PROPHYLACTIC CLIPPING AFTER COLORECTAL ENDOSCOPIC RESECTION PREVENTS BLEEDING OF LARGE, PROXIMAL POLYPS: META-ANALYSIS OF RANDOMIZED TRIALS

Short title: Prophylactic clipping for PPB prevention

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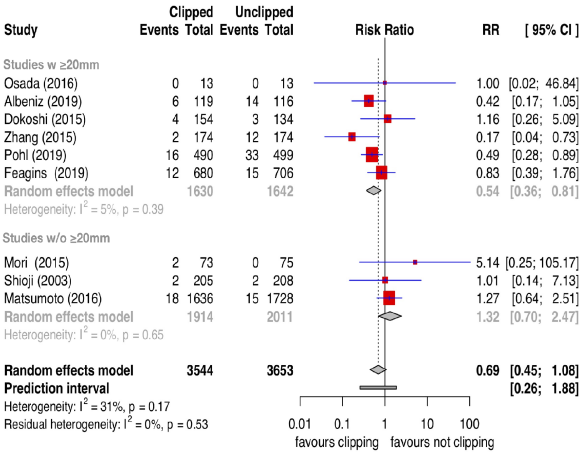
Abbreviations:

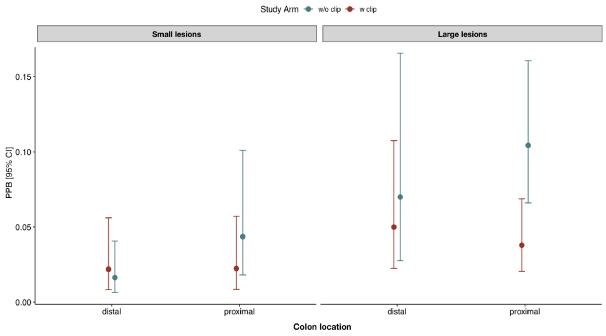
- Colorectal Cancer (CRC)
- Post-polypectomy (delayed) bleeding (PPB)
- European Society of Gastrointestinal Endoscopy (ESGE)
- Randomized controlled trials (RCTs)
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- Intention-to-treat (ITT)
- Per-protocol (PP)
- Risk ratios (RR)
- Prediction interval (PI)
- Odds ratios (ORs)

Clipping vs not clipping in preventing Post-Polypectomy Bleeding



Sub-analysis of size according to location.

PPB risk: Clipping vs Not-Clipping
Large and proximal polyps: 3.8% vs 10.0%
Small and distal polyps: 2.2% vs 1.6% (ns)



Clipping appeared to be beneficial after resection of large and proximal lesions

Abstract:

Background & Aims: The benefits of prophylactic clipping to prevent bleeding after polypectomy are unclear. We conducted an updated meta-analysis of randomized trials to assess the efficacy of clipping in preventing bleeding after polypectomy, overall and according to polyp size and location.

Methods: We searched the Medline/PubMed, EMBASE, and Scopus databases randomized trials that compared effects of clipping vs not clipping to prevent bleeding after polypectomy. We performed a random-effects meta-analysis to generate pooled relative risks (RRs) with 95% CIs. Multilevel random-effects meta-regression analysis was used to combine data on bleeding after polypectomy and estimate associations between rates of bleeding and polyp characteristics.

Results: We analyzed data from 9 trials, comprising 7197 colorectal lesions (22.5% 20 mm or larger, 49.2% with proximal location). Clipping, compared with no clipping, did not significantly reduce the overall risk of post-polypectomy bleeding (2.2% with clipping vs 3.3% with no clipping; RR, 0.69; 95% CI, 0.45–1.08; *P*=.072). Clipping significantly reduced risk of bleeding after removal of polyps that were 20 mm or larger (4.3% had bleeding after clipping vs 7.6% had bleeding with no clipping; RR, 0.51; 95% CI, 0.33–0.78; *P*=.020) or that were in a proximal location (3.0% had bleeding after clipping vs 6.2% had bleeding with no clipping; RR, 0.53; 95% CI, 0.35–0.81; *P*<.001). In multilevel meta-regression analysis that adjusted for polyp size and location, prophylactic clipping was significantly associated with reduced risk of bleeding after removal of large proximal polyps (RR, 0.37; 95% CI, 0.22–0.61; *P*=.021) but not small proximal lesions (RR, 0.88; 95% CI, 0.48–1.62; *P*=0.581).

Conclusions: In a meta-analysis of randomized trials, we found that routine use of prophylactic clipping does not reduce risk of post-polypectomy bleeding, overall. However, clipping appeared to reduce bleeding after removal of large (more than 20 mm), proximal lesions.

Key words: comparison, colonoscopy, complication, PPB

BACKGROUND

Colonoscopy and endoscopic resection of precancerous lesions significantly decreases the risk of Colorectal Cancer (CRC) incidence and death [1-3]. However, endoscopic procedures might result in adverse events, such as post-procedural pain, intra- or post-procedural bleeding, perforation and even death [4]. Post-procedural (delayed) bleeding (PPB) after polypectomy and endoscopic mucosal resection is the most common major adverse event, ranging from 1% to 6% [5,6]. Larger lesion size and proximal location are well-established risk factors for PPB [7,8]. PPB may require the need for hospitalization, blood transfusion, and further endoscopic or more invasive treatments, representing a risk for the patient and a burden to the health system.

Despite lack of high quality evidence, prophylactic clipping has been advocated as a technique to reduce the risk of PPB. For instance, the European Society of Gastrointestinal Endoscopy (ESGE) suggests that there may be a role for prophylactic clipping, and that this decision be based on patient risk factors [4]. However, this recommendation has been graded as weak since it is based on low quality evidence. Previous meta-analysis, mostly analyzing studies with small lesions (<20 mm) and at high risk of bias, reported no protective effect of prophylactic clipping for non-pedunculated lesions [9-11]. Recently, high-quality randomized controlled trials (RCTs) have been published, investigating the efficacy of prophylactic clipping primarily for lesions larger than 20 mm. However, there is uncertainty on the overall efficacy of clipping and whether it is possible to identify sub-groups that may benefit from prophylactic clipping. This issue is clinically relevant considering the costs and technical complexity of clipping.

We performed a systematic review and meta-analysis of all available RCTs to clarify the role of prophylactic clipping in preventing post polypectomy bleeding following endoscopic resection of colorectal lesions.

METHODS

The methods of our analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) on October 2019.

The following methods are reported in **appendix 1**: data sources and search strategy, the selection process, data extraction and the quality assessment.

Inclusion and exclusion criteria

For the purpose of our meta-analysis, we screened all clinical studies for the following *inclusion criteria*:

(I) Population: all adults undergoing endoscopic resection of colorectal lesions.

(II) Intervention: post-polypectomy prophylactic closure of mucosal defects with hemoclips.

(III) Comparison: no prophylactic clipping post-polypectomy.

(IV) Outcome: risk of delayed post-polypectomy bleeding.

(V) Study design: only randomized controlled trials were considered.

Exclusion criteria were as follows:

(I) Essential information not available;

(II) Studies not published as full text article;

(III) Studies not published in the English language;

(IV) Studies considering as comparator any intervention strategy for post procedural bleeding prophylaxis (i.e. cauterization of post-procedural ulcer floor by argon plasma coagulation, injective strategies, use of topical hemostatic agents, etc).

(V) studies including less than 10 patients in each group

Study end-points

The primary aim of this study was to assess the efficacy of endoscopic clipping for the prevention of PPB. We included all patients randomly assigned to the clipping group in the intention-to-treat (ITT) analysis. When both sets of data were provided, values from ITT were preferred to per-protocol (PP). A per-protocol (PP) analysis was also conducted, including only those patients who underwent a complete closure of the mucosal defect. PPB was defined as any post procedural clinically evident hematochezia that required medical intervention (hospitalization, blood transfusion, repeated colonoscopy, angiography or surgery) or caused a more than 2 g/dL decrease in the blood hemoglobin concentration.

The secondary aim of the study was to determine the effect of risk factors (patient and lesion) on the risk of PPB with and without clipping. The risk factors taken into account were: patient age and gender, use of antiplatelet/anticoagulant therapy, as well as lesion characteristics such as the polyp size; morphology and location (proximal), and histology (serrated and adenomatous). Lesions ≥20mm were defined as 'large' and morphology was described according to the Paris classification [13]. Lesion location was defined as per the reporting in the studies. An additional secondary aim was to assess the efficacy of endoscopic clipping for the prevention of other post-procedural adverse events such as perforation.

Statistical Analysis

All statistical analyses were conducted with the R program (version 3.5.1, 2018-07-02) [14]. In particular, we used the meta [15] and metafor [16] libraries in R to conduct the meta-analysis and meta-regression analysis. All tests are two tailed. For all tests, a probability level less than .05 was considered significant. Study characteristics were summarized using descriptive statistics. Risk ratios (RR) and 95% CIs were estimated with the Mantel-Haenszel (fixed-effects model) and the DerSimonian-Laird (random-effects model) methods. The summary effect sizes from random-effects meta-analysis (assumption that the effects estimated in the different studies were not identical) were calculated. We assessed statistical heterogeneity between studies by visual inspection of forest plots and by the I^2 and $\chi 2$ statistics for heterogeneity. I^2-values of 0-30%, 30-60%, 50-90% and 75-100% were classified as low, moderate, substantial and considerable heterogeneity, respectively. We also calculated the 95% CI for pooled estimates, as well as the prediction interval (PI) [17].

Sensitivity analyses were performed to assess the stability of the results, namely, a single study in this meta-analysis was omitted one at a time to assess the influence of the individual study to the pooled RR [18]. Visual inspection of funnel plot asymmetry was conducted along with the Egger's weighted regression method to assess publication bias ($P<0.05$ was considered statistically significant).

Meta-Regression Analysis of relative risk estimates and subgroup analyses

We conducted a meta-regression analysis to investigate the impact of various risk factors on the study estimates of relative risk. The natural logarithm of the risk ratio was the dependent variable, and study level characteristics (e.g., number of participants, mean age, percentage of males, the percentage of proximal polyps, the percentage of large polyps) were entered as explanatory factors. As the first step, we performed univariate regression analyses for each factor. All significant factors

(at a significance level of $p<0.10$) were then included in a multivariable regression model. The estimated coefficients of the regression model corresponded to differences in the log risk ratios for one unit of difference in the explanatory factor (continuous variable) or for each category relative to the baseline category (for categorical explanatory variables). Of note, input percentages (e.g., the percentage of proximal polyps) were analyzed as continuous variables, expressed originally as decimal fractions. The percentages were multiplied by 10 before entering in the regression model. Therefore, a change of 1 unit on the scaled variables corresponded to a change of 0.10 (10%) in the original variables. Subgroup analyses were also performed according to the polyp location (proximal vs. distal colon) and size (large vs. small polyps).

Multilevel (random-effects) model: meta-analysis of rates of PPB with clipping versus no clipping

As a subsequent step, we performed a multilevel regression analysis to estimate the rates of PPB associated with clipping versus no clipping. The outcome measure in this analysis was the proportion of PPB transformed via logits. Since the studies included in the analysis reported multiple outcome measures, we used a multilevel meta-analysis method to combine data, with random effects at both the study level and at the outcome level (see Appendix 1). The multilevel model was extended by including predictor variables (i.e., study group, prevalence of large lesions and proximal colon location) in an attempt to determine variables that moderate the effect. In this model, predictor variables were aggregated at the study-arm level. We also considered appropriate interactions between these variables. Data were presented as odds ratios (ORs) and 95% CIs. This analysis was an indirect way to deal with aspects such as the possibility of effect modification by polyp characteristics, and to examine for decreasing bleeding risk with clipping vs. not clipping.

RESULTS

Study characteristics and quality

The initial literature search resulted in 1112 articles (**Figure 1**). A total of 9 trials were included in the final analysis [19-27]. Study characteristics are shown in Table 1. Studies were published between 2003 and 2019 in USA (n=3), Europe (n=1) and Asia (n=5). Five studies involved multiple centers, while 4 studies were single-center experiences. The objective assessment of the risk of bias is reported in **Supplemental Table 1 (Appendix 2)**.

The total number of participants included in the intention-to-treat analysis was 4557 (2288 in the clipping and 2,269 in the control group), and the individual study sample size ranged from 26 to 1,499 patients. Mean patient age ranged from 60.5 to 72.7 years. A total of 7197 colorectal lesions were analyzed (3544 clip and 3653 control group). The percentage of proximal polyps ranged from 25% to 92% with the mean percentage at 49.2%. The mean size of polyps ranged from 7.8 mm to 37.3 mm with an average polyp size of 18.6 mm. Of the analyzed studies, 3 included only patients with polyps > 20 mm; 3 with patients having polyps of any size (mean percentage of lesions ≥20 mm, 19.4%), whereas the remaining 3 studies included only lesions <20 mm in size.

