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Practice Patterns, Predictors of Use and Clinical Efficacy of Endoscopic Clips for Prevention of Delayed Post-polypectomy Bleeding

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Practice Patterns, Predictors of Use and Clinical Efficacy of Endoscopic Clips for Prevention of Delayed Post-polypectomy Bleeding

by

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Abstract

Colonoscopy reduces colorectal cancer through the removal of pre-cancerous polyps, which exposes patients to potential adverse events. Endoscopic clips are used by practitioners to prevent delayed post-polypectomy bleeding. This thesis reports the results of two studies performed with the aim of evaluating the practice patterns and clinical efficacy of prophylactic clipping during polypectomy. A meta-analysis of randomized trials showed that prophylactic clipping is not efficacious in preventing delayed bleeding during routine polypectomy, especially among polyps < 10 mm. A large retrospective cohort study then described clinical parameters associated with clip usage. We demonstrated that use of clips increased over time in a high-volume outpatient endoscopy unit. Furthermore, a high degree of variability in clipping patterns existed between endoscopists, including among polyps < 10 mm, where no efficacy exists. Taken together, these results reveal an urgent need for effective knowledge translation to eliminate this ineffective and costly practice during routine polypectomy.

Preface

This manuscript-based thesis is comprised of two unmodified articles written on prophylactic endoscopic clipping that have both been prepared for peer-reviewed publication. I have drafted both manuscripts and am credited on both as the first author. All original work has been granted institutional approval by the University of Calgary's Conjoint Health Research Ethics Board (REB14-2314).

Manuscript 1) **Forbes N**, Frehlich L, James MT, Hilsden RJ, Kaplan GG, Wilson TA, Lorenzetti DL, Tate DJ, Bourke MJ, Heitman SJ. Routine Prophylactic Endoscopic Clipping is Not Efficacious in the Prevention of Delayed Post-Polypectomy Bleeding: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One 2017 (prepared for submission).

Manuscript 2) **Forbes N**, Hilsden RJ, Kaplan GG, James MT, Lethebe C, Maxwell C, Heitman SJ. Practice Patterns and Predictors of Prophylactic Endoscopic Clip Usage following Polypectomy. Am J Gastroenterol 2017 (prepared for submission).

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Dedication

This MSc dissertation is dedicated to my family members, for their unwavering support. Special thanks to my dearest Elle, without whose love and encouragement none of this would be possible.

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List of Symbols, Abbreviations, Acronyms and Nomenclature

AOR	adjusted odds ratio
APC	argon plasma coagulation
ASA	American Society of Anesthesiologists
ASA	acetylsalicylic acid
CAG	Canadian Association of Gastroenterology
CAGS	Canadian Association of General Surgeons
CCSC	Forzani & MacPhail Colon Cancer Screening Centre
CENTRAL	Cochrane Central Registry of Controlled Trials
CI	confidence interval
CRC	colorectal cancer
DAD	Discharge Abstract Database
DOAC	direct oral anticoagulant
DPPB	delayed post-polypectomy bleeding
EMBASE	Excerpta Medica Database
EMR	endoscopic mucosal resection
ESD	endoscopic submucosal dissection
FIT	fecal immunohistochemical testing
FOBT	fecal occult blood test
GEE	generalized estimating equation
GI	gastroenterology/gastroenterologist
IPB	intra-procedural bleeding

KT	knowledge translation
LF	Levi Frehlich
LSL	laterally spreading lesion
NACRS	National Ambulatory Care Reporting System
NF	Nauzer Forbes
NSAID	non-steroidal anti-inflammatory drug
OAC	oral anticoagulant
OR	odds ratio
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
SJH	Steven J Heitman
UGI	upper gastrointestinal
WF-EMR	wide-field endoscopic mucosal resection
I^2	I-squared statistic for heterogeneity
χ^2	Chi-squared statistic

Epigraph

The best preparation for tomorrow is to do today's work superbly well.

Sir William Osler, MDCM, Bt, FRS, FRCP

Chapter One – Introduction

Colorectal Cancer Screening

Colorectal cancer (CRC) accounts for substantial morbidity and mortality among Canadians. In 2016, there were an estimated 26,000 incident cases of CRC, with over 2,000 of these being diagnosed in Alberta.[4] CRC is responsible for 12.0% and 11.6% of all cancer-related deaths in Canada for men and women, respectively.[4] In addition, CRC imposes a considerable healthcare resource burden. American data show that the costs of care for those with CRC in 2000 was considerably higher than $7 billion, with an expected doubling of these expenditures by the year 2020.[5]

In most cases, the pathogenesis of CRC initially involves the development of pre-cancerous adenomatous polyps that accumulate mutations and transition to cancer through the well-established adenoma-carcinoma sequence.[6] This process usually takes place over a number of years, although more rapid pathways to cancer have been recognized.[7] The risk of CRC increases with both the number and size of adenomas, in addition to advancing patient age.[8] Men have a higher lifetime risk of CRC than women,[4] as do patients with a family history of advanced adenomatous polyps and cancer.[9]

CRC screening decreases its incidence as well as the mortality and morbidity associated with the disease.[10, 11] The Canadian Cancer Society recommends stool testing as the main CRC screening modality for average risk patients, with a positive test prompting endoscopic evaluation.[12] This suggested approach is reinforced by the recent Colorectal Cancer Screening Guidelines put forth by the Canadian Task Force on Preventive Health Care.[13] In Alberta, this is accomplished through fecal immunohistochemical testing (FIT) every 1-2 years, the performance of which increases the probability of discovering advanced

colorectal neoplasia during subsequent diagnostic colonoscopy. Whereas only 6% of average risk individuals have advanced neoplasia on screening colonoscopy,[14] the positive predictive value (PPV) of FIT for advanced neoplasia has been reported at up to 35-40%.[15, 16] Patients at higher risk for CRC (for instance, those with a strong family history, or polyposis syndromes) are typically referred directly for screening colonoscopy as the initial diagnostic modality of choice. Ultimately, the benefits of screening are realized through identifying patients with earlier stage cancers and through preventing CRC via removal of pre-malignant polyps at the time of colonoscopy,[17, 18] a technique known as polypectomy.

Risks Associated with Polypectomy

Colonoscopy permits direct visualization of the entire large bowel. It is therefore regarded as the gold standard diagnostic test for the detection of polyps and CRC, while offering the opportunity for simultaneous interventions, including polypectomy. However, colonoscopy is not infallible or without risk, and adverse events associated with the procedure are well established. Post-colonoscopy cancers ('interval cancers') are known to occur, representing an estimated 7-9% of all CRC cases.[19] Colonoscopy is also associated with several well-described procedural risks, including post-colonoscopy pain, luminal bleeding, bowel perforation, medical issues related to bowel cleansing or sedation, and even death.[20] The performance of polypectomy in particular increases the risks of bleeding and perforation. Canadian population-based data showed estimated pooled bleeding and perforation rates of 0.16% and 0.09%, respectively, with these risks increasing 10-fold and 3-fold, respectively, for cases involving polypectomy.[21] The bleeding risk can be even further

amplified (5-15%) in cases where polypectomy is performed for large lesions measuring 20 mm or greater in the right side of the colon.[22]

Post-polypectomy bleeding can be seen endoscopically at the time of the polypectomy, but it can also be delayed. Intra-procedural bleeding (IPB) occurs immediately after the index polypectomy and is directly observed endoscopically. It is not usually viewed as a true adverse event, but rather as a technical interference, as long as the patient's clinical course remains unaltered.[23] Delayed post-polypectomy bleeding (DPPB) can occur up to 30 days following the index procedure, and is defined as bleeding after discharge that requires any of emergency assessment, admission, transfusion or repeat intervention.[22, 24, 25] Several factors increase the likelihood of DPPB.[23, 25-34] In a large prospective study, these factors included increasing lesion size, proximal colonic location, lack of epinephrine contained in the injectate used during polypectomy, and significant patient comorbidity.[25] DPPB occurred at rates of between 1 and 16% following endoscopic mucosal resection (EMR) of lesions ≥ 20 mm, depending on how many of these risk factors were present.[25] Right-sided polypectomies are thought to carry a higher bleeding risk because the cecum is thin-walled relative to the colon and rectum.[34, 35] Another large prospective study showed that IPB predicted subsequent DPPB, with an odds ratio (OR) of 2.16.[23] Moreover, the results of a large retrospective study of > 5,000 patients further supports that increasing lesion size (≥ 10 mm) and IPB both predict DPPB, with ORs of 4.6 and 2.9, respectively. This latter study also showed a non-significant trend toward increased DPPB after piecemeal resection (OR 5.1, 95% CI 0.5 to 47.7).[33] Finally, certain medications that affect the coagulation cascade, including antiplatelet agents, may also have an impact on post-polypectomy bleeding;

however, supporting evidence is conflicting.[36-38] Guidelines encourage the discontinuation of thienopyridines (such as clopidogrel or prasugrel) and other antiplatelet agents (such as ticagrelor) for 5 to 7 days prior to polypectomy, whereas aspirin (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) can be continued during the periprocedural period.[39, 40] The periprocedural management of traditional oral anticoagulants (OACs, such as warfarin) and novel direct oral anticoagulants (DOACs) is more complex, and requires consideration of the indication for the drug and the risk of the procedure performed. This is especially true given the rapid onset of action of DOACs. [39, 40]

Methods to Treat Intra-procedural Bleeding

There are several endoscopic modalities that can be used in the treatment of immediate adverse events seen at the time of polypectomy. These include injection of dilute epinephrine, contact thermal coagulation using the snare tip soft coagulation method, use of hemostatic forceps, application of inert hemostatic sprays, and placement of endoscopic clips.[41-44] Endoscopic clips are small metallic devices that are deployed through the endoscope and then targeted toward a lesion of interest. They are comprised of opposable prongs that can oppose or approximate tissue, which makes them ideal for closing endoscopic defects or closing tissue around a bleeding source, either alone or in combination with other modalities. There have been several widely reported uses for clips, including treatment of non-variceal upper gastrointestinal bleeding,[45] and treatment of immediate bleeding following polypectomy.[46]

Endoscopic Clips for Prevention of Delayed Post-polypectomy Bleeding

Given their ability to stop immediate bleeding, a potential role of endoscopic clips to prevent bleeding is a tantalizing hypothesis. However, data on the efficacy of endoscopic clips to prevent delayed post-polypectomy bleeding (DPPB) are limited and inconsistent. This may be owing to the inability to target a specific high-risk target when preventing DPPB, versus when treating IPB. A 2013 retrospective study that included only larger polyps ≥ 20 mm showed a benefit of clipping; within this high-risk group, full closure of polypectomy defects by endoscopic clip had a beneficial odds ratio (OR) of 0.17 on delayed bleeding.[22] Otherwise, the majority of studies performed have failed to show any benefit of prophylactic clipping on delayed bleeding, and, in fact, have shown trends toward increased risk when only partial clipping is performed rather than full defect closure.[22, 47, 48] The studies assessing the effect of prophylactic clipping (compared to no clipping) on delayed post-polypectomy bleeding are summarized in Table 1.1.

