPB from RCT evidence. However, in the only observational study to assess this subgroup, there was no statistically significant benefit to clipping, with a risk ratio of 0.97 (95% CI 0.34 to 2.74) [13].

While less clear, prophylactic clipping may also have a role among other select intermediate-risk subgroups, such as those with polyps measuring ≥ 20 mm anywhere in the colon. Among these lesions, RCT data suggest a modest benefit of clipping, with a risk ratio of 0.54 (95% CI 0.35 to 0.83); however, pooled observational data from over 3000 patients did not demonstrate a significant benefit. Of note, only two studies have individually demonstrated a benefit of clipping in this subgroup (one observational and one RCT) [12, 39]. In patients with proximal polyps of all sizes, clipping was not beneficial, regardless of study design. DPPB outcomes between clipped and unclipped patients on antiplatelet and/or anticoagulant agents could not be assessed via meta-analysis given the heterogeneous categorizations of these medications between studies in addition to the unclear

Table 3 Summary of subgroup and meta-regression analyses

Subgroups	Number of Studies	Pooled RR (95% CI)	Inter-study heterogeneity (I^2) (%)	Meta-regression summary (RCT)	Meta-regression summary (OBS)
RCTs	11	0.70 (0.53, 0.94)*	2	–	–
RCTs enrolling all polyp sizes	5	0.96 (0.62, 1.48)	0		
RCTs enrolling polyps ≥ 10 mm only	4	0.69 (0.36, 1.34)	15		
RCTs enrolling polyps ≥ 20 mm only	2	0.47 (0.29. 0.77)*	0		
Observational studies	9	0.96 (0.61, 1.51)	62		
Single-center studies	12	0.89 (0.55, 1.44)	58	–	–
Multi-center studies	8	0.74 (0.57, 0.97)*	0		
North American studies	6	0.72 (0.37, 1.40)	76	–	–
European studies	4	0.68 (0.42, 1.11)	0		
Asian studies	10	1.04 (0.76, 1.43)	11		
Studies published prior to 2016	9	0.63 (0.35, 1.13)	35	–	–
Studies published in or after 2016	11	0.93 (0.68, 1.26)	51		
Proximal polyps	6	0.82 (0.44, 1.52)	71	*p* value 0.39(10 observations)	*p* value 0.60 (2 observations)
Distal polyps	6	1.24 (0.71, 2.16)	14		
≥ 10 mm polyps	12	0.71 (0.47, 1.06)	55	*p* value 0.18 (8 observations)	*p* value 0.27 (7 observations)
< 10 mm polyps	3	1.54 (0.65, 3.65)	35		
≥ 20 mm polyps	10	0.63 (0.43, 0.92)*	15	*p* value 0.04* (9 observations)	*p* value 0.12 (7 observations)
< 20 mm polyps	6	1.31 (0.96, 1.79)	2		
≥ 20 mm proximal polyps	4	0.57 (0.30, 1.07)	36		
All others	6	1.26 (0.82, 1.93)	12		
Pedunculated polyps	5	1.70 (1.06, 2.72)*	0	*p* value 0.006* (8 observations)	*p* value 0.43 (3 observations)
Non-pedunculated polyps	6	0.47 (0.21, 1.06)	82		

RCT randomized controlled trial, *OBS* observational study, *RR* risk ratio, *CI* confidence interval

*Statistically significant

reporting of cessation, resumption, and/or bridging patterns, all of which could potentially impact outcomes.

The usefulness of prophylactic clipping has been debated for years. A major distinction of our meta-analysis is that it included data from both observational and randomized studies. This is of particular importance for this topic, given the large disparities in benefits between the RCT and observational data. These discrepancies are difficult to fully account for, but are likely explained by several factors. First, it is well established that the efficacy of interventions reported in RCTs variably translates to real-world effectiveness, given concerns over external validity arising from carefully selected patients in trial settings [16]. Furthermore, differences may also result from variable application of an intervention in a real-world setting (versus an RCT, where this is usually standardized) and less closely monitored patients in observational studies. In the case of clipping, this discrepancy may be particularly evident, as clip closure within RCTs is performed by select highly-trained expert endoscopists recruited to participate. Conversely, clipping in observational studies, particularly retrospective studies, may be performed by all endoscopists practicing within a given center or centers, many of whom have had no formal training in advanced polypectomy or clipping.