Effect of clipping on PPB risk

Based on data reported by all 9 trials, the estimates of PPB risk between the control and clip groups were 3.3% (95% CI:1.9-5.7%) and 2.2% (95% CI:1.2-3.9%) (multilevel random-effect model accounting for the underlying heterogeneity between and within trials), respectively (**Appendix 3. Supplemental Figure 1**). No significant difference between the 2 groups was noted for the risk of PPB when a random-effects model was applied (RR= 0.69, 95% CI:0.45-1.08, p=0.072, **Figure 2**). Moderate heterogeneity among the studies existed ($I^2 = 31\%$, p=0.170), and the likelihood of publication bias was low (p=0.42) (**Appendix 3. Supplemental Figure 2**). The results of the meta-analysis did not change substantially when data from "per-protocol" analysis were combined (**Appendix 3. Supplemental Figure 3**). The results of the "Leave-One-Out" sensitivity analysis are reported in **Appendix 2. Supplemental Table 2**. Only one study that evaluated patients with lesions <20 mm was determined to have a substantial influence on the overall effect size [23]. After removing this trial (in a sensitivity analysis) the heterogeneity was significantly reduced (I^2=8.2%) and the pooled (random-effects) RR was 0.58 [0.39; 0.88]. To further investigate the impact of study level characteristics on RR estimates, we performed a meta-regression analysis (**Table 2**). The analysis showed that use of prophylactic clipping was associated with a significant

reduction in PPB as the percentage of large lesions in the study population increased. The meta-regression coefficient for the percentage of large (≥20 mm) lesions was 0.92 (95% CI: 0.85-0.98), indicating that for every 10% increase in the percentage of large lesions, the RR of PPB decreased by 8% (95% CI:2-15%) if prophylactic clipping was utilized (**Appendix 3. Supplemental Figure 4**). This finding was remarkably robust in the multilevel multivariate analysis (**Appendix 2. Supplementary Table 3**).

Effect of clipping on PPB risk according to polyp size

A sub-group analysis by polyp size (large versus small polyps) confirmed the above meta-regression result (**Figure 3**). A beneficial effect of clipping was determined among studies including ≥20mm polyps (RR=0.51; 95% CI:0.33-0.78), while among those with <20mm polyps, there was no significant benefit (RR=1.04; 95% CI:0.60-1.79). According to multilevel random-effects meta-regression analysis, the estimated rates of PPB among ≥20mm and <20mm lesions were 7.6% (95% CI:4.9-11.5%) and 1.8% (95% CI:1.1-2.9%), respectively, in the control group compared to 4.3% (95% CI:2.5-7.1%) and 1.4% (95% CI:0.9-2.4%), respectively, in the prophylactic clipping group (**Appendix 2. Supplemental Table 4 Appendix 3. Supplemental Figure 5**). Again, the multilevel model indicated showed a protective effect of clipping for large polyps that remained significantly after adjusting for the prevalence of proximal polyps (OR, 0.53; 95% CI:0.31-0.90).

Effect of clipping on PPB risk based on polyp location with sub-analysis by size.

Seven trials with available data on proximal/distal lesions (1618/1648 clipped and 1650/1720 control groups) were included in this analysis. **Figure 4** graphs the risk ratios and 95% CIs from the individual trials and the pooled results. Among proximally located lesions, there was a significant association between use of prophylactic clipping and risk of PPB (RR=0.53; 95% CI:0.35-0.81). However, among distally located lesions there was no significant difference between the 2 groups and risk of PPB (RR=1.01; 95% CI: 0.43-2.37). This association was corroborated by both sensitivity analysis among studies defining proximal lesions as those located proximal to the splenic flexure (including transverse colon), and those defining proximal lesions as in the cecum, ascending colon or hepatic flexure (**Appendix 3. Supplemental Figure 6 and 7**). According to a multilevel random-effects meta-regression analysis, the estimated rates of PPB in the distal and proximal colon were 2.7% (95% CI:1.3-5.4%; PI:0.5-12.3%) and 6.2% (95% CI:3.4-11.1%; PI:1.3-24.3%), respectively, in the control group compared to 3.3% (95% CI:1.6-6.5%; PI:0.7-14.6%) and 3.0% (95% CI:1.5-5.7%; PI:0.6-13.2%), respectively, in the clip group (**Appendix 3. Supplementary**

Figure 8). The above model showed a protective effect of clipping for proximally located polyps (clipped proximal vs. unclipped proximal polyps, OR, 0.46; 95% CI:0.24-0.88) (Appendix 3 Table 5).

After adjusting for the prevalence of large lesions in the multilevel model, the benefit of clipping in reducing PPB was significant only for large proximal lesions (clipped versus unclipped polyps, OR, 0.37; 95% CI:0.22-0.61; p=0.021), but not for small proximal lesions (clipped versus unclipped polyps, OR, 0.88; 95% CI:0.48-1.62; p=0.581). This finding was remarkably robust in sub-group and sensitivity analyses (Figure 5 and Appendix 3 Supplementary Figure 9). Clipping was also not beneficial for large distal lesions (RR:0.70; 95% CI:0.22-2.27), although this outcome mainly depended by the lack of benefit in only one large series (**Appendix 3. Supplementary Figure 10**), and for small distal lesions (RR:1.34; 95% CI:0.42-4.35; **Figure 5**).

Perforations.

Data on perforation were available in 6 studies. In total, 14 perforation events were reported (6/1074, 0.56% in the clip and 8/1085, 0.74% in control group) with a RR of 0.70; 95% CI:0.25-1.91; p=0.480; I2 = 0.0%), indicating no significant differences between groups.

Additional analysis

The quality of evidence was assessed by applying the GRADE methodology. The level of evidence for RCTs was downgraded due to low-moderate quality of the included RCTs (assessed by Cochrane risk bias tool for randomized studies) and the inconsistency owing to heterogeneity among patients (i.e. different indications to resection in term of lesion size or location). Details can be found in **Appendix 2. Supplemental Table 6.**

Additional technical features such as types of clips used and electrosurgical unit characteristics are detailed in **Appendix 2. Supplemental Table 7.**

DISCUSSION

According to our meta-analysis, routine practice of endoscopic clipping as a prophylactic intervention does not reduce the risk of post-polypectomy bleeding. However, clipping was effective in reducing the risk of PPB by nearly 50% for large lesions (≥20 mm). If such lesions do not undergo endoscopic clipping, there was 4-fold increase in the baseline risk of PPB as compared with those <20 mm. Such benefit appeared to be limited to large lesions located in the proximal colon.

The results of our analysis are relevant for several reasons. Meta-analysis of randomized trials is considered as the strongest evidence for clinical recommendations. The lack of efficacy of prophylactic clipping after any polypectomy was confirmed by our results showing no significant difference in PPB risk between the 2 groups (clip vs control group). This was further confirmed by the 'leave-one-analysis' – i.e. clipping became significantly effective when excluding this series – as this was the largest series on small lesions. This inference is a distinctive advantage of our analysis, as the previous systematic reviews were not powered enough to perform it [9-11, 30-32].

Our analysis showed the clinical relevance of two main factors: polyp size and location, on both the absolute risk of PPB and the relative efficacy of clipping, as well as their hierarchical interaction. Our adjusted estimates attributed a nearly 2-fold increase – from 4.3% to 7.6% – in the risk of PPB for lesions ≥20 mm. This finding was supported by two additional results. First, the PPB risk estimate proportionally increased as the percentage of ≥20 mm increased in the included studies. Secondly, such cut-off size was the only significant risk factor associated at meta-regression with PPB risk.

While showing an increase in the PPB risk according to size, our data also showed a clear reduction in PPB risk with clipping. A 50% reduction in PPB for those with clipped ≥20 mm lesions directly translated to a NNT of 23 for lesions to be clipped in order to prevent one additional bleeding. A recent US-based study showed significant cost-savings when adopting such a cut-off [33].

Regarding location, our data support proximal location as possible risk factor for PPB risk and clipping efficacy. In the control group we observed a 2-fold increase in the risk for PPB for polyps located in the distal versus the proximal colon – from 2.7% to 6.2% respectively. Regarding the interaction between size and location, size ≥20 mm appeared to be the primary determinant of PPB risk. Thus, the benefit of clipping was clear in large proximal lesions, while it was absent for small lesions, even when they were located in the proximal colon. On the other hand, the risk of

PPB and clipping efficacy was somewhat intermediate – albeit not statistically significant – for large and distal lesions. This was mainly attributed to the lack of the effect of clipping in a large study on ≥20 mm lesions [26]. However, this was not confirmed by other studies generating some uncertainty on the benefit of prophylactic clipping for large distal lesions. Thus, the decision for large and distal lesions should be tailored, especially taking into consideration other patient- and polyp-risk factors for PPB, such as the use of anti-thrombotic agent or intra-procedural bleeding. The studies included in our analysis did not reveal significant heterogeneity nor publication bias. This indicates that the effect is homogeneous across the different series, suggesting generalizability and reproducibility of the results. Of note, the only study that contributed to the slight heterogeneity on our primary end-point [23] included only small polyps, suggesting that such size inclusion criteria could explain the slight degree of heterogeneity, as confirmed by subsequent meta-regression and subgroup results. In addition, the observation that the effect is orientated towards clipping efficacy in the vast majority of the cases strengthens the robustness of our observation.

Our data pair with recent cost-effectiveness analysis (using Medicare cost data and CMS billing codes) focusing on the impact of adoption of routine prophylactic clipping in practice from a payer perspective, considering relevant patient- and polyp-specific factors [33]. Considering that clips are expensive and their placement might be technically demanding, prophylactic clipping tailored for a subgroup of higher risk lesions/patients would decrease in parallel both adverse events and costs. Our data support the use of clipping for any large proximal lesion, excluding its use for those <20 mm and those located in the distal colon. On the other hand, the choice for large distal ones is likely to be less effective, and should be individualized according to also patient characteristics [34].

There are the limitations to our study. First of all, the paucity of data about patient's comorbidities and the management of antithrombotic therapies prior to endoscopic resection in many of the included studies limited our ability to infer on this relevant topic. Thus, high quality RCTs are needed to determine whether prophylactic clips should be suggested after resecting small (<20 mm) and distal lesions in patients on antithrombotic therapies. Secondly, some of the included studies were of low to moderate quality, limiting the quality of our recommendations. Furthermore, study limitations such as lack of blinding of outcome assessors could almost be considered as intrinsic of RCTs evaluating endoscopic procedures, yet remaining the best possible evidence. Also, several patients included in the analysis underwent multiple resections. In case of bleeding, it is sometimes difficult to determine which polypectomy site was bleeding in patients who did not undergo colonoscopy. Further, even in cases requiring endoscopy the bleeding site may remain

uncertain. Last, we were not able to stratify data according to technical variables that might affect the risk of bleeding (and the effect of clipping) such as hemoclips or electrosurgical unit characteristics (Supplemental Table 7).

In conclusion, the results of our meta-analysis of RCTs do not support the routine use of prophylactic clipping for the prevention of PPB. However, clipping appeared to be beneficial in patients with large (>20 mm) and proximal lesions.

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Figure caption

Figure 1. PRISMA flow diagram. RCTs: randomized controlled trials

Figure 2. Forest plot comparing clipping vs. not clipping arm. The relative risk of developing a post-(delayed) polypectomy bleeding (PPB) event for polyps clipped or unclipped is displayed. The line-of-no-effect (vertical line) separates outcomes that favor clipping and not clipping. The squared red boxes represent the point estimates and the horizontal lines represent the associated 95% confidence intervals for each study. The area of each square is proportional to the study's weight in the meta-analysis. Overlapping confidence intervals of the individual studies and an I^2 value of 31% with a non-significant p-value (0.17) indicates homogeneity of the studies. Studies were separated according to size criterion for polyp inclusion: studies including large lesions in their datasets (i.e., with, w lesions ≥20mm) and those including only lesions<20mm (i.e., without, w/o ≥20mm).

Figure 3 - Subgroup analysis of relative risk of developing post-polypectomy (delayed) bleeding events (PPB) with and without clipping for large polyps versus small polyps. For each subgroup, the relative risk of developing PPB for polyps clipped or unclipped is displayed. The line-of-no-effect (vertical line) separates outcomes that favor clipping and not clipping. The squared red boxes represent the point estimates and the horizontal lines represent the associated 95% confidence intervals for each study. The area of each square is proportional to the study's weight in the meta-analysis. Overlapping confidence intervals of the individual studies and I^2 values with non-significant p-values indicates homogeneity of the studies.