The data have also been reviewed via systematic review. Meta-analyses on multiple prophylactic endoscopic modalities (including clipping) have been conducted, and have concluded that none are effective in the prevention of delayed post-polypectomy bleeding.[49, 50] A 2016 meta-analysis that focused solely on clipping drew similar conclusions. However, this latter review missed important studies, and did not consider clinically relevant subgroup analyses.[51]

Cost-Effectiveness of and Practice Patterns of Prophylactic Clipping

The decision to use endoscopic clips is an expensive one, with each clip costing approximately $100, and with clips often used in multiples. The cost-effectiveness of prophylactic clip placement following polypectomy has been evaluated in two modeling studies. In a decision analytics modeling study published in 2013, prophylactic clip placement was only cost-effective in a sensitivity analysis where a very high bleeding risk was assumed in patients on antiplatelet agents.[52] Furthermore, the results were dependent on the assumed effectiveness of endoscopic clips, which is yet unestablished.[52] A second cost-effectiveness study from 2016 concluded that, even when clipping is 100% efficacious, the cost of a prophylactic strategy carries a six-fold expenditure compared to not clipping, and thus is not cost-effective compared to simply treating delayed bleeding.[53]

Despite these data, the use of prophylactic clipping appears to be increasing. A survey of polypectomy practices among American gastroenterologists was conducted in 2004, at which time nearly 70% reported using no method to prevent bleeding from polyps with large stalks (> 1 cm in diameter). Among those that did, 76% reported using injection of epinephrine, while clips were seldom used.[54] A more recent survey conducted among Israeli gastroenterologists confirmed a higher usage of prophylactic clips, with 58% of surveyed clinicians stating they had used clips in their practice on large stalks to prevent delayed bleeding.[55]

Outline of Dissertation

Prophylactic clips are a relatively facile and thus appealing option for endoscopists to potentially prevent delayed post-polypectomy bleeding. However, contemporary data to support this practice remain conflicting. Thus, it is critical that the clinical efficacy of prophylactic clipping be clarified thorough a systematic review and meta-analysis of best available evidence. Furthermore, it is equally important to define current practice patterns and clinical predictors of prophylactic clipping in the context of data on their efficacy. In this manner, practitioners and health care decision makers alike will be better positioned to define the settings where use of these devices is appropriate, to educate practitioners regarding their misuse, and to design future studies where additional data are required.

The work contained in this dissertation is an important component of a broad program of research that seeks to establish the utility (or lack thereof) of prophylactic endoscopic clips in the prevention of DPPB. Chapters Two and Three each represent independent manuscripts prepared for publication. Chapter Two presents a systematic review and meta-analysis of randomized controlled trials assessing whether prophylactic clipping (versus the absence of prophylactic clipping) is efficacious in preventing DPPB. This review provides a current state of the evidence regarding the efficacy of prophylactic clips and focusses on analyses of higher-risk patients where clipping may be beneficial. Chapter Three presents the results of a retrospective cohort study of over 12,000 polypectomies in over 5,000 patients. This represents the 'real-world' experience of contemporary clinical practice at a high-volume endoscopy unit serviced by a range of community and academic gastroenterologists and colorectal surgeons of varying clinical experience. Described within

this study are important clinical predictors of prophylactic clipping at the endoscopist, patient and polyp levels. In addition, temporal trends and inter-endoscopist variability with regard to clipping are described. Finally, Chapter Four synthesizes the conclusions of the above two studies, discussing clinical implications, opportunities for knowledge translation and/or policy change, and directions for future research.

Figures and Tables

Table 1.1. Studies assessing the effect of prophylactic clipping on delayed bleeding after colonoscopic polypectomy.

First Author	Journal	Year	Study Design/ Details	OR for Clipping (95% CI/p-value)	n (Patients/Polyps)
Boumitri[51]	Ann Gastroenterol	2016	Meta-analysis	1.49 (0.56 – 4.00)	13,009 / 18,415
Matsumoto[56]	Dig Endosc	2016	RCT	1.27 (p = N/S)	1,499 / 3,365
Albeniz[47]	Clin Gastroent Hep	2016	Prospective Cohort (Subgroup)	1.59 (0.78–3.23) partial clipping 0.36 (0.12–1.02) full/ closure	1,214 / 1,255
Dokoshi[57]	Biomed Res Int	2015	RCT	4 events vs. 3 (p = N/S)	156 / 288
Zhang[58]	Gastroint Endosc	2015	RCT (Polyps ≥ 1 cm only)	**0.16 (p = 0.01)****	348 / 348
Rai[59]	Gastroint Endosc (Abstract)	2015	Meta-analysis	1.14 (0.31 – 1.47)	12,108 / 8,354
Feagins[48]	Dig Dis Sci	2014	Retrospective	3.00 (0.31 – 29.40)	368 / 1,311
Liaquat[22]	Gastroint Endosc	2013	Retrospective (Polyps ≥ 2 cm only)	**0.17 (p = 0.01)****	463 / 524
Kim[29]	J Gastroent Hep	2013	Retrospective (Subgroup, incl. APC/epi)	0.97 (p = 0.94)	53 / 474
Qumseya[31]	Dig Dis Sci	2013	Retrospective (Subgroup, incl. UGI)	N/S (p = 0.06)	? / 935
Quintanilla[60]	J Interv Gastroent	2012	RCT	1 event vs. 0 (p = N/S)	98 / 105
Gimeno-Garcia[28]	Eur J Gastroent Hep	2012	Retrospective (Subgroup, incl. epi)	1.93 (p = 0.32)	352 / 412
Shioji[61]	Gastroint Endosc	2003	RCT	1.01 (p > 0.99)	253 / 413
Sobrino-Faya[62]	Rev Esp Enferm Dis	2002	Retrospective	1 event vs. 0 (p = N/S)	? / 223

RCT = randomized controlled trial; CI = confidence interval; APC = argon plasma coagulation; EMR = endoscopic mucosal resection; UGI = upper gastrointestinal; epi = epinephrine; ** = significant effect of prophylactic clipping on delayed post-polypectomy bleeding rate

Chapter Two – Routine Prophylactic Endoscopic Clipping is Not Efficacious in the Prevention of Delayed Post-polypectomy Bleeding: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Abstract

Background and Aims

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

Methods

We searched electronic databases and other relevant sources for randomized controlled trials assessing the efficacy of prophylactic clipping, versus no clipping, for preventing DPPB. Pooled relative risks were obtained using a fixed-effects model. Meta-regression and subgroup analyses were also performed.

Results

A total of 2,057 citations were initially identified. Five randomized controlled trials satisfied all criteria for inclusion. The quality of included studies was generally low to moderate. A total of 2,452 patients underwent 4,456 polypectomies. DPPB occurred at an overall pooled rate of 2.4%. No overall benefit of clipping for preventing DPPB was observed, with a pooled relative risk of 0.90 (95% confidence interval, CI, 0.54 to 1.45). No significant patient or polyp factors predicting DPPB were found through meta-regression or subgroup analyses. No publication bias was identified.

Conclusions

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

Introduction

Removal of pre-cancerous adenomatous polyps during colonoscopy reduces the incidence and mortality associated with colorectal cancer (CRC).[6, 17, 18, 63] However, polypectomy may be associated with adverse events, including sedation-related complications, pain, bleeding, bowel perforation, and even death.[21] Post-polypectomy bleeding can occur in the immediate setting (observed endoscopically at the time of polypectomy), but it can also be delayed. Delayed post-polypectomy bleeding (DPPB) is typically seen within 14 days,[22] and is defined as luminal bleeding occurring up to 30 days following the procedure.[24] Larger lesion size and proximal colonic location are among the well-established risk factors for DPPB.[25]

Endoscopic clips are effective for the treatment of immediate post-polypectomy bleeding and small perforations recognized during colonoscopy.[46] Increasingly, practitioners of colonoscopy are using endoscopic clips to prevent DPPB, yet data to support this practice are few and conflicting. A 2013 observational study included patients with polyps ≥ 20 mm; within this higher-risk group, full closure of polypectomy defects was associated with reduced frequency of DPPB.[22] By virtue of its non-randomized design, this retrospective study was prone to bias. Among the few randomized controlled trials (RCTs) performed to date, [56-58, 60, 61] only one has shown a beneficial effect of clipping.[58] The remainder have failed to show a benefit of prophylactic clipping on DPPB, and, in fact, have even shown trends toward increased risk when only partial defect closure is accomplished.[48, 64] Previous meta-analyses studying this question have concluded no effect of prophylactic

clipping in the prevention of DPPB;[49, 51] however, important data have been published since they were carried out.[58]

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

Methods

Objectives and Study Protocol

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

The study protocol was registered through PROSPERO International Prospective Register of Systematic Reviews, and assigned the identifier PROSPERO 2016: CRD42016039860. The systematic review and meta-analysis were both conducted and reported according to the PRISMA statement recommendations,[2] included in Appendix A. Two reviewers (NF, LF) searched the online databases MEDLINE, Pubmed, EMBASE (Excerpta Medica Database), and CENTRAL (Cochrane Central Registry of Controlled Trials). No date limits were applied from inception through November 10, 2016. The same two reviewers also searched the references of all identified relevant published manuscripts, systematic reviews and abstracts of major North American gastroenterology meetings (American College of Gastroenterology, Digestive Diseases Week, Canadian Digestive

Diseases Week) between January 1, 2013 and November 10, 2016. In addition, the tables of contents of major gastroenterology journals relevant to the field (Gastroenterology, American Journal of Gastroenterology, Gastrointestinal Endoscopy, Endoscopy and Surgical Endoscopy) were searched from January 1, 2013 to November 10, 2016. Experts in the field were contacted for any information or knowledge regarding ongoing or unpublished studies. In addition, study authors were contacted for any relevant information missing from publications. Finally, clinical trial registries were accessed to identify ongoing/unpublished trials, and these included clinicaltrials.gov, vacsp.gov, CENTRAL, www.controlled-trials.com/mrct, and isrctn.com.