The skill required to successfully close a post-polypectomy defect is dependent on the location, shape and size of the defect, and experience and expertise are critical components for success. Furthermore, some polyps are impossible to close completely via clipping, regardless of endoscopist-related factors [11]. Within observational studies, the decision of whether or not to clip is left to the discretion of the endoscopists, and therefore, it is likely that

post-polypectomy lesions that were deemed at higher risk of bleeding were the ones that were clipped. These factors underscore the need for practitioners to take pause when considering the application of prophylactic post-polypectomy clipping in real-world clinical settings. When one introduces the added consideration of the costs required to prevent DPPB, a relatively rare event with a generally benign prognosis [24, 40], the utility of clipping becomes even more questionable [41]. Therefore, we recommend that in the absence of more convincing evidence, prophylactic clipping should only be considered by trained expert endoscopists performing large EMRs, especially in the proximal colon and when the defect can be fully closed.

In addition to assessing outcomes between study designs, other strengths of our study include the inclusion of several studies published in 2020 not previously included [13, 36, 42, 43]. In addition, we excluded data on polyps removed by endoscopic submucosal dissection (ESD), a distinct procedure with its own risk profile [15], and thus not appropriate for pooling together with polypectomy or EMR data [44]. Furthermore, we also performed rigorous quality and risk of bias assessments for both randomized and observational studies. Finally, we performed several clinically and methodologically guided subgroup and meta-regression analyses. Interestingly, the practice of prophylactic clipping was found to increase the risk of DPPB for pedunculated polyps. This finding could be partially explained by clipping having been employed in the absence of combination therapy with epinephrine, which has been proven beneficial [45].

Our study also has important limitations. First, we excluded studies that were only available in abstract form. We made this decision to minimize unmeasured heterogeneity in our results due to possible differences in methodology. However, we also acknowledge that the exclusion of grey literature may increase the likelihood of publication bias. Furthermore, we were unable to quantitatively assess the effect of prophylactic clipping in patients taking antiplatelet and/or anticoagulant medications. Though it is possible that this population may derive higher benefits from clipping, it may be difficult to prove this for two main reasons. First, sample size issues could prohibit outcome assessments in this population within prospective studies, and second, missing data in retrospective studies regarding cessation, resumption, and bridging patterns is all too common. Additionally, statistical heterogeneity was moderate to considerable between included studies for most subgroups in addition to the overall primary outcome, indicating that important differences in endoscopist and/or patient populations and study methodologies likely exist. Finally, we did not set a minimal input study sample size for inclusion in our meta-analysis; therefore, small study effects could have influenced our findings. In combination, these limitations should lead readers to interpret our findings cautiously overall.

In conclusion, our findings suggest that prophylactic clipping likely results in little to no difference in DPPB following removal of the vast majority of polyps. In patients with one or more polyp(s) $\geq$ 20 mm, prophylactic clipping reduces DPPB, especially for lesions in the proximal colon. However, external factors such as endoscopist skill level likely influence widespread generalizability to real-world practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00464-021-08398-x.

Authors contribution NF conceived of and designed the study and co-drafted the manuscript and is the guarantor of the manuscript. KB and ZWM co-drafted the manuscript. All authors analysed and interpreted the data. All authors critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript.

Funding None.

Compliance with ethical standards

Disclosures Dr. Forbes is a consultant for Boston Scientific, is on the speakers' bureau for Pentax Medical and has received unrelated funding from Pentax Medical. Dr. Kaplan is a speaker and/or consultant for AbbVie, Janssen, Pfizer, Gilead and Takeda and has received unrelated research funding from Ferring, Janssen, AbbVie, GlaxoSmithKline, Merck and Shire. Dr. Bourke has received unrelated research funding from Cook Medical, Olympus Medical, and Boston Scientific. Dr. James has received unrelated research funding from AmGen Canada. All disclosures are unrelated to this work. Dr. Bishay, Dr. Meng, Mr. Frehlich, Dr. Hilsden and Dr. Heitman have no potential conflicts of interest or financial ties to disclose.

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