Figure 4 – Subgroup analysis comparing clipping vs. not clipping arm for successful control of post-polypectomy (delayed) bleeding events (PPB) for distally and proximally located lesions. For each subgroup, the relative risk of developing a PPB for polyps clipped or unclipped is displayed. The line-of-no-effect (vertical line) separates outcomes that favor clipping and not clipping. The squared red boxes represent the point estimates and the horizontal lines represent the associated 95% confidence intervals for each study. The area of each square is proportional to the study's weight in the meta-analysis. Overlapping confidence intervals of the individual studies and a I^2 value with a non-significant p-value indicates homogeneity of the studies.

Figure 5 – Sub-analysis of size according to location. In this analysis, results from the studies were analyzed according two subgroups: studies including more than 50% of large lesions in their analysis sets were considered “large” polyps, the others “small” polyps. The PPB risks for clipped and unclipped large and proximal polyps were 3.8% (95% CI:2.1-6.9%) and 10.0% (95% CI:6.6-16.7%) (RR, 0.34; 95% CI:0.19-0.65), while PPB risks for small and proximal polyps were 2.2% (95% CI:0.9-5.7%) and 4.3% (95% CI:1.1-10.1%), respectively, (RR. 0.50; 95% CI:0.16-1.57). The corresponding features for clipped and unclipped large and distal polyps were 5.0% (95% CI:2.2-10.7%) and 7.0% (2.8-16.6%), respectively, (RR:0.70; 95% CI:0.22-2.27), while PPB risks for small and distal polyps were 2.2% (95% CI:0.8-5.6%) and 1.6% (95% CI:0.7-4.1%), respectively (RR:1.34; 95% CI:0.42-4.35).

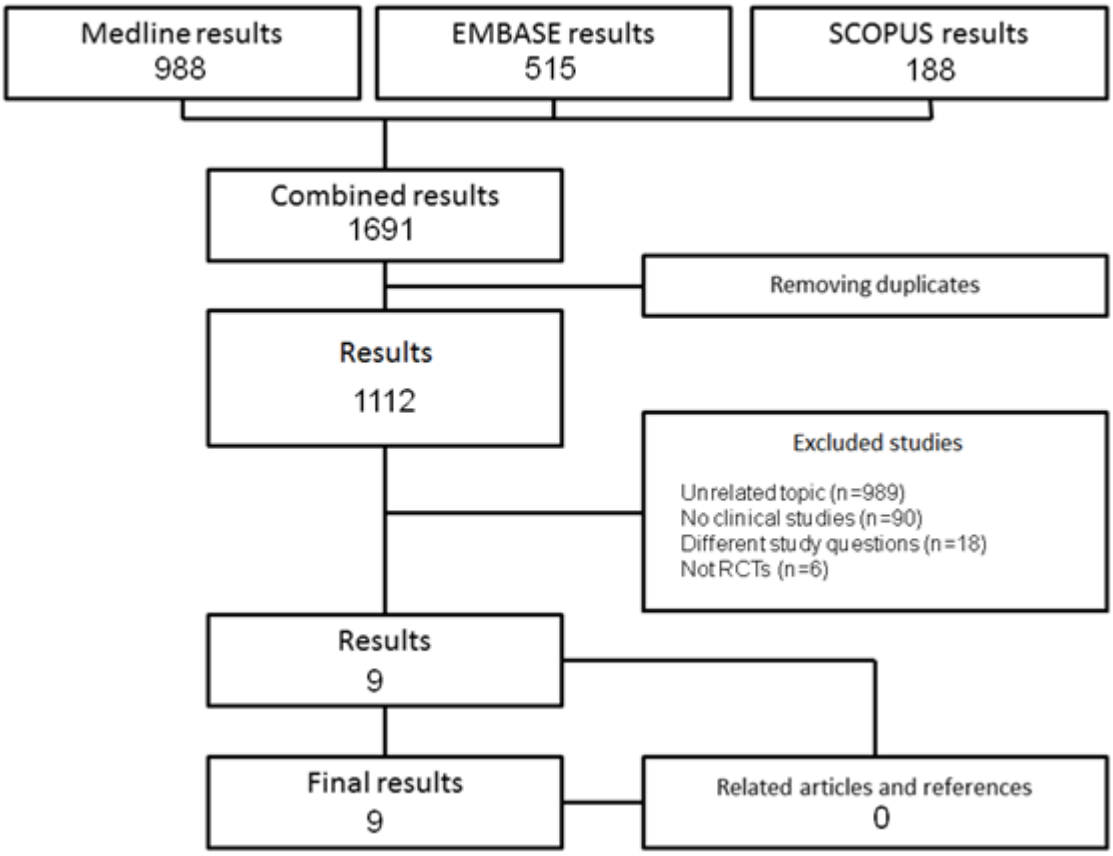
Table 1 - Study characteristics. NA: Not available; * standardized methods to measure polyp size were used

Trial	Country	Randomization Level (patients/polyps)	Randomization Time (pre/post resection)	Patients (clipped/ unclipped)	Male (clipped/ unclipped)	Mean Age (clipped/ unclipped), years	Polyps (clipped/ unclipped)	Inclusion criteria for polyp size	# of large lesions (clipped/ unclipped)	# of proximal lesions (clipped/ unclipped)
Albeniz[25] (2019)	Spain	Patients	Post	235 (119/116)	158 (77/81)	71.9 (72.7/71.1)	235 (119/116)	≥20 mm*	235 (119/116)	213 (109/104)
Dokoshi[20] (2015)	Japan	Patients	Pre	157 (89/68)	NA	67.4 (67.1/67.8)	288 (154/134)	polyps of any size (5%, ≥20 mm)	14 (8/6)	74 (40/34)
Feagins[27] (2019)	US	Patients	Post	1050 (530/520)	1015 (516/499)	64.25 (64.5/64)	1386 (680/706)	polyps of any size * (39% ≥20 mm)	222 (101/121)	536 (261/275)
Matsumoto[23] (2016)	Japan	Patients	Pre	1499 (752/747)	1047 (534/513)	60.75 (60.5/61)	3364 (1636/1728)	<20 mm	0 (0/0)	1668 (823/845)
Mori[21] (2015)	Japan	Polyps	Pre	NA	NA	NA	148 (73/75)	<20 mm*	0 (0/0)	42 (21/21)
Osada[24] (2016)	Japan	Patients	NA	26 (13/13)	13 (9/4)	67.5 (68.8/66.2)	26 (13/13)	≥20 mm	26 (13/13)	18 (8/10)
Pohl[26] (2019)	US	Patients	Pre	919 (455/464)	547 (265/282)	65.1 (65.1/65.1)	989 (490/499)	≥20 mm*	989 (490/499)	658 (327/331)

Shioji[19] **(2003)**	Japan	Polyps	Post	323 (156/167)	248 (118/130)	63.5 (64/63)	413 (205/208)	<20 mm	0 (0/0)	187 (97/90)
Zhang[22] **(2015)**	China	Patients	NA	348 (174/174)	219 (112/107)	66.05 (67.9/64.2)	348 (174/174)	polyps of any size (36% ≥20 mm)	130 (63/67)	101 (50/51)

Table 2 Meta-analysis of overall risk of Post-Polypectomy Bleeding (PPB) - Meta-regression results