Literature Search and Identification of Primary Studies

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

The initial screen was intentionally broad to encompass all potentially relevant

literature. No RCT filter was applied such that relevant observational literature could also be extracted for perusal of articles and references. Agreement between reviewers was quantified using Cohen's kappa coefficient. Any potential disagreement between reviewers was resolved by deciding vote (SJH). Articles were reviewed in full if either NF or LF felt it was warranted. Studies with observational designs, reviews, non-human studies, pediatric studies, and studies comparing clips to other modalities were excluded. This focused step-wise strategy was designed to capture randomized trials that compared clipping to no clipping for meta-analysis.

Data Extraction

A data extraction form was created to collate information from each identified study, and can be found in Appendix C. Data elements were pre-specified for extraction with the intent to include all relevant study details, as well as potential predictors and/or modifiers of bleeding and other adverse event outcomes. The data elements included: relevant citation and authorship data, study country and design, sample size, mean age, gender distribution, and categories of polyp size (<5 mm, 5-9 mm, 10-14 mm, 15-19mm, ≥20mm), location (proximal vs. distal or colonic segment) and macroscopic classification (flat, sessile, or pedunculated), along with patient use of medications of interest (anticoagulant and/or antiplatelet agents), endoscopist specialty, and average number of clips used.[56-58, 60, 61] Outcome data collected included: duration of follow-up, and numbers of cases in each group of bleeding, perforation, post-polypectomy syndrome, and abdominal pain, in addition to mean procedural time and cost. [56-58, 60, 61] One trial studied the effect of clipping on both post-endoscopic mucosal resection (EMR) as well as post-endoscopic submucosal dissection

(ESD) adverse events.[58] Our review focused on standard polypectomy techniques. As such, the corresponding author was contacted who then provided data among the randomized EMR cases separately. We did not include the ESD cases in our analysis.

Trials then underwent an assessment of quality by both reviewers, including a final rating.[1] Discrepancies between the reviewers were resolved by consensus (SJH). The elements of the quality and bias assessments were designed to meet the Cochrane standards for reporting of meta-analyses.[1]

Statistical Analysis

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

Univariate meta-regression analyses were performed to investigate potential mediators of heterogeneity. These were performed according to study characteristics as well as pre-specified variables associated with an increased risk of delayed bleeding; specifically, polyp size, shape, and anticoagulant status were selected, in addition to single- versus multi-centered trial design. Subgroup analyses were then performed on statistically significant variables identified through univariate meta-regression or on variables deemed to be clinically significant despite a lack of statistical significance. Publication bias was assessed by applying Egger's and Begg's tests and creating funnel plots. All statistical analyses were

performed using STATA version 14 (StataCorp, College Station, TX, USA).

Results

Identification of Studies for Meta-Analysis

The overall search and study selection results are displayed in Figure 1.[2] The search identified 2057 citations (after removing duplicates). No citations were identified through searches among the other sources. The initial title and abstract screen resulted in the exclusion of 1919 articles, with an overall inter-rater agreement (for article selection) of 0.73 (Cohen's kappa). Any article that was selected for full text review by either reviewer underwent full text screening by both reviewers. The next round of full text screening excluded a further 133 articles, with 5 randomized controlled trials ultimately identified for inclusion in the meta-analysis. Cohen's kappa coefficient for inter-rater agreement was 1.00 for the second screen. Reasons for exclusion following full-text review included the following: the manuscript posed a different study question than that pre-specified (118 studies), the study was not a RCT design (9 studies), the study combined multiple endoscopic prevention modalities (3 studies), or the publication presented duplicate data from a previously reviewed trial (3 studies).

Characteristics of Included Studies

Pertinent characteristics of the five studies included in the meta-analysis are summarized in Table 1. A total of 4,456 polyps were analyzed (2,202 clipped and 2,254 unclipped); 20.6% of the polyps were ≥ 1 cm, and 49.1% had a proximal location (transverse

colon or more proximal). Of the 5 studies, 4 were performed in Asia (3 in Japan). Most studies were recent, with only one (authored by Shioji *et al*.[61]) performed over five years ago. All but one study (by Matsumoto *et al.*,[56] also the largest) was single-centered. The event rate was low overall, with delayed bleeding occurring in 1.0 to 4.0 percent of patients across all five studies. The study by Zhang *et al.*[58] included patients treated by either EMR or ESD; data on EMR procedures only are presented (and were analyzed accordingly) after contacting the authors for study data.

Assessment of Study Quality

Individual components of trial quality for each RCT, as assessed according to the Cochrane Risk of Bias Tool,[1] are summarized in Table 2. Study quality was generally low-moderate, with two studies lacking reporting of allocation concealment and only one trial specifying blinding of outcome assessors.

Effect of Clipping on Delayed Bleeding

There was no overall difference in the pooled relative risk (RR) of DPPB in the clipping group compared to the non-clipping group (RR = 0.90; 95% confidence interval, CI, 0.54 to 1.51) using a fixed effects model (Figure 2). There was a low degree of heterogeneity between the five studies, indicated by an I^2 value of 19.7%. Univariate meta-regression and subgroup analyses were then performed for several important variables, with none yielding statistically significant results. Specifically, meta-regression failed to show a statistically significant effect of prophylactic clipping among any of the following groups: pedunculated vs. non-pedunculated polyps, polyps ≥ 5 vs. < 5 mm, polyps ≥ 10 vs. < 10 mm, polyps ≥ 20 vs.

< 20 mm, and patients on vs. off anticoagulant/antiplatelet medications (Table 3). Meta-regression and subgroup analyses were also performed to assess whether results differed for single-centered vs. multi-centered trials, with no significant difference observed (Table 3). Subgroup analyses were performed on a-priori selected clinically important polyp characteristics, and these are displayed in Table 4. Overall, no protective effect of clipping was seen across all polyp characteristics, though a trend was seen towards a protective effect with polyp size ≥ 10 mm, with a RR of 0.51 (95% CI 0.23 to 1.16). The subgroup with polyps ≥ 20 mm had a limited sample size of 122. Begg's and Egger's tests yielded no significant evidence of small study bias, with p-values of 0.31 and 0.47, respectively. A funnel plot (Figure 3) also yielded no clear visual evidence of small study effects.

Discussion

This systematic review and meta-analysis examining the efficacy of prophylactic endoscopic clipping for prevention of DPPB identified 5 RCTs that included a total of 4,456 polypectomies among 2,362 patients. The overall delayed bleeding rate was 2.4% (57 patients), consistent with previous reports where DPPB ranged from to 0.5 to 7.2%.[23, 26, 28-31, 34, 48, 65] We found no overall effect of prophylactic clipping on the risk of DPPB, with a pooled RR of 0.90 for clipping compared to no clipping (95% CI 0.54 to 1.51).

The overall heterogeneity was low, as suggested by the I^2 value of 19.7%.[1] However, this assessment was limited by low power given the small number of included studies. We did not find statistically significant factors in the meta-regression or subgroup analyses associated with a lower relative risk of DPPB following prophylactic clipping. Larger polyps

(≥ 10 mm) were associated with a non-statistically significant reduction in DPPB (RR=0.51, 95% CI 0.23 to 1.16). The wide confidence intervals suggest our study was underpowered to detect a significant difference. This lack of power is further supported by the small overall number of polyps measuring ≥ 20 mm in the included studies, with only 122 polyps and 7 bleeding events. Thus, additional RCT-level evidence focused on larger polyps and other higher risk settings (e.g. right sided lesions or among patients exposed to anticoagulants and/or antiplatelet agents) is warranted.

This meta-analysis has several important strengths. The broad search strategy provides a thorough and up-to-date review of the current state of evidence regarding the efficacy of prophylactic endoscopic clips for prevention of DPPB. By limiting the analysis to RCTs, our findings are less prone to bias than previous reviews which pooled results from both experimental and observational study designs.[51] Nevertheless, our objective assessment of the literature revealed low-moderate overall quality among the included studies (Table 2). Significant study limitations were identified including lack of blinding of outcome assessors and inconsistent allocation concealment.

A recent network meta-analysis evaluating multiple prophylactic endoscopic modalities (including clipping) concluded that none were effective in the prevention of DPPB.[49] In addition, a second meta-analysis that focused solely on clipping drew similar conclusions.[51] Our meta-analysis adds to the existing literature by including the one trial that showed a benefit of clipping in the prevention of DPPB.[58] Zhang *et al.*[58] enrolled patients who underwent both EMR and ESD, but we were able to pool the EMR data alone in our meta-analysis. The inclusion of this study is important, since it showed a benefit of prophylactic

clipping with a RR of 0.21 among EMR cases (95% CI 0.05 to 0.92).[58] This is the only RCT to date that has shown a benefit of prophylactic clipping, possibly as a result of limiting their enrollment to lesions ≥ 10 mm or sessile morphology. Thus, the results of our systematic review and meta-analysis highlight not only the need for additional high quality RCTs, but trials focused on higher risk lesions or among patient populations at higher risk of bleeding that are more likely to benefit from prophylactic endoscopic clipping.

There are clinical scenarios for which prophylactic clipping is currently recommended based on available evidence. Mechanical hemostatic prophylaxis, which can include placement of prophylactic endoscopic clips, may be efficacious in preventing bleeding following removal of large pedunculated polyps. In this scenario, and in contrast to sessile or flat lesions, where vascular supply is usually broad and multifocal, the blood supply in large pedunculated lesions is generally limited to a few or one larger blood vessel(s) within the stalk, and hemostasis by conventional electrosurgical means cannot be assured.[66] Mechanical prophylaxis, using a detachable loop, or a snare with clip(s), has been shown to decrease post-polypectomy bleeding from pedunculated polyps ≥ 20 mm.[67, 68] The efficacy of clipping alone in this context has not been studied, and thus, our meta-analysis does not address this question. Nevertheless, European guidelines currently recommend pre-treatment of pedunculated polyps with heads ≥ 20 mm or stalks ≥ 10 mm using either mechanical prophylactic measures or injection of dilute epinephrine.[69] Deploying a clip or multiple clips across a thick stalk to achieve tissue ischemia can be technically challenging, and use of a detachable loop also has its limitations; hence, feasibility and cost should also be considered in future studies and clinical guidelines.

Despite its strengths, this study has limitations. The included trials were generally small and underpowered to demonstrate treatment effects within important subgroups. Small sample size and insufficient reporting of data also limited our ability to pool within strata (e.g. increasing polyp size, polyp location) and to evaluate the effect of prophylactic clipping on other adverse events and procedure-related outcomes, such as delayed perforation; however, this is uncommon with modern electrosurgical techniques. This limitation was most evident in the analysis of lesions ≥ 20 mm. In addition, most of the included studies followed evidence-based guidelines, and thus anticoagulant and antiplatelet medications were typically held pre-procedure.[70] Thus, the potential for clips to lower the risk of DPPB among patients at potentially greater risk of bleeding remains unknown. Finally, the included trials were conducted in a relatively small number of countries; most originated from Japan and 4 out of 5 were conducted in Asia. With a paucity of Western clinical trials addressing this important question, the generalizability of our findings may be less certain.

The results of this meta-analysis can help inform clinical practice. At the present time, despite the widespread use of prophylactic endoscopic clipping, there is little if any evidence to support this approach in any therapeutic environment. Endoscopic clips are also costly.[71] Furthermore, clipping is not always a benign intervention, with uncommon reports of complications following their deployment.[60] These factors, when combined with our pooled results demonstrating a lack of clinical efficacy of prophylactic clips among all-comers, ought to make practitioners take pause. Non-judicious use of these devices as a means to help the endoscopist 'sleep better at night' cannot be justified. More appropriate practice necessitates

a careful case-by-case consideration of all relevant patient-, endoscopist-, polyp- and procedure-related factors before making the decision on whether or not to prophylactically clip a polypectomy site. In particular, use of prophylactic clips for small polyps < 10 mm appears ineffective, outside of their potential usefulness in selected higher-risk circumstances (ie: patients with recent exposure or immediate need of anti-coagulants/ antiplatelet agents). More data are urgently needed to better serve our patients and rationalize health care costs. Ultimately, additional high quality and adequately powered randomized trials are needed to determine whether prophylactic clips are efficacious in preventing DPPB following removal of large pedunculated and larger non-pedunculated lesions.

Figures and Tables

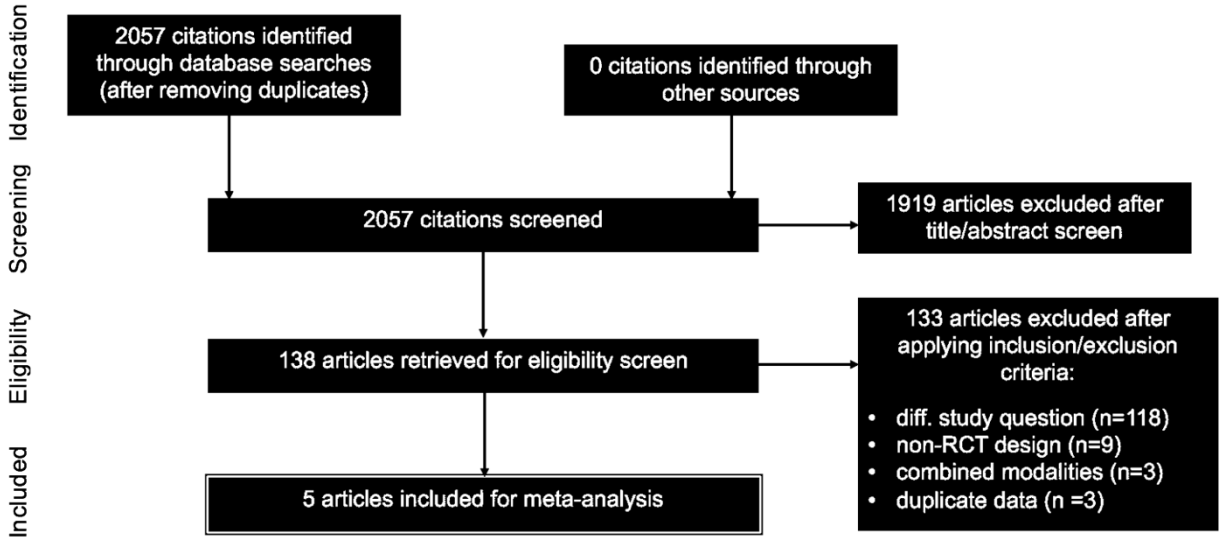

Figure 2.1. Study flow diagram[2] detailing methodology for initial study identification, screening, eligibility and final inclusion for analysis.

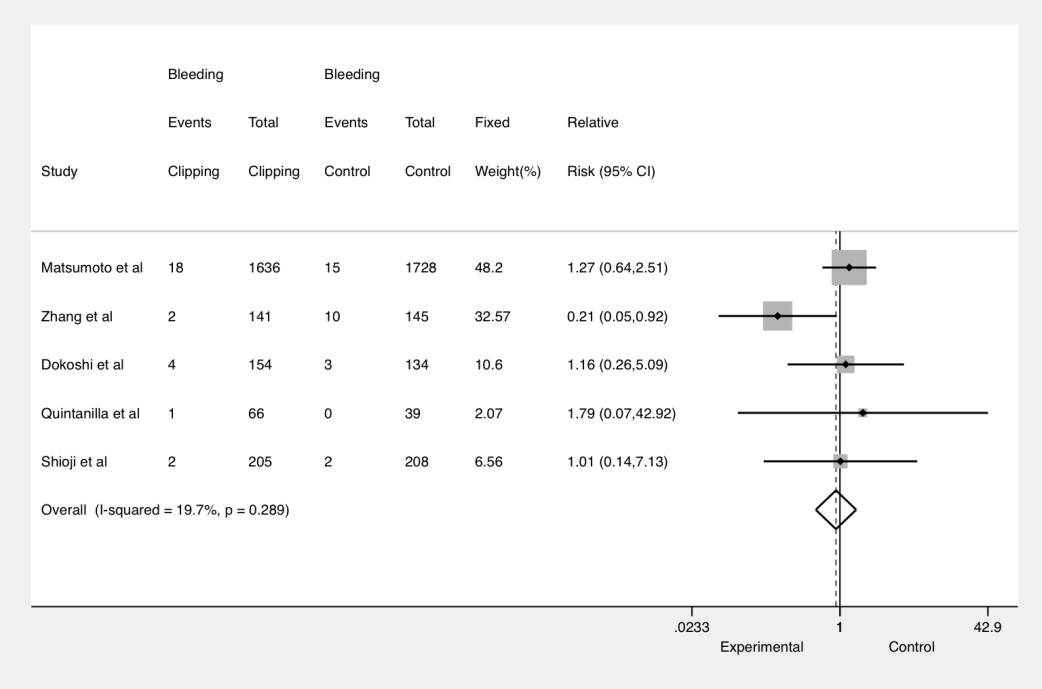

Figure 2.2. Forest plot comparing clipping and non-clipping for prevention of delayed post-polypectomy bleeding.