	Univariate Meta-regression analysis			**Multivariate Meta-regression analysis**		
Variable	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**
No. of participants (per 100-individual increase)	1.03	1.00-1.06	0.051	1.01	0.98-1.05	0.438
Mean patient age, year						
<66 years	1					
>65 years	0.54	0.23-1.26	0.155			
Country						
US/Europe	1					
Asia	0.99	0.33-3.00	0.991			
Percentage of male participants	0.99	0.40-0.33	0.957			
Percentage of large lesions	0.92	0.85-0.98	0.017	0.92	0.86-0.99	0.042
Percentage of proximal lesions	0.88	0.74-1.05	0.152			
Percentage of non-polypoid lesions	1.27	0.21-7.54	0.792			
Percentage of non-pedunculated lesions	0.14	0.01-4.21	0.256			
Percentage of adenomatous lesions	1.10	0.78-1.52	0.680			
Percentage of serrated lesions	0.11	0.00-5.72	0.276			
Percentage of patients with antiplatelet therapy	0.02	0.00-3.78	0.144			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EMBASE results
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SCOPUS results
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Combined results
1691
Removing duplicates
Results
1112
Excluded studies
Unrelated topic (n=989)
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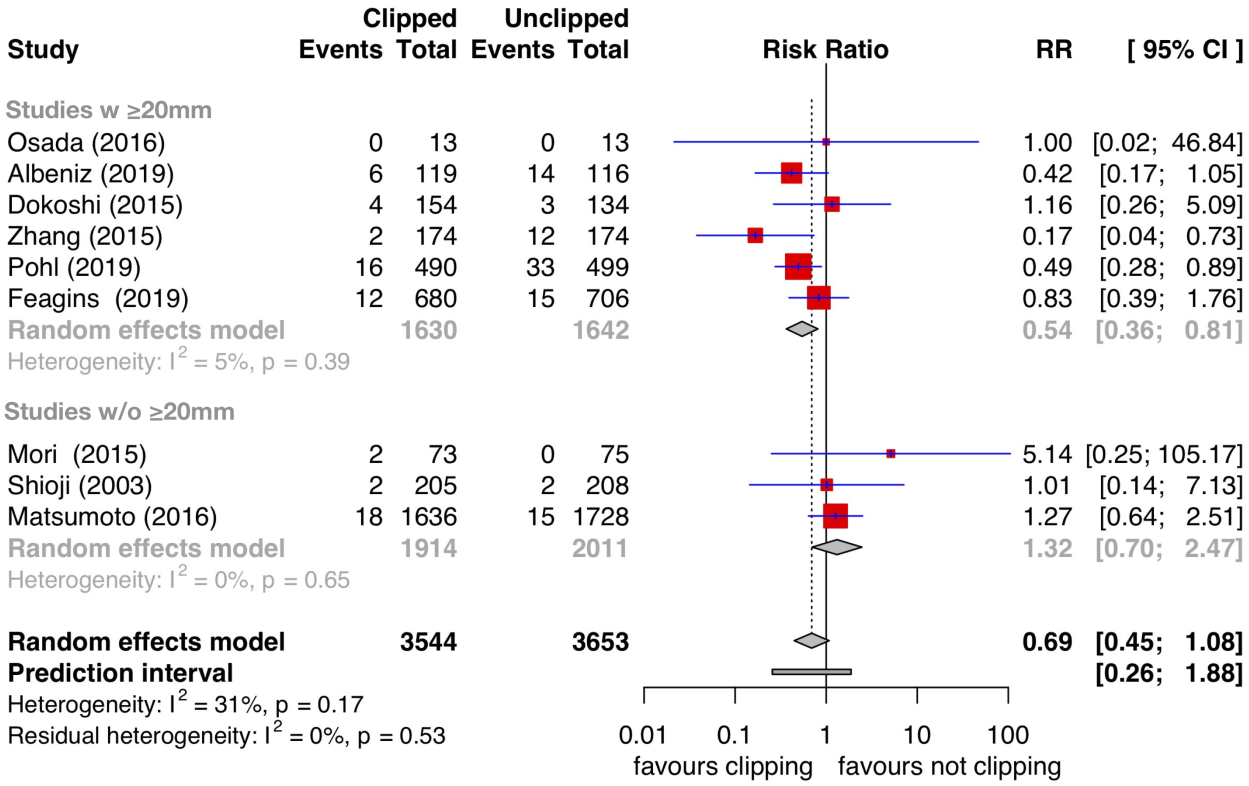
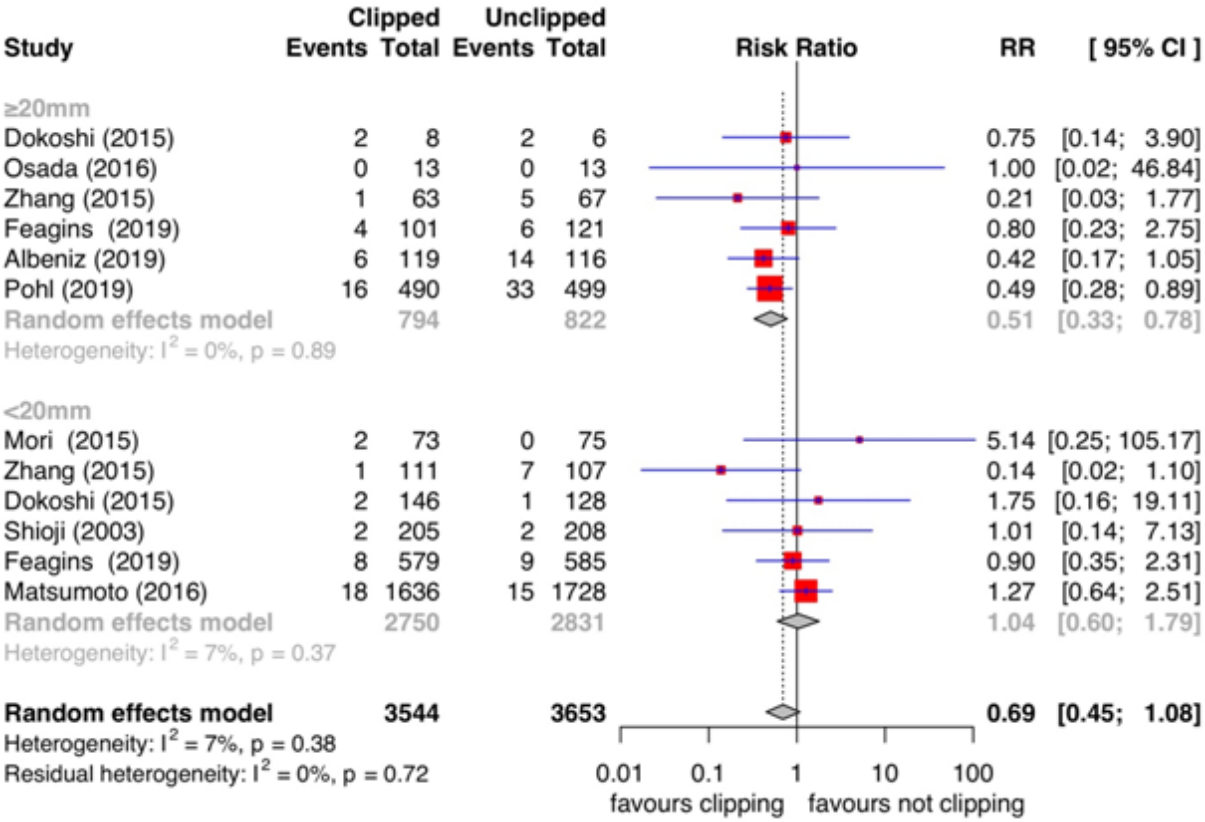
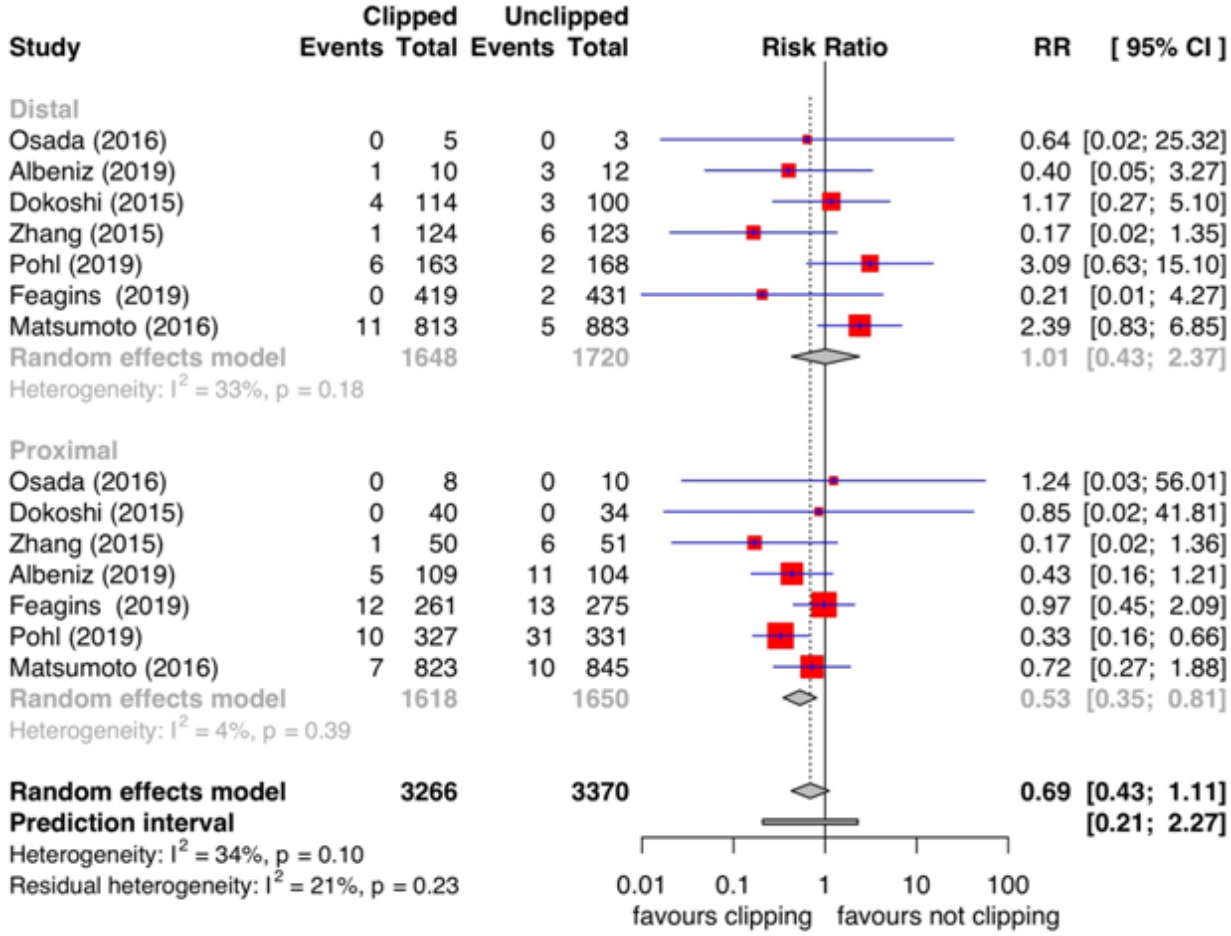
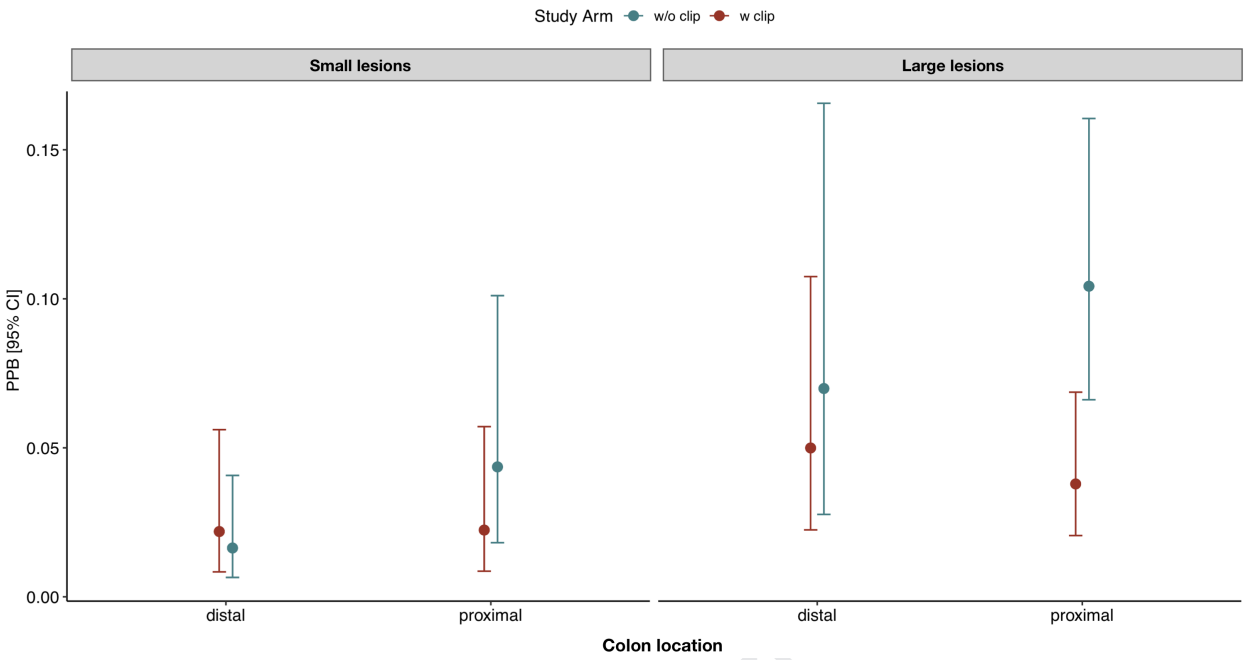
Different study questions (n=18)
Not RCTs (n=6)
Results
9
Final results
9
Related articles and references
0


Study
Clipped Events Total
Unclipped Events Total
Risk Ratio
RR [95% CI]
Studies w ≥20mm
Osada (2016) 0 13 0 13 1.00 [0.02; 46.84]
Albeniz (2019) 6 119 14 116 0.42 [0.17; 1.05]
Dokoshi (2015) 4 154 3 134 1.16 [0.26; 5.09]
Zhang (2015) 2 174 12 174 0.17 [0.04; 0.73]
Pohl (2019) 16 490 33 499 0.49 [0.28; 0.89]
Feagins (2019) 12 680 15 706 0.83 [0.39; 1.76]
Random effects model 1630 1642 0.54 [0.36; 0.81]
Heterogeneity: I^2 = 5%, p = 0.39
Studies w/o ≥20mm
Mori (2015) 2 73 0 75 5.14 [0.25; 105.17]
Shioji (2003) 2 205 2 208 1.01 [0.14; 7.13]
Matsumoto (2016) 18 1636 15 1728 1.27 [0.64; 2.51]
Random effects model 1914 2011 1.32 [0.70; 2.47]
Heterogeneity: I^2 = 0%, p = 0.65
Random effects model 3544 3653 0.69 [0.45; 1.08]
Prediction interval [0.26; 1.88]
Heterogeneity: I^2 = 31%, p = 0.17
Residual heterogeneity: I^2 = 0%, p = 0.53
0.01
0.1
1
10
100
favours clipping
favours not clipping


Study
Clipped Events Total
Unclipped Events Total
Risk Ratio
RR [95% CI]
≥20mm
Dokoshi (2015) 2 8 2 6 0.75 [0.14; 3.90]
Osada (2016) 0 13 0 13 1.00 [0.02; 46.84]
Zhang (2015) 1 63 5 67 0.21 [0.03; 1.77]
Feagins (2019) 4 101 6 121 0.80 [0.23; 2.75]
Albeniz (2019) 6 119 14 116 0.42 [0.17; 1.05]
Pohl (2019) 16 490 33 499 0.49 [0.28; 0.89]
Random effects model 794 822 0.51 [0.33; 0.78]
Heterogeneity: I^2 = 0%, p = 0.89
<20mm
Mori (2015) 2 73 0 75 5.14 [0.25; 105.17]
Zhang (2015) 1 111 7 107 0.14 [0.02; 1.10]
Dokoshi (2015) 2 146 1 128 1.75 [0.16; 19.11]
Shioji (2003) 2 205 2 208 1.01 [0.14; 7.13]
Feagins (2019) 8 579 9 585 0.90 [0.35; 2.31]
Matsumoto (2016) 18 1636 15 1728 1.27 [0.64; 2.51]
Random effects model 2750 2831 1.04 [0.60; 1.79]
Heterogeneity: I^2 = 7%, p = 0.37
Random effects model 3544 3653 0.69 [0.45; 1.08]
Heterogeneity: I^2 = 7%, p = 0.38
Residual heterogeneity: I^2 = 0%, p = 0.72
0.01 0.1 1 10 100
favours clipping
favours not clipping


Study
Clipped Events Total
Unclipped Events Total
Risk Ratio
RR [95% CI]
Distal
Osada (2016) 0 5 0 3 0.64 [0.02; 25.32]
Albeniz (2019) 1 10 3 12 0.40 [0.05; 3.27]
Dokoshi (2015) 4 114 3 100 1.17 [0.27; 5.10]
Zhang (2015) 1 124 6 123 0.17 [0.02; 1.35]
Pohl (2019) 6 163 2 168 3.09 [0.63; 15.10]
Feagins (2019) 0 419 2 431 0.21 [0.01; 4.27]
Matsumoto (2016) 11 813 5 883 2.39 [0.83; 6.85]
Random effects model 1648 1720 1.01 [0.43; 2.37]
Heterogeneity: I^2 = 33%, p = 0.18
Proximal
Osada (2016) 0 8 0 10 1.24 [0.03; 56.01]
Dokoshi (2015) 0 40 0 34 0.85 [0.02; 41.81]
Zhang (2015) 1 50 6 51 0.17 [0.02; 1.36]
Albeniz (2019) 5 109 11 104 0.43 [0.16; 1.21]
Feagins (2019) 12 261 13 275 0.97 [0.45; 2.09]
Pohl (2019) 10 327 31 331 0.33 [0.16; 0.66]
Matsumoto (2016) 7 823 10 845 0.72 [0.27; 1.88]
Random effects model 1618 1650 0.53 [0.35; 0.81]
Heterogeneity: I^2 = 4%, p = 0.39
Random effects model 3266 3370 0.69 [0.43; 1.11]
Prediction interval [0.21; 2.27]
Heterogeneity: I^2 = 34%, p = 0.10
Residual heterogeneity: I^2 = 21%, p = 0.23
0.01
0.1
1
10
100
favours clipping
favours not clipping



Appendix 1

Data sources and search strategy

We performed a comprehensive literature search in PubMed, EMBASE and SCOPUS (up to October 25th 2019) electronic databases to identify studies evaluating the role of prophylactic clipping in preventing post-polypectomy bleeding. PROSPERO was searched for ongoing or recently completed systematic reviews. Electronic searches were supplemented by manual searches of references of included studies and review articles.