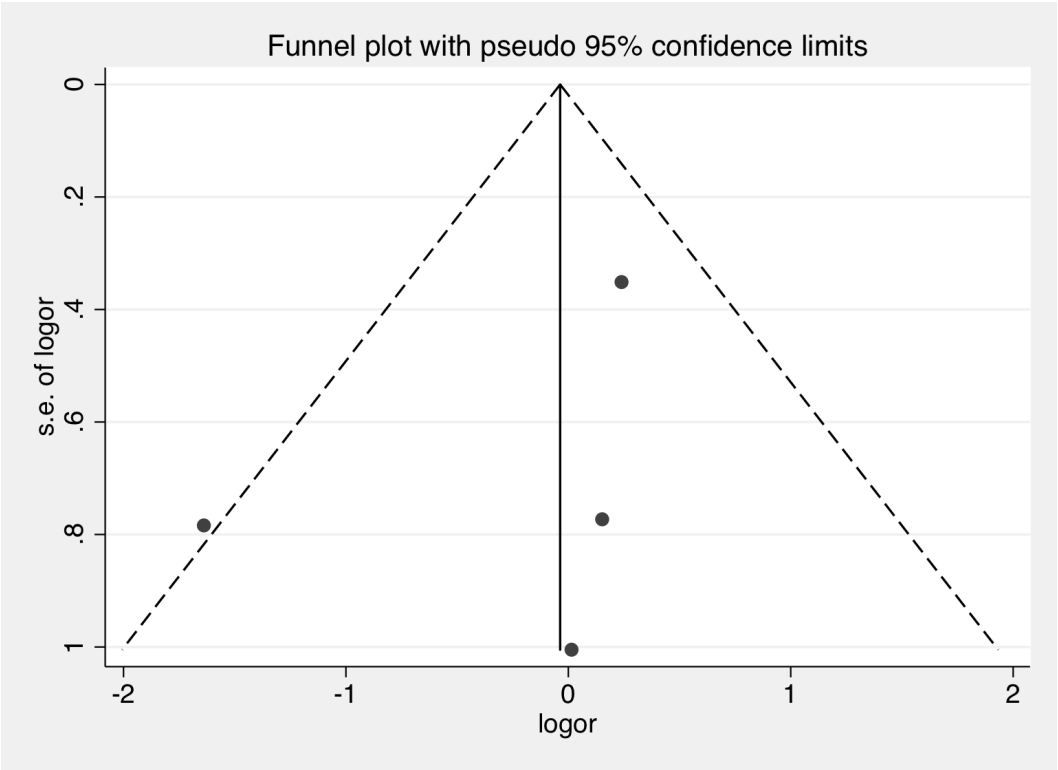

Figure 2.3. Funnel plot assessing small study effects with regards to the protective effect of clipping (versus no clipping).

Table 2.1. Summary of characteristics of RCTs included in the meta-analysis.

Author	Year	Country	Centers	Patients	Polyps (clipped, unclipped)	Bleeding events (clipped, unclipped)	Polyps with proximal location* (%)	Polyps with size ≥1cm (%)
Matsumoto[56]	2016	Japan	Multiple	1499	3364 (1636, 1728)	33 (18, 15)	1668/3364 (49.6)	339/3364 (10.1)
Zhang[58]	2015	China	Single	286	286 (141, 145)	12 (2, 10)	N/A	286/286 (100.0)
Dokoshi[57]	2015	Japan	Single	156	288 (154, 134)	7 (4, 3)	N/A	104/288 (36.1)
Quintanilla[60]	2012	Spain	Single	98	105 (66, 39)	1 (1, 0)	N/A	105/105 (100.0)‡
Shioji[61]	2003	Japan	Single	323	413 (205, 208)	4 (2, 2)	187/413 (45.3)	N/A

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

‡All polyps in this study were pedunculated

Table 2.2. Measures of quality of RCTs included in the meta-analysis.[1]

	Matsumoto[56]	**Zhang[58]**	**Dokoshi[57]**	**Quintanilla[60]**	**Shioji[61]**
Selection bias					
Random sequence generation	present	absent	absent	present	absent
Allocation concealment	absent	present	present	absent	present
Performance bias					
Blinding of participants and personnel	absent	absent	absent	absent	absent
Detection bias					
Blinding of outcome assessment	absent	present	absent	absent	absent
Attrition bias					
Incomplete outcome data	none	none	none	some	none
Reporting bias					
Selective reporting	none	none	none	none	none
Other bias					
Other sources of bias	none	none	none	none	none
Overall assessment of quality					
Overall quality	Moderate	Moderate-high	Low	Low-moderate	Moderate

Table 2.3. Meta-regression analyses performed to assess for potential heterogeneity of effect of prophylactic clipping between various clinically relevant subgroups (fixed effects models applied).

Variable	**Odds ratio (OR) of DPPB**	**95% CI for OR**	**p value**	**Number of observations**
Pedunculated polyps (vs. other morphologies)	1.42	0.21 to 2.28	0.66	8
Patients on anticoagulant / antiplatelet medications (vs. on no relevant medications)	1.03	0.16 to 5.81	0.96	6
Polyp size ≥ 5 mm (vs. < 5 mm)	0.88	0.00 to >100	0.96	3
Polyp size ≥ 10 mm (vs. < 10 mm)	0.45	0.01 to 22.37	0.47	4
Polyp size ≥ 20 mm (vs. < 20 mm)	0.60	0.07 to 5.43	0.56	6

Table 2.4. Subgroup analyses performed to assess effect of prophylactic clipping on various clinically relevant subgroups (fixed effects models applied).

Variable	**Relative risk**	**95% CI**	**Heterogeneity (I^2)**	**Number of trials**	**Polyps (clipped, unclipped)**	**Bleeding events (clipped, unclipped)**
Pedunculated polyps	1.20	0.63 to 2.28	Low (0.0%)	4	3239 (1575, 1664)	33 (18, 15)
Patients on anticoagulant/ antiplatelet medications	0.87	0.32 to 2.36	Low (7.8%)	3	889 (444, 445)	13 (6, 7)
Polyp size ≥ 5 mm	0.88	0.47 to 1.65	Moderate-high (63.3%)	3	2094 (1064, 1030)	38 (18, 20)
Polyp size ≥ 10 mm	0.51	0.23 to 1.16	Low-moderate (31.1%)	3	730 (415, 315)	25 (10, 15)
Polyp size ≥ 20 mm	1.11	0.31 to 3.99	Low (0.0%)	3	122 (82, 40)	7 (5, 2)
Proximal polyp location*	2.18	0.76 to 6.26	Low (0.0%)	1	1,668 (823, 845)	16 (11,5)

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

Chapter Three – Practice Patterns and Predictors of Prophylactic Endoscopic Clip Usage following Polypectomy

Abstract

Background

Endoscopic clips are commonly used during polypectomy to reduce the risk of delayed bleeding, although this practice is not supported by evidence.

Objectives

Our study aimed 1) to identify variables associated with use of prophylactic clips, and 2) to explore variability in practice patterns between endoscopists.

Design and Setting

Retrospective cohort study in a single high-volume endoscopy unit dedicated to screening-related colonoscopies.

Patients and Outcomes

Colonoscopies involving polypectomy, with or without clipping, were reviewed from 2008-2014. The primary outcome was prophylactic clipping status, both at the patient level and per polyp. Hierarchical regression models yielded adjusted odds ratios (AORs) to determine predictors of prophylactic clipping.

Results

From 2008 to 2013, the proportion of clipped cases increased from 1.9% to 9.2%, for an absolute increase of 7.3% (95% CI 6.4 to 8.2%), or a relative increase of 384%.

5,739 colonoscopies involving 12,746 polypectomies were analyzed. Relative to polyp size < 1 cm, size ≥ 2 cm was associated with higher clip usage (AOR 5.10; 95% CI 4.27 to 6.09). Right-sided polyp location predicted clipping (AOR 2.98; 95% CI 2.47 to 3.60) relative to the rectum.

Limitations

Single center study, retrospective design.

Conclusions

Significantly increased clip usage over time was shown. Prophylactic clip usage was associated with established risk factors for delayed bleeding. Given that available evidence does not support prophylactic clipping, particularly for small polyps, there is an urgent need to educate practitioners, standardize practice, and limit healthcare resource utilization.

Introduction

Endoscopic resection of pre-cancerous polyps is effective in reducing the incidence and mortality from colorectal cancer.[17] However, polypectomy is associated with adverse events including bleeding and perforation.[21]

Intra-procedural bleeding (IPB) during polypectomy, and especially during endoscopic mucosal resection (EMR), is relatively common,[72] but is generally considered a technical interference, provided the patient's clinical course is unaltered.[23] In contrast, delayed post-polypectomy bleeding (DPPB), which may occur up to 30 days following the procedure, can increase morbidity and result in increased healthcare utilization through unplanned emergency room visits, hospital admissions, blood transfusions and repeat interventions.[22, 24, 25] There are several well-established risk factors for DPPB, including increasing polyp size, proximal colonic location, patient comorbidity, and a history of IPB during the index procedure.[25, 33]

Endoscopic clips are important tools available to the endoscopist for treating IPB.[69] While also an appealing option to prevent DPPB given their ease of use, evidence to support their role in this context is less clear. Randomized controlled trial data have not demonstrated a clear benefit of clips in the prevention of DPPB. A recent systematic review and meta-analysis of 5 randomized controlled trials showed no efficacy of clips in preventing DPPB among polyps < 10 mm.[73] However, it remains uncertain whether these devices are efficacious following more complex polypectomy, or in higher-risk scenarios such as in patients requiring antithrombotic or anticoagulant agents. Recent clinical practice

guidelines support the practice of mechanical hemoprophylaxis for large pedunculated polyps with stalks ≥ 10 mm.[69]

Despite a lack of evidence to support their use, surveys of endoscopists suggest that clips are being used with increasing frequency to prevent DPPB.[54, 55] However, there is a paucity of data examining endoscopist-, patient- and polyp-related predictors of prophylactic clipping. In order to promote and standardize evidence-based best practice, it is important to quantify the use of clips over time, and to understand the settings in which endoscopists are using clips for the prevention of DPPB. In addition, it is crucial to determine whether provider-level variability in clinical practice exists. Therefore, the objectives of our study were to determine the correlates of prophylactic clip usage and to explore variability in clinical practice between endoscopists through analysis of a large retrospective cohort generated at a high-volume outpatient endoscopy unit.

Methods

Study Design and Setting

The study was granted institutional approval by the University of Calgary Conjoint Health Research Ethics Board (REB14-2314). In this retrospective cohort study, polypectomy cases from 2008 to 2014 were reviewed at the Forzani & MacPhail Colon Cancer Screening Centre (CCSC) in Calgary, Alberta, Canada. The CCSC is a publically funded endoscopy unit dedicated to CRC screening-related colonoscopies. Procedures are performed by both academic and community-based gastroenterologists and colorectal surgeons. Eligibility for colonoscopy at the CCSC requires that patients be between the ages

of 18 and 75 years of age, asymptomatic, and without significant medical comorbidities. Patients at the CCSC are allocated to endoscopists from a general pool, so that a similar case mix by indication is achieved. No institutional policy existed regarding the use of prophylactic endoscopic clips during the study timeframe.

Study Cohort

To be included in the final study cohort, a patient needed to undergo endoscopic removal of at least one polyp. Cases involving polypectomy, with or without clipping, were identified based on nursing instrument usage records from the endoscopy reporting program endoPRO (Pentax Medical, Montvale, New Jersey, USA). We then manually reviewed the records of clipped polypectomy cases (polypectomy cases in which at least one endoscopic clip was used) in chronological order from 2008 to 2014. A random sample of unclipped cases (cases involving polypectomy, but no clipping) was simultaneously reviewed in order to maintain a roughly equal balance of clipped and unclipped cases. A total of 7,179 colonoscopies from January 1, 2008 to December 31, 2014 were reviewed. All patients satisfying the above criteria were eligible for inclusion, regardless of indication for the index procedure. Only cases where clipping was performed for prophylaxis were included in the clipped cohort. If both prophylactic and non-prophylactic clipping occurred in a case, the case was excluded from analysis. A flow chart describing the inclusion and exclusion of all procedures and polyps leading to the final study cohort can be found in Figure 3.1.

Demographic and Clinical Variables

Standardized scannable data abstraction forms were created to collect relevant endoscopist-, patient- and polyp-level data for each case in both the clipped and unclipped groups (Appendix D). All data elements were determined for each case through retrospective electronic review of the endoscopist's report, nurses' report(s), pathology submission form(s), and images acquired during the procedure from endoPRO. Case-based data elements retrieved included patient age, gender, medications of interest (including antiplatelet and anticoagulant drugs), procedural indication and year, endoscopist specialty, and endoscopist experience at the time of the procedure. Endoscopist experience was defined as years of independent practice performing colonoscopy, and was calculated using public licensing registers and/or direct inquiry. As it was possible for a practitioner's experience bracket to change during the study period, the year was cross-referenced for each case to ensure correct coding for each endoscopist.

Polyp-based data elements included polyp size, shape and location, resection technique, presence/type of submucosal injectate, presence of piecemeal resection, use of adjunctive modalities, and clipping status. For clipped polyps, data were collected on the number of clips applied (and fired, if different), timing of clip application (before or after polypectomy, or both), clip indication, and presence of full polypectomy defect closure (versus partial closure or targeted vessel clipping). A maximum of 15 polyps were reviewed for each case. Where a case contained more than 15 polypectomies, the following hierarchy was employed to ensure inclusion of: 1) clipped lesions, 2) lesions ≥ 10 mm or larger, and 3) all remaining polyps from proximal to distal location. Two reviewers (NF and CM) were

responsible for data acquisition. Cohen's kappa coefficient was calculated to determine inter-rater agreement based on a sample of 50 cases; following this, each reviewer abstracted roughly equal numbers of cases independently.

Outcome Measurements

The primary outcome of interest was clipping status, both on a per-patient and a per-polyp basis. All cases during which at least one clip was applied for prophylaxis against DPPB were labelled as 'clipped' (versus 'unclipped'); similarly, each polypectomy site that was clipped prophylactically against DPPB was labelled as 'clipped'.

Statistical Analysis

Descriptive statistics were calculated for all variables. These included mean and standard deviation for continuous variables and proportions for categorical variables together with 95% confidence intervals. Student's t-test was used to compare continuous values, while Chi-Square (χ^2) test was used to compare categorical variables. Univariable and multivariable logistic regressions were then performed to determine predictors of prophylactic clipping. The generalized estimating equation (GEE) was used to analyze clustered data, with a covariance structure that adjusts standard error estimates to reflect the possibility of multiple polyps in a single patient. Univariable logistic regression was first performed. A multivariable regression model encompassing endoscopist-, patient- and polyp-related variables was then created to yield reportable adjusted odds ratios (AORs) of prophylactic clipping assumed common to all possible values for the other covariates. All

potentially collinear variables (polypectomy technique, whether or not submucosal injectate was used, and the presence or absence of piecemeal resection) were removed from the final multivariable model, as these were deemed predicated upon the truly independent polyp-related variables (size, shape and location). Endoscopist-related variables were also removed from the model to avoid issues with sub-clustered data. A final multivariable model using the GEE was thus created.

We performed a separate analysis of inter-endoscopist variability in clipping practices. The final GEE model was used to estimate the predicted probability of clipping for each of the polyps in the cohort. These predicted probabilities were then stratified into pre-determined groups. Clipping probability brackets were chosen such that each contained a similar number of polyps within the study sample. We then calculated the observed proportion of clipped cases for each of the endoscopists across each stratum of predicted clipping probabilities. The observed proportions were plotted against the predicted probability for those endoscopists that performed at least 5 polypectomies in each group. Temporal trends in prophylactic clipping were also analyzed. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA) and R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Temporal Trends in Prophylactic Clip Usage

The proportion of prophylactic clips applied per year, relative to total number of procedures involving polypectomy, is shown in Figure 3.2. The proportion of

prophylactically clipped cases increased from 1.9% to 9.2%, for an absolute increase of 7.2% (95% CI 6.3 to 8.1%), or a relative increase of 384%, from 2008 to 2013, the last year for which all clipped cases were manually reviewed prior to data analysis.

Demographic and Clinical Characteristics

A total of 5,739 colonoscopies (2,753 using one or more prophylactic clip(s) and 2,986 without clips) met inclusion criteria and were analyzed as part of the final study cohort. The final cohort included 12,746 polypectomies (3,115 clipped and 9,631 unclipped). Cohen's kappa statistic for inter-rater agreement between the two primary abstracters was 0.82, where agreement constituted no differences between reviewers in any data elements recorded for an entire procedure. The most common reasons for exclusion were: presence of non-prophylactic clip(s) placed following polypectomy (for instance, to control intra-procedural bleeding), lack of sufficient information for analysis after review of all available records, and absence of polypectomy performed during colonoscopy (misclassification as a result of coding from the initial database). A total of 59 endoscopists performed colonoscopies during the study period; 52 were gastroenterologists and 7 were colorectal surgeons. Descriptive results at the patient and polyp levels are summarized in Tables 3.1 and 3.2, respectively. Statistically significant differences were found in the proportion of patients undergoing colonoscopy for positive stool occult blood testing (fecal immunohistochemical test [FIT] or fecal occult blood test [FOBT]), with 14.4% of patients in the clipped cohort versus 6.3% in the unclipped cohort ($p < 0.001$). Larger polyps were more common in the clipped cohort, with 61.6% of clipped resected polyps being ≥ 1 cm, compared

to 23.7% in the unclipped cohort ($p < 0.001$). Pedunculated polyps comprised 31.6% of the clipped cohort compared to 13.0% of the unclipped cohort ($p < 0.001$).

Correlates of Prophylactic Clip Usage

Univariable logistic regression modelling was applied to the cohort to yield unadjusted odds ratios (ORs) of prophylactic clipping (versus not prophylactically clipping), and these can be found in Table 3.3. After removing collinear and potentially sub-clustered variables, the final multivariable model yielded AORs of prophylactic clipping, summarized in Table 3.4. Relative to polyp size < 1 cm, sizes 1-1.9 cm and ≥ 2 cm were associated with increased clip usage (AOR 1.91; 95% CI 1.70 to 2.13 and AOR 5.10; 95% CI 4.27 to 6.09, respectively). Right-sided polyp location also predicted clipping, with an AOR of 2.98 (95% CI 2.47 to 3.60) relative to rectum.

Variability in Clipping Practices Between Endoscopists

The distribution of polyps in the cohort by calculated probability of being prophylactically clipped according to the final GEE model is shown in the histogram in Figure 3.3. Most of the polyps studied were at a relatively low probability of being clipped, with a decrease in the number of polyps as the probability of clipping increased.

Variability in clipping practices between endoscopists was then assessed for various categories of clipping probability, based on the final multivariable model. Starting with all 59 endoscopists, those who performed fewer than 5 polypectomies in any clipping probability category were removed from the analysis. The overall results that included 29

endoscopists are shown in Figure 3.4. Considerable variability was found between practitioners across all predicted clipping probabilities. However, most endoscopists demonstrated a positive relationship toward greater observed proportions of clipped polyps with increasing predicted clipping probability. There was also a high degree of variability between endoscopists for polyps < 10 mm, a subgroup within which prophylactic clipping has been shown to be inefficacious.[73] This is shown in Figure 3.5.

Discussion

Prophylactic clipping following polypectomy is a common intervention. We and others have demonstrated an increasing frequency of this practice over time. Our study identified endoscopist-, patient- and polyp- level predictors of prophylactic clipping, through analysis of a large retrospective cohort. There was considerable variability between endoscopists across all categories of polyp clipping probability. Notably, we observed frequent use of prophylactic clipping among low-risk polyps < 10 mm, where no efficacy presently exists.[73]

Previous studies of various designs have reported risk factors for DPPB.[23, 25-33, 74] Our results established relevant clinical predictors of prophylactic clipping that align with several of these known DPPB risk factors. Endoscopists were more likely to apply prophylactic clips for larger lesions, right-sided lesions, and flat or pedunculated polyps, all characteristics that have previously been shown to increase the risk of DPPB.[23, 25-33, 74] Our study also revealed several important clipping predictors related to endoscopist factors and polypectomy technique that have not previously been associated with higher rates of DPPB.