We identified studies using the following medical subject headings (MeSH) and the keywords “clip”, “clipping”, “polypectomy”, “bleeding” and “endoscopic resection”. The search was restricted to English language.

The Medline search strategy was: “((((((("surgical instruments"[MeSH Terms] OR ("surgical"[All Fields] AND "instruments"[All Fields]) OR "surgical instruments"[All Fields] OR "clip"[All Fields]) AND polypectomy[All Fields]) OR (("surgical instruments"[MeSH Terms] OR ("surgical"[All Fields] AND "instruments"[All Fields]) OR "surgical instruments"[All Fields] OR "clip"[All Fields]) AND endosopic[All Fields] AND resection[All Fields])) OR (("surgical instruments"[MeSH Terms] OR ("surgical"[All Fields] AND "instruments"[All Fields]) OR "surgical instruments"[All Fields] OR "clip"[All Fields]) AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields]))) OR (clipping[All Fields] AND polypectomy[All Fields])) OR (clipping[All Fields] AND endosopic[All Fields] AND resection[All Fields])) OR (clipping[All Fields] AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields]))”

Selection process

Two review authors (M.S.; R.M.) independently screened the titles and abstracts yielded by the search against the inclusion criteria. Full reports were obtained for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. Review author pairs then screened the full text and abstract reports and decided whether these met the inclusion criteria. Disagreements were resolved through discussion of all the authors. The reasons for excluding trials were recorded. Neither of the review authors was blinded to the journal titles or to the study authors or institutions. When there were multiple articles for a single study, we used the latest publication and supplemented it, if necessary, with data from the more complete version.

Data extraction

Using standardized forms, two reviewers (M.S.; R.M.) extracted data independently and in duplicate from each eligible study. Reviewers resolved disagreements by discussion. Unresolved disagreements were resolved by two arbitrators (C.H.; A.R.). The following data were extracted for each study including the publication status, the study design and location, the number of centers involved, the number of patients, patient characteristics (mean/median age, gender, anti-thrombotic therapies), the number of all lesions, the number of procedures, mean/median lesion size, lesion location (proximal, distal), lesion aspect and histology, adverse events (bleedings, perforation surgery), mean/median lesion size. The corresponding authors of the included studies were asked for missing data.

Quality assessment

Quality was assessed by the Cochrane risk bias tool for randomized studies. Two reviewers (M.S., R.M.) assessed quality measures for included studies and discrepancies were adjudicated by collegial discussion. The overall quality of evidence was appraised by applying GRADE methodology[1] for the primary outcomes

Multilevel (random-effects) model: meta-analysis of rates of PPB with clipping in comparison to not-clipping.

The effect size of the meta-analysis was the transformed logit proportion of PPB. The current meta-analysis included studies reporting multiple effect sizes (one for each study arm). Multiple effects sizes within the same study may be correlated, violating the assumption of statistical independence. Thus, a multilevel meta-analytic model was employed, taking into account the potential clustering effects within studies. This approach adds random effects for each effect size within each study to the traditional random-effect model. Therefore, there are two random effects: the first random effect represents the variability between effect sizes assessed in the same study (i.e., between-outcomes or within-study variance), whereas the second random effect represents the variability among the effects observed in different studies (i.e., the between-study variance). For model fitting, we used the rma.mv function in metafor package in R package[2].

The random effects at the level of outcome and study were specified as a list of one-sided formulas in the random argument of the rma.mv function. The REML method was used and It was assumed a compound symmetry structure for the random effects (i.e., the correlation coefficient ρ for the correlation between the different outcomes was constant across studies). The model assumed independent sampling errors of effect size estimates. This is an appropriate assumption because there was no overlap in the patients used to compute outcome data in the two study arms. Subsequently, the multilevel model was extended by including predictor variables of delayed bleeding events (i.e., study arm, prevalence of large lesions and proximal colon location) in an attempt to find variables that moderate the effect. We also considered appropriate interactions between these variables. Data were presented as odds ratios (ORs) and 95% CIs.

1. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64: 383–394.
2. Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. Journal of Statistical Software, 36(3), 1-48. URL: http://www.jstatsoft.org/v36/i03/

Appendix 2. Supplemental Table 1: Evaluation of bias of RCTs included in the meta-analysis.

Study	Random sequence generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Adequate assessment of incomplete outcome	Selective reporting avoided	No other bias
Albeniz (2019)	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Dokoshi (2015)	Unclear risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Feagins (2019)	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Matsumoto (2016)	Low Risk	Unclear risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Mori (2015)	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Osada (2016)	Unclear risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Pohl (2019)	Low Risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Shioji (2003)	Unclear risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk
Zhang (2015)	Unclear risk	Low Risk	High risk	High risk	Low Risk	Low Risk	Low Risk

Appendix 2, Supplemental Table 2 Meta-Analysis of by-polyp delayed post-polypectomy bleeding events and clips use: "Leave-One-Out" Sensitivity.

	Influential analysis (Fixed effects model)				**Influential analysis Random effects model)**			
	RR [95%-CI]	**p-value**	**tau2**	**I2**	**RR [95%-CI]**	**p-value**	**tau2**	**I2**
Omitting Albeniz (2019)	0.72 [0.51; 1.00]	0.051	0.140	32.10%	0.76 [0.46; 1.23]	0.265	0.140	32.09%
Omitting Dokoshi (2015)	0.65 [0.47; 0.90]	0.010	0.155	37.00%	0.66 [0.41;1.08]	0.096	0.155	36.94%
Omitting Feagins (2019)	0.64 [0.45; 0.91]	0.012	0.200	38.20%	0.67 [0.39; 1.14]	0.145	0.199	38.12%
Omitting Matsumoto (2016)	0.56 [0.39; 0.803]	0.002	0.031	8.40%	0.58 [0.39; 0.88]	0.009	0.031	8.28%
Omitting Mori (2015)	0.65 [0.47; 0.89]	0.008	0.104	29.40%	0.67 [0.43; 1.02]	0.064	0.104	29.39%
Omitting Osada (2016)	0.67 [0.49; 0.92]	0.013	0.162	39.50%	0.69 [0.43; 1.10]	0.122	0.161	39.44%
Omitting Pohl (2019)	0.77 [0.52; 1.11]	0.163	0.147	28.60%	0.77 [0.46; 1.29]	0.320	0.147	28.51%
Omitting Shioji (2003)	0.66 [0.48; 0.91]	0.012	0.163	38.90%	0.68 [0.42; 1.10]	0.115	0.162	38.84%
Omitting Zhang (2015)	0.74 [0.536; 1.03]	0.077	0.033	11.00%	0.75 [0.52; 1.09]	0.137	0.032	10.92%
Pooled estimate	**0.67 [0.49; 0.92]**	**0.013**	**0.126**	**31.10%**	**0.69 [0.45; 1.08]**	0.072	**0.126**	**27.54%**

Appendix 2, Supplemental Table 3 Multilevel meta-regression analysis of PPB events.

	Ors	**95% CI**	**P-value**
Unclipped polyps (reference level)	1		
Clipped polyps	1.06	(0.66-1.75)	0.804
Percentage of large lesions (as a continuous variable)	1.28	(1.16-1.42)	<0.001
Use of Clip x Percentage of large lesions	0.92	0.85-0.98	0.016
Percentage of proximal lesions (as a continuous variable)	0.86	(0.67-1.10)	0.223

Appendix 2, Supplemental Table 4 - A multilevel random effect model with study arm, polyp lesion (large vs. small polyps), and their interaction term was fitted to the data. The two-way interaction term between polyp size and study arm was statistically significant. Results from the model shows a protective effect of clipping for large polyps (clipped large vs. unclipped large, OR, 0.54; 95% CI:0.30-0.97), while no protective effect of clipping was seen among small polyps (clipped small vs. unclipped small, OR:0.79; 95% CI:0.43-1.44; p=0.435).

	Multilevel Meta-regression analysis		
	ORs	**95% CI**	**P-value**
Clipped large vs. Unclipped large polyps	0.54	(0.30-0.97)	0.041
Unclipped small polyps vs. Unclipped large polyps	0.22	(0.12-0.40)	<0.001
Clipped small vs. Unclipped small polyps	0.79	0.43-1.44	0.435
Clipped small vs. Clipped large polyps	0.36	(0.19-0.66)	<0.001

Appendix 2, Supplemental Table 5 - A multilevel random effect model with study arm, proximal colon location and their interaction term was fitted to the data. The two-way interaction term between colon location and study arm was statistically significant (p=0.017). Results from the model shows a protective effect of clipping for proximal polyps (clipped proximal vs. unclipped proximal polyps, OR, 0.46; 95% CI:0.24-0.88), while no protective effect of clipping was seen among distal polyps (clipped distal vs. unclipped distal polyps, OR:1.21; 95% CI:0.56-2.62; p= 0.631). After adjusting for the prevalence of large lesions in the multilevel model, the benefit of clipping in reducing PPB was significant only for large proximal lesions (clipped versus unclipped polyps, OR, 0.34; 95% CI:0.19-0.65; p=0.021), but not for small proximal lesions (clipped versus unclipped polyps, OR, 0.88; 95% CI:0.48-1.62; p=0.581).

	Multilevel Meta-regression analysis		
	ORs	**95% CI**	**P-value**
clipped proximal vs. unclipped proximal polyps	0.46	(0.24-0.88)	.0018
unclipped distal vs. unclipped proximal polyps	0.42	(0.24-0.73)	<0.001
clipped distal vs clipped proximal polyps	1.09	(0.61-1.95)	0.764
clipped distal vs. unclipped distal polyps	1.21	0.56-1.38	0.631

Appendix 2, Supplemental Table 6. GRADE evidence profile for efficacy of clipping vs. no clipping strategy in reducing post procedural bleeding.

* Risk of bias was judged as serious due to the low-moderate quality of the included randomized controlled trials.