Raising a polyp with a submucosal cushion substantially increased the odds of prophylactic clipping, an effect which was even greater when epinephrine was added to the injectate (over and above saline, and with or without methylene blue). This predictor may be a surrogate of polyp morphology. We showed a lower odds of prophylactic clip placement following cold snare polypectomy compared to polypectomy with cautery. This finding was expected, given the role of cautery in the proposed mechanism of DPPB,[75] and the lower adverse event profile associated with cold snare techniques in polyps of small and intermediate sizes.[76, 77] Finally, the presence of antiplatelet medications significantly increased the adjusted odds of clipping. While not unexpected, these medications have previously inconsistently been associated with DPPB.[27, 30, 37]

There was considerable inter-endoscopist variability. Overall, endoscopists were more likely to clip polyps of increasing risk. However, polyps at highest risk of being clipped (with a predicted probability ≥ 60%) were inconsistently clipped, with individual endoscopists clipping these lesions 20-90% of the time (Figure 3.4). More importantly, this variability also existed among low risk polyps (Figures 3.4 and 3.5), where endoscopists clipped all polyps < 10 mm 0–35% of the time (Figure 3.5). This is important, given the majority of polyps in our study (and most of typical screening colonoscopy practices) fall into this category (Figure 3.3), where no empirical evidence exists to support the use of prophylactic clips.[69, 73] These findings demand a clarion call for practice change, especially given this relatively common yet ineffective practice of deploying prophylactic clips comes at high health care expenditure.[52, 53]

We observed variability in clipping practices within a single tertiary care center, and therefore, it is likely that such patterns exist on an equal or even larger scale when one considers all academic and private endoscopy centers across tertiary and smaller community practice settings. Thus, a crucial opportunity now presents itself for endoscopist education. Endoscopy room nurses and trainees within gastroenterology and surgical subspecialty training programs should also be targeted. It is worth noting that surgeons were half as likely to clip compared to gastroenterologists in our study. Furthermore, gastroenterologists were responsible for greater than 90% of the procedural volume in our cohort, and therefore, accounted for substantially more prophylactic clipping, both in relative and absolute terms. The reasons for this remain unclear.

Our study has several strengths. We analyzed a large cohort of over 5,000 patients with just under 13,000 polypectomies; therefore, the sample size of our data set was well-powered to determine correlates of prophylactic clipping. A comprehensive medical record review of the endoscopist's note, pathology submission details, images and nurse's note was undertaken for each eligible procedure during the study period. This ensured the capture of as many detailed data points as possible. Several independent predictors of clipping were identified, some which align closely with known risk factors for DPPB, and some which have not previously been elucidated.

The primary limitation of our study is that the data were generated from a single center. However, the CCSC is a large regional endoscopy unit in which approximately 17,500 screening-related colonoscopies are performed annually by academic and non-academic gastroenterologists and colorectal surgeons with a wide range of individual experience and

annual procedural volumes. As such, the results of our study should be applicable to other centers. In fact, it is plausible that even greater inter-endoscopist variability exists in other centers. Another limitation was the study's retrospective design, which prohibits its ability to determine causal relationships. In this case, our outcome of interest (whether or not to prophylactically clip) was driven by endoscopists' decisions, and therefore, the clinical associations of clipping are still valid as predictors of clinical practice. The chart review design also introduced the possibility of misclassification bias and missing data. However, this risk was mitigated by training data abstractors, using standardized abstraction forms (Appendix D), performing a pilot test, calculating and reporting inter-rater reliability, holding regular abstraction meetings to minimize disagreement, and excluding any records that were incomplete.[78] Another limitation was the inability for our study to determine whether the presence of traditional or novel oral anticoagulants (OACs or NOACs) have an effect on clipping practices, due to a relatively healthy patient population. Lastly, our cohort was limited to screening colonoscopies performed in patients with low comorbidity, and therefore, it is unclear whether these results are generalizable to settings in which clipping practices might differ, such as in-hospital colonoscopy.

At present, there are relatively few clinical circumstances in which prophylactic clipping may be indicated. Prophylactic mechanical measures, including clip placement, should be considered when resecting large pedunculated polyps. Devices such as detachable loops or clips have been shown to reduce bleeding after resection of pedunculated polyps ≥ 20 mm.[67, 79] European guidelines therefore recommend using either mechanical hemostasis or injection of epinephrine for pedunculated polyps with stalks ≥ 10 mm or heads ≥ 20 mm.[69]

There may also be a role for prophylactically clipping flat or sessile defects ≥ 20 mm, though the evidence for benefit in this scenario is less robust and requires further study.[22, 73, 80]

In conclusion, we have reported important clinical predictors of prophylactic clipping and have demonstrated high endoscopist variability in clipping practices among both low-risk and high-risk lesions at a large-volume tertiary screening center. This finding, coupled with an increased frequency of prophylactic clipping over time, is at odds with best available evidence. It now becomes essential to leverage these findings to facilitate knowledge translation and education of practitioners of colonoscopy in order to standardize prophylactic clipping practices, especially given the high cost associated with clips. Additional large cohort studies and randomized clinical trials are required to determine the optimal settings in which prophylactic clipping should be employed.

Figures and Tables

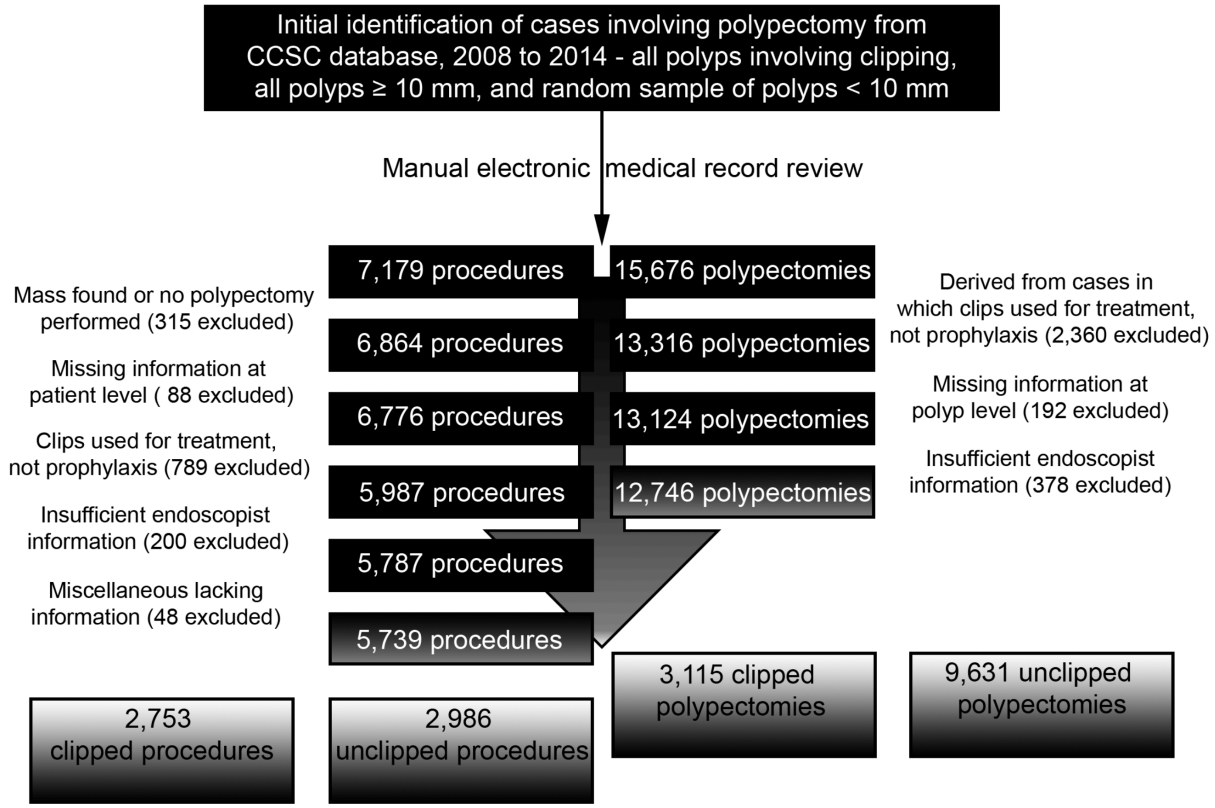

Figure 3.1. Flow chart describing procedures and polypectomies included and excluded in final cohort.