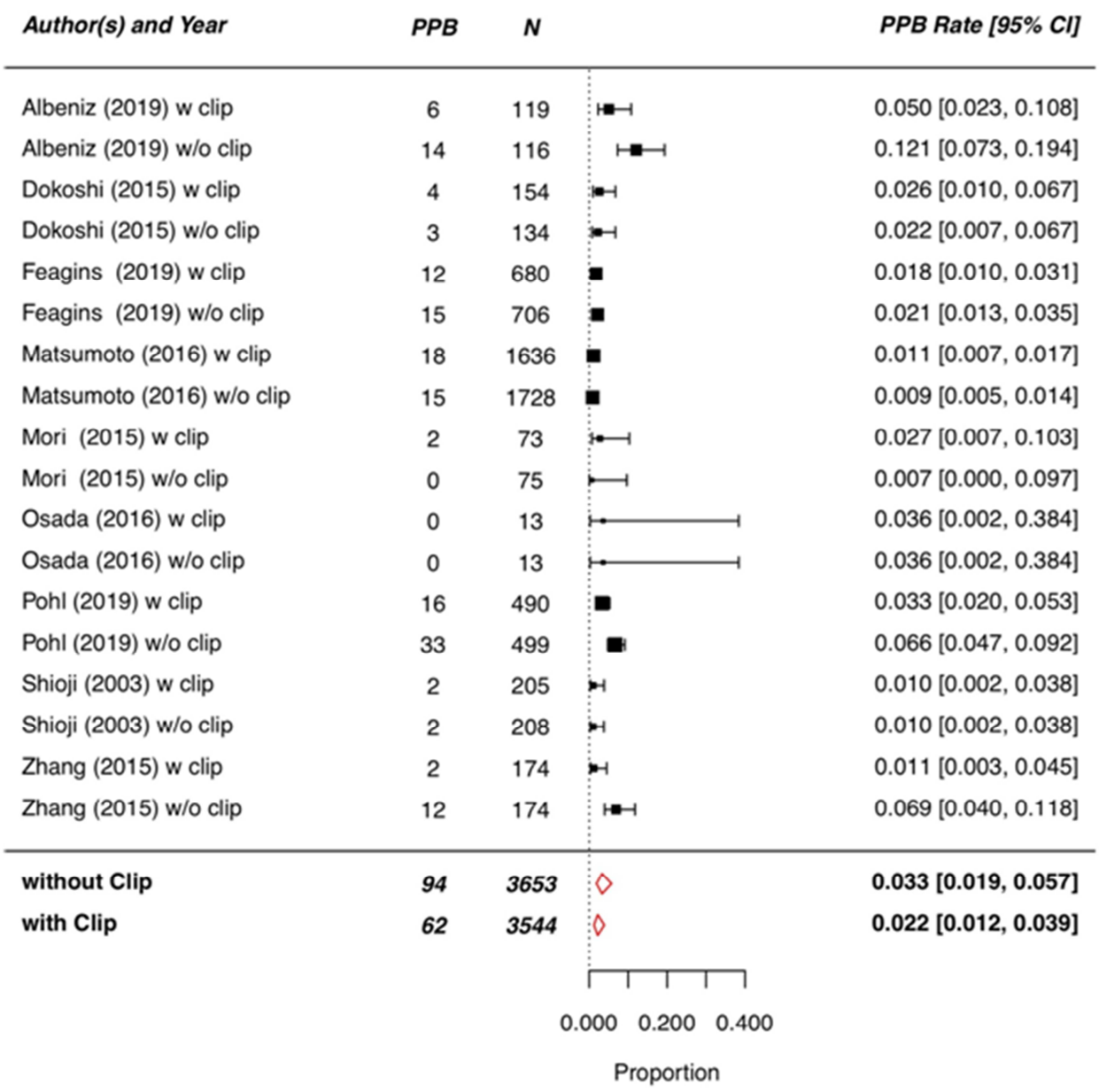
** Inconsistency risk was judged as serious due to heterogeneity among patients (i.e. different indications to resection in term of lesion size or location).

	Quality assessment					Summary of findings			Quality
Outcome, No. of studies, design (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	PPB in Clipping	PPB in No Clipping	Relative Risk (95%CI)	
All lesions, 9 RCTs	Serious*	Serious**	Not serious	Not serious	Not serious	62/3,544	94/3653	0.69 (0.45-1.08)	⊕⊕OO Low
Large (>20mm) lesions, 6 RCTs	Serious*	Not serious	Not serious	Not serious	Not serious	29/794	60/822	0.51 (0.33-0.78)	⊕⊕⊕O Moderate
Proximal lesions, 7 RCTs	Serious*	Not serious	Not serious	Not serious	Not serious	35/1618	71/1650	0.53 (0.35-0.81)	⊕⊕⊕O Moderate

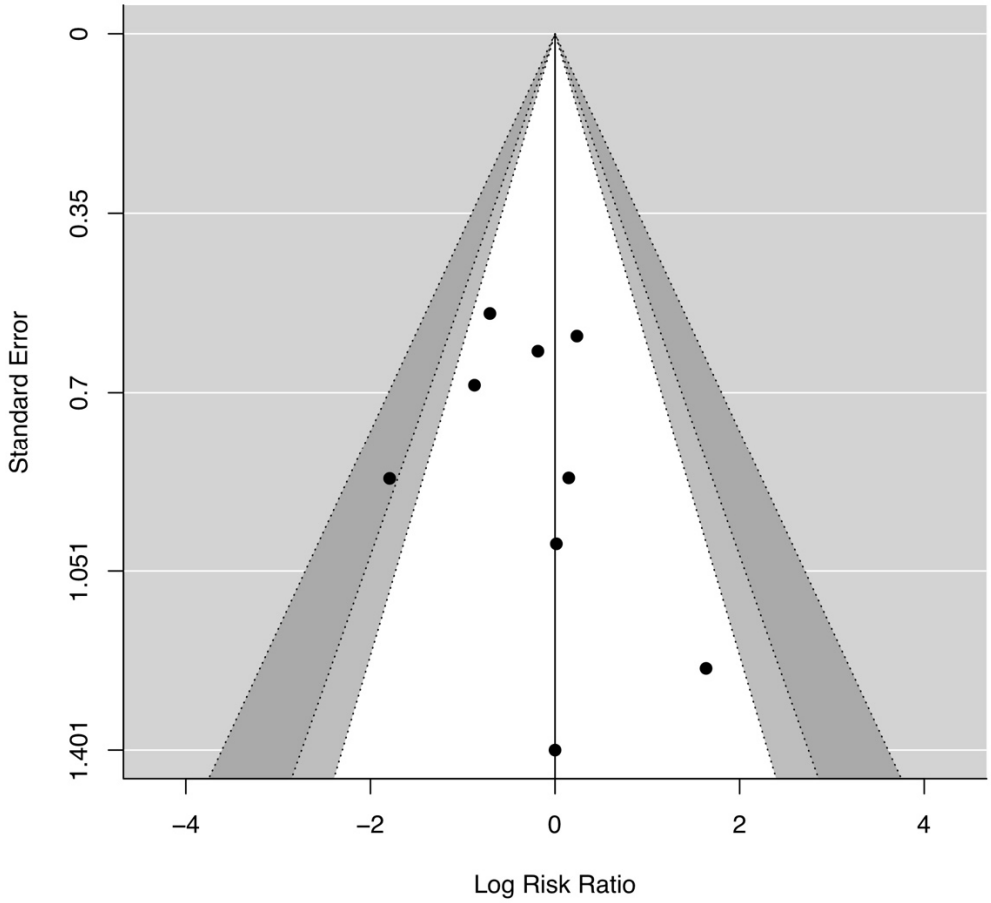
Appendix 2, Supplemental Table 7. Technical features. NA: Not available.

Study	Electrosurgical generators	Clips
Albeniz (2019)	ERBE (ICC200, VIO 200 or VIO300); Endocut mode	Micro-Tech, Nanjing, China
Dokoshi (2015)	ERBE (ICC200 or VIO300); Endocut mode	HX-610-135, Olympus, Tokio, Japan
Feagins (2019)	NA	NA
Matsumoto (2016)	ERBE (ICC200 or VIO200); Olympus (ESG-100, PSD.60)	NA
Mori (2015)	ERBE (VIO300); Swift mode	HX-610-135, Olympus, Tokio, Japan
Osada (2016)	ERBE (VIO300); Endocut mode	ZEOCLIP ZP-CH ZeonMedical, Tokio, Japan
Pohl (2019)	ERBE generators; Endocut or forced coagulation modes	Resolution clip, Boston Scientific, Marlborough, US Resolution 360 clip, Boston Scientific, Marlborough, US
Shioji (2003)	Olympus (UES-10); blended current.	HX-5QR-1, Olympus, Tokio, Japan
Zhang (2015)	ERBE (ICC200 or VIO300); Endocut mode	HX-610-135, Olympus, Tokio, Japan Resolution clip, Boston Scientific, Natic, US

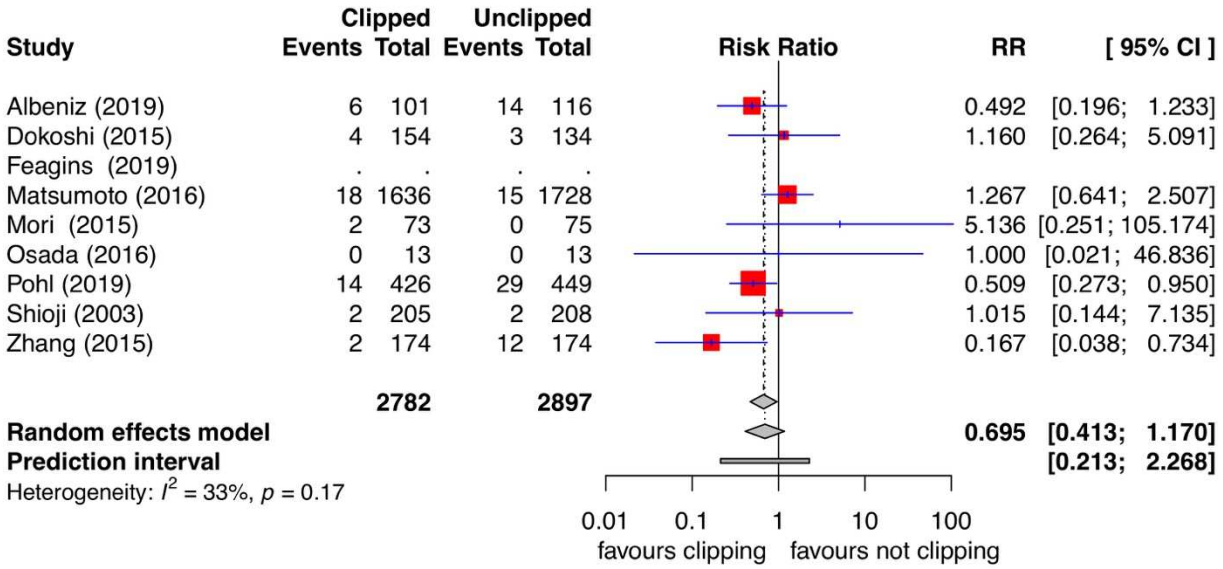
Appendix 3, Supplemental Figure 1: Meta-Analysis of PPB rates of delayed bleeding - a multilevel random effects model accounting for the underlying heterogeneity between and within trials was used to estimate the pooled rates of PPB.



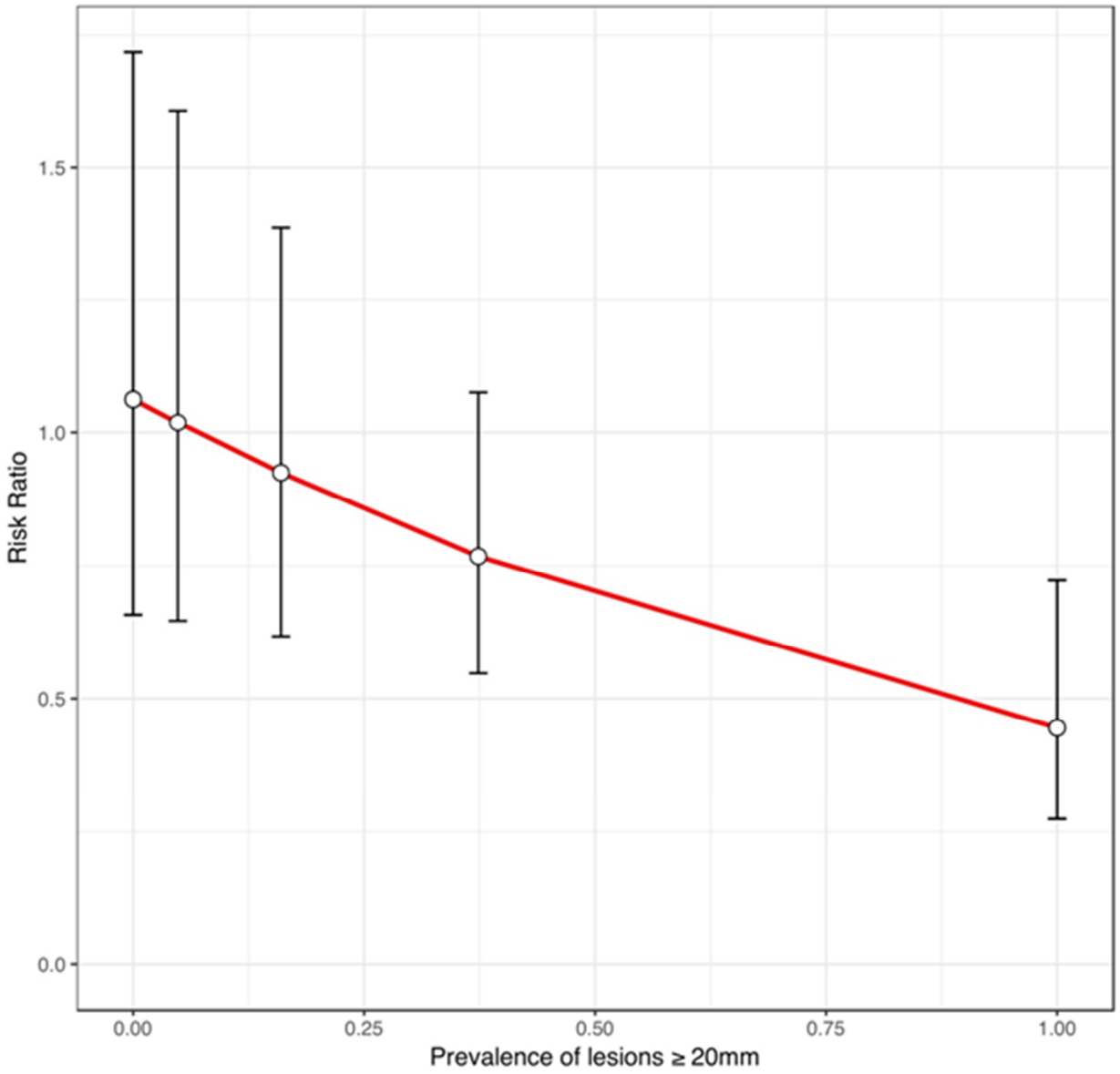
Appendix 3, ***Supplemental Figure 2:*** Funnel plot of publication bias – Ratio Risk of PPB (i.e., post-polypectomy bleeding).



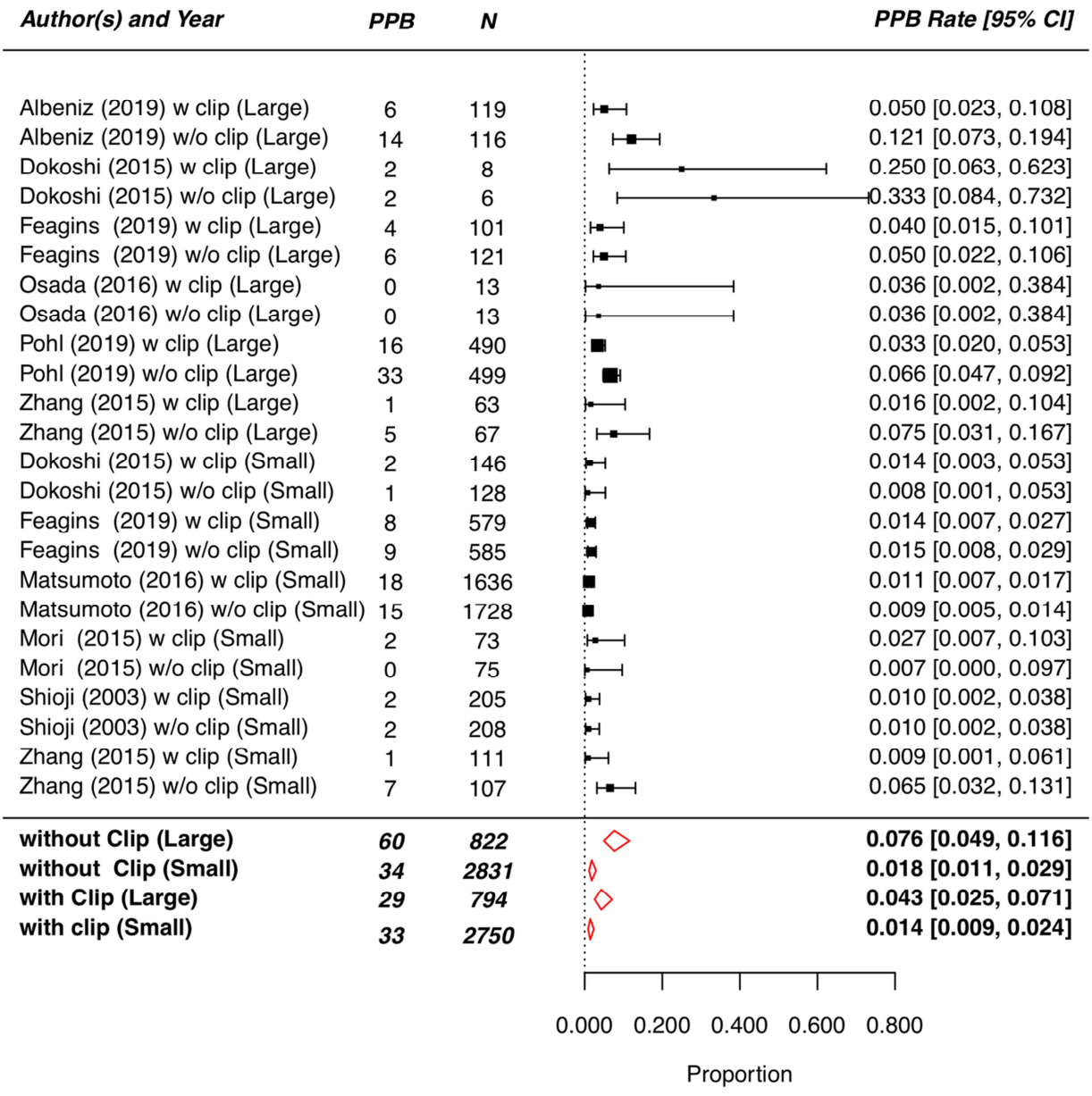
Appendix 3, ***Supplemental Figure 3:*** Meta-Analysis of relative risk of post-polypectomy bleeding (PPB) - results from per-protocol analysis (i.e., PPB after completion of clipping). The study by Matsumoto had substantial influence on the pooled effect size estimate.



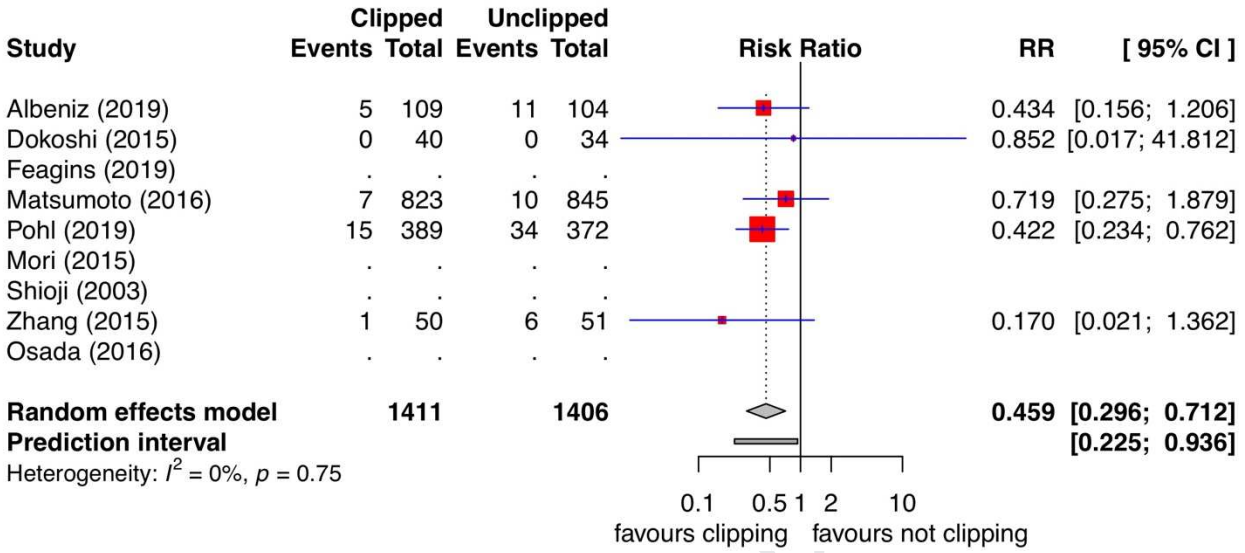
Appendix 3. ***Supplemental Figure 4*** **–** The Figure shows a plot of the risk ratio estimate (derived from the meta-regression model) as a function of the percentage (decimal number) of large lesions. The estimated risk ratio of PPB associated with clip use was not significantly different from 1 for a prevalence of large lesions of 0% (only small lesions included, RR=1.06; 95% CI: 0.66-1.72), indicating an equal PPB risk on average for small clipped and unclipped polyps. However, we found increasingly large effects as the prevalence of large lesions increases. The estimated risk ratios of PPB for clipped (versus unclipped) polyps were 0.69 (95% CI:0.50-0.95) and 0.44 (95% CI:0.27-0.72) for percentages of large lesions of 0.50 and 1.00, respectively.



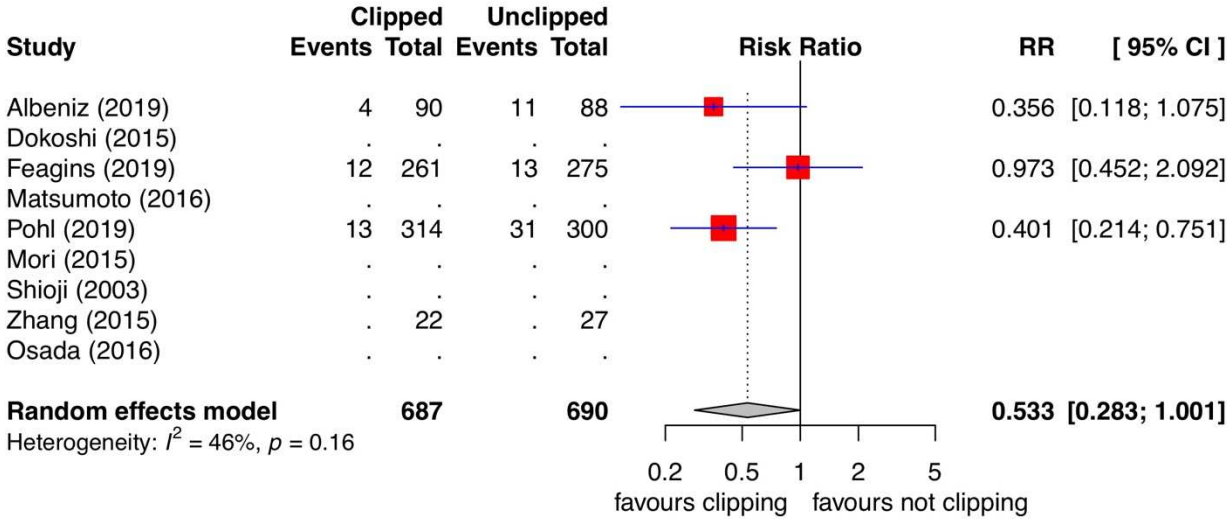
Appendix 3, Supplemental Figure 5: Meta-Analysis of PPB rates for large and small polyps -a multilevel random effects model accounting for the underlying heterogeneity between and within trials was used to estimate the rates of PPB for large and small lesions with and without clips. In our dataset, 3 studies reported data on both large and small lesions, 3 studies only on large lesions and the remaining 3 studies only on small lesions. Therefore, this analysis included 12 effect size estimates (6 for each study arm) of PPB among large polyps (n=1616 polyps) and 12 effect size estimates (6 for each study arm) of PPB among small polyps (n=5581 polyps).



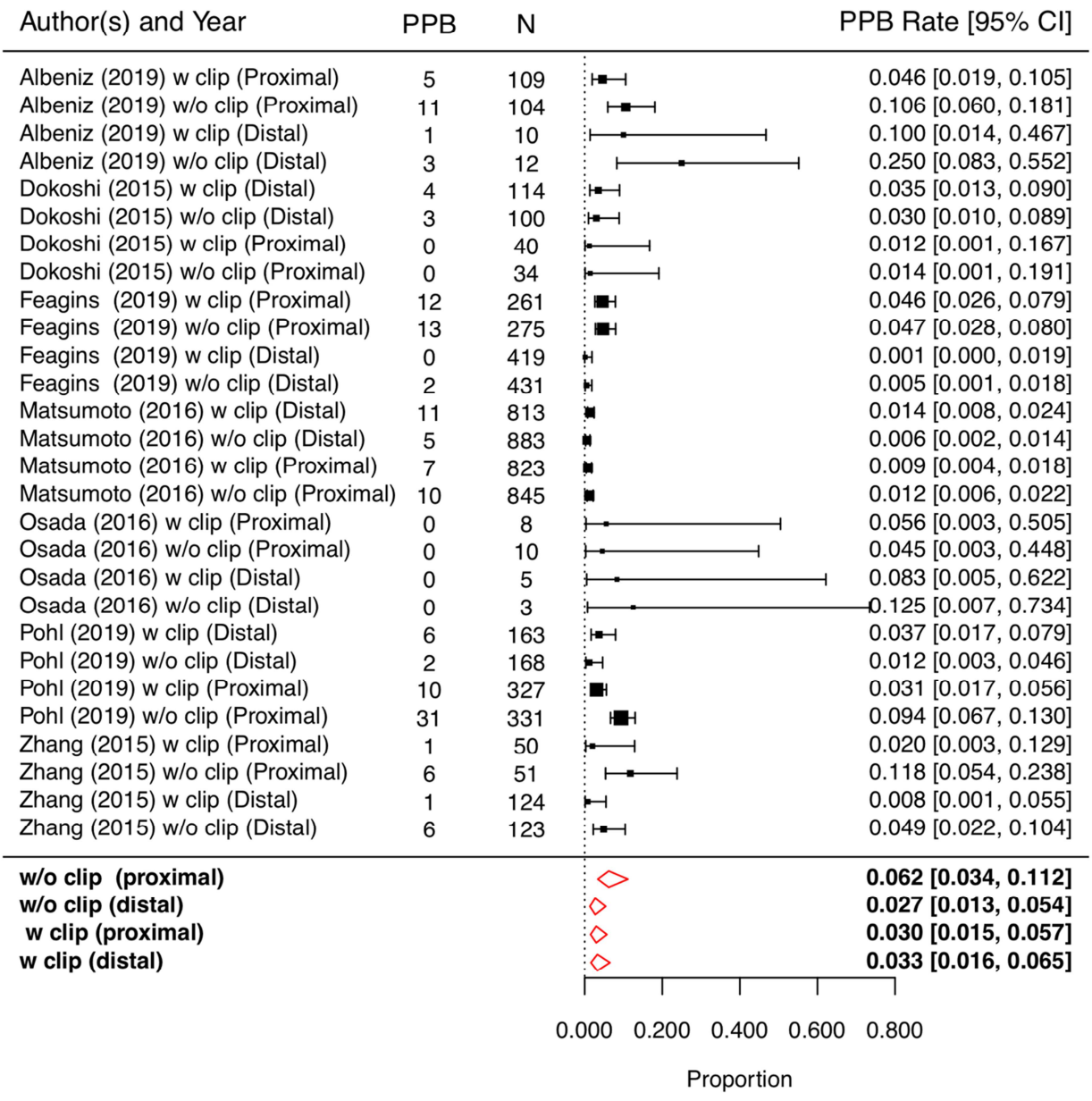
Appendix 3, Supplemental Figure 6: Meta-Analysis of relative risk of delayed bleeding - results from a sensitivity analysis among studies defining proximal lesions as sited proximally to the splenic flexure (including transverse colon).



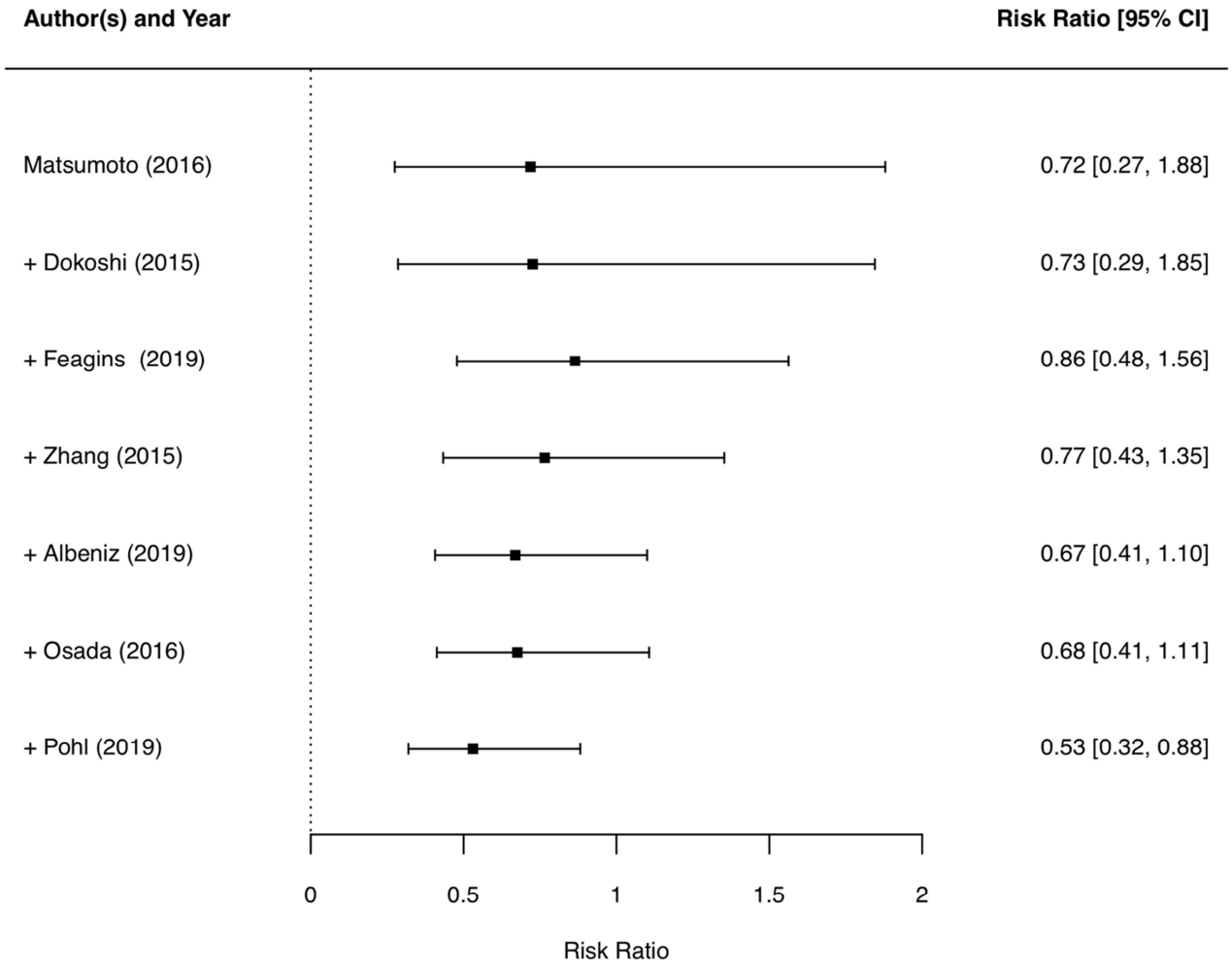
Appendix 3, Supplemental Figure 7: Meta-Analysis of relative risk of delayed bleeding - results from a sensitivity analysis among studies defining proximal lesions as lesions sited in cecum, ascending colon and hepatic flexure.



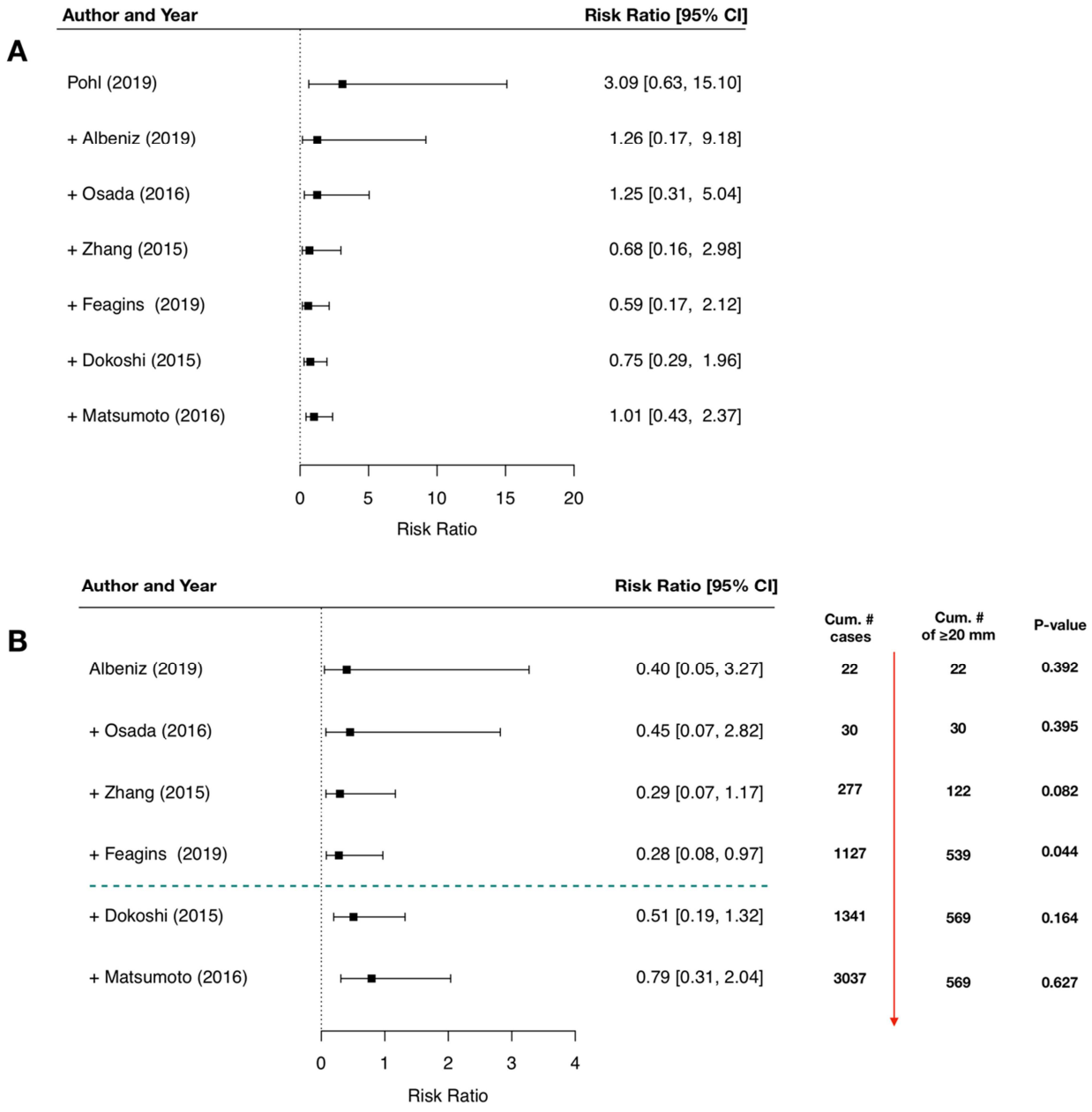
Appendix 3, Supplemental Figure 8: Meta-Analysis of PPB rates of delayed bleeding in the proximal colon location - a multilevel random effects model accounting for the underlying heterogeneity between and within trials was used to estimate the rates of PPB for proximally and distally located lesions with and without clips. The analysis included 7 studies (n=6,636 polyps) with available count data for proximal (n=3268) and distal lesions (n= 3368). Therefore, 14 effect size estimates (7 for each study arm) of PPB among distal and 14 effect size estimates (7 for each study arm) of PPB among proximal polyps were combined.



Appendix 3, Supplemental Figure 9: Forest plot, showing the results from a cumulative meta-analysis of the relative risk of PPB for clipped and unclipped polyps in the proximal colon. The cumulative meta-analysis was based on the study prevalence of large lesions and on a random-effect model. The analysis shows how the overall estimate changes as studies with increasing prevalence of large lesions are added to the pool. Each study was added to the next one, and the summary effect was calculated at each step. Results from the cumulative meta-analysis suggest that studies with large lesions may overestimate the effect of clip in lowering the risk of PPB in the proximal colon.



Appendix 3, Supplementary Figure 10 - A) Forest plot, showing the results from a cumulative meta-analysis of the relative risk of PPB for clipped and unclipped polyps in the distal colon. The cumulative meta-analysis was based on the study prevalence of large lesions (descending order) and on a random-effect model. Results from the cumulative meta-analysis suggested that the study by Polh may underestimate the protective effect of clip for large distal lesions. B) A sensitivity analysis excluding the study by Pohl. After excluding this study (in a sensitivity analysis), studies including large lesions demonstrated a significant negative association between clip use and risk of PPB in the distal colon, supporting the hypothesis of a protective effect of clip for large distal polyps (RR:0.28; 95% CI:0.08-0.97; p=0.044). However, when studies reporting on small lesions were successively added to the analysis, the magnitude of the treatment effect began to increase and became non-significant. Note. Cum. #, cumulative number of cases.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
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.	5
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.	Appendices
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendices
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).	Appendices
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.	Appendices
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendices
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.	Appendices
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	Appendices
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Appendices
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 -10
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 -10
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).	8 -10
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.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 -10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendices
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendices
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).	11 - 12
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).	11 - 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11 - 12
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.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

What you need to know:

Background and Context: It is not clear whether prophylactic clipping prevents bleeding after polypectomy.

New Findings: A meta-analysis of randomized trials showed that routine use of prophylactic clipping does not reduce risk of post-polypectomy bleeding, overall. However, clipping appeared to reduce bleeding after removal of large (more than 20 mm) and proximal lesions.

Limitations: This was a meta-analysis of previous studies. Further prospective studies are needed.

Impact: Only large (more than 20 mm) and proximal colorectal lesions should be clipped to prevent bleeding after polypectomy.

Lay Summary: This study showed the applying a clip prevents bleeding after removal of large polyps, in specific regions of the colon, but does not prevent bleeding of all polyps overall.