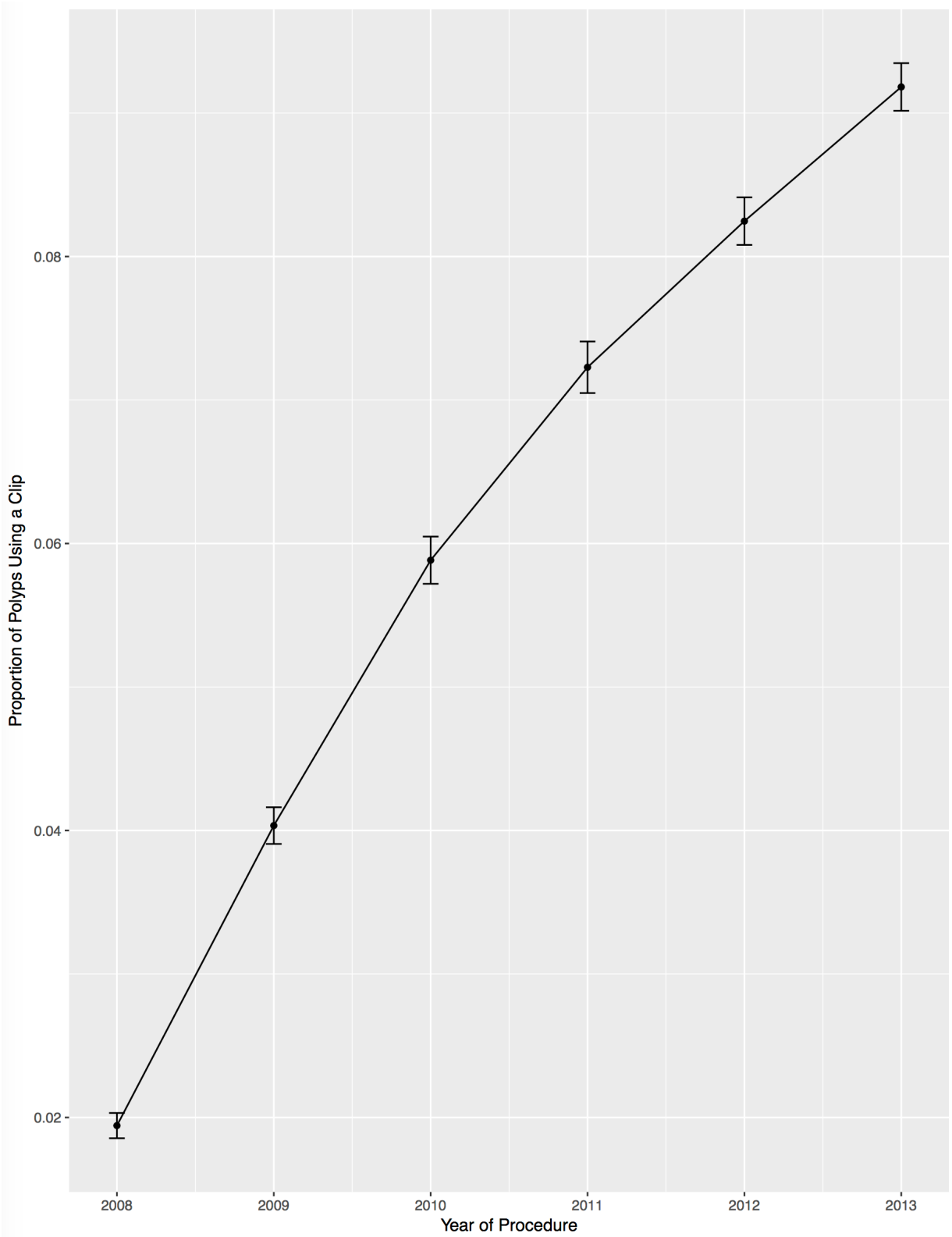

Figure 3.2. Proportion of polyps prophylactically clipped over time, relative to all cases in which polypectomy was performed.

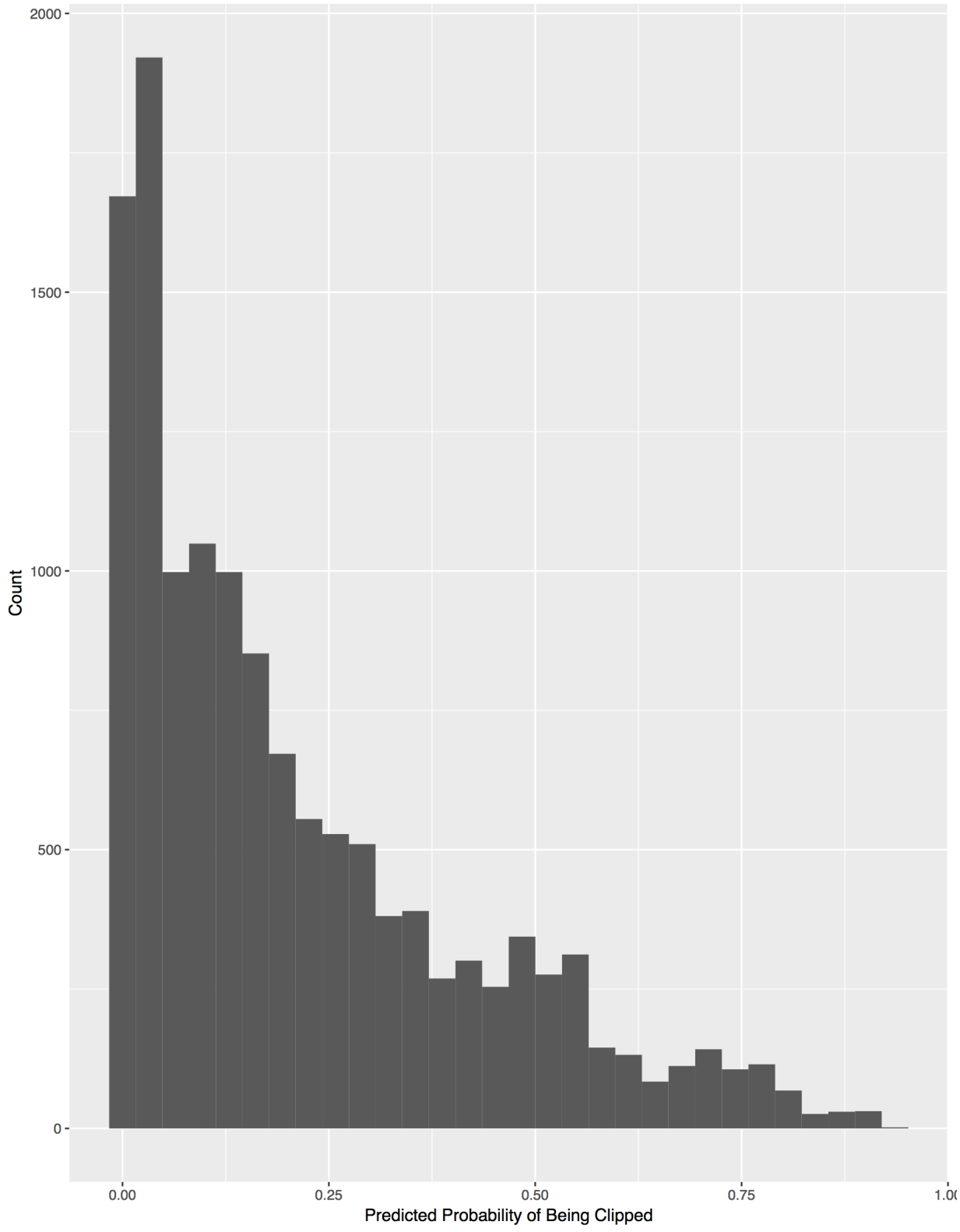

Figure 3.3. Number of polyps in overall cohort by overall predicted probability of clipping, based on final multivariable model.

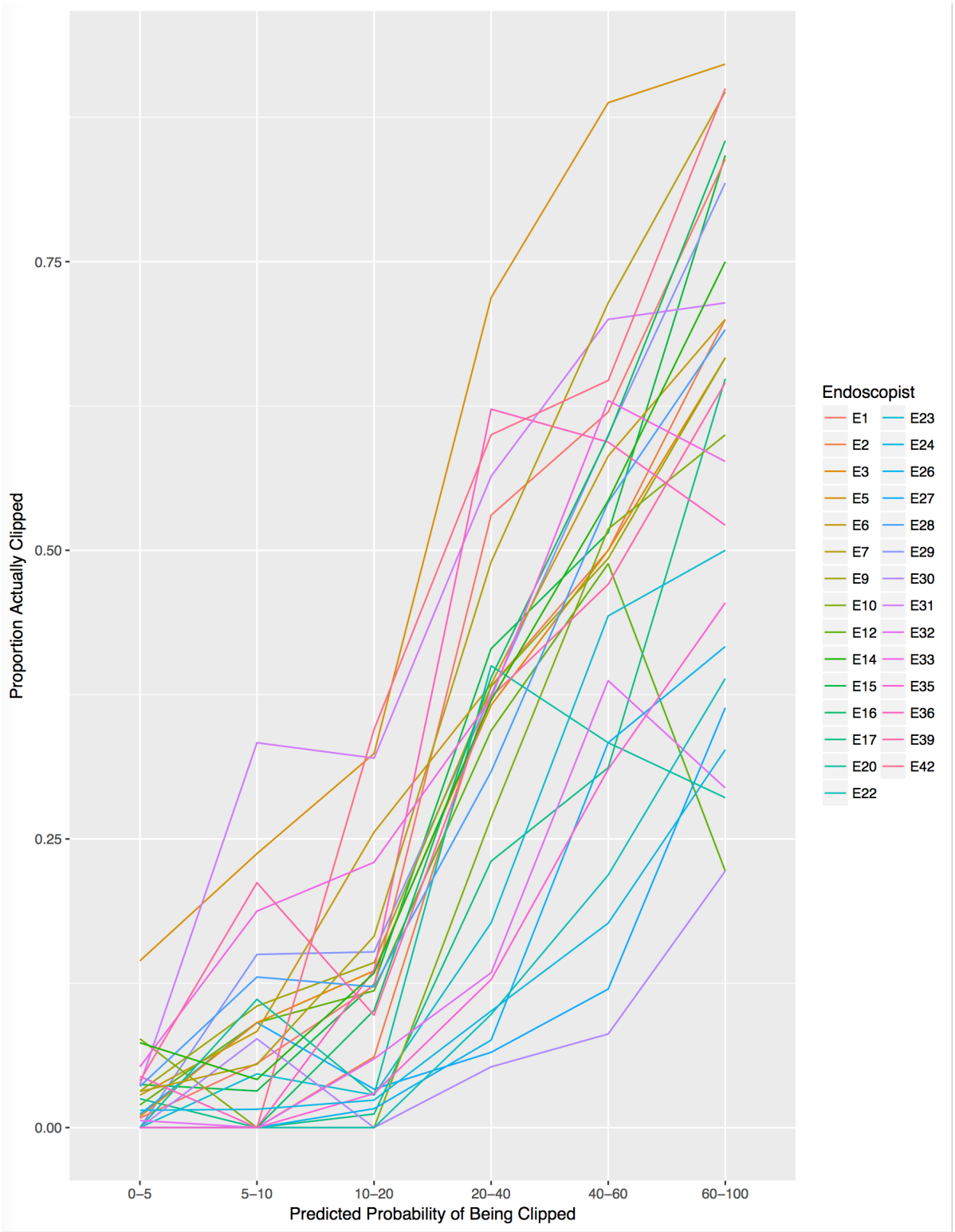

Figure 3.4. Inter-endoscopist variability in prophylactic clipping; proportion of polyps prophylactically clipped by predicted probability of clipping, based on final multivariable model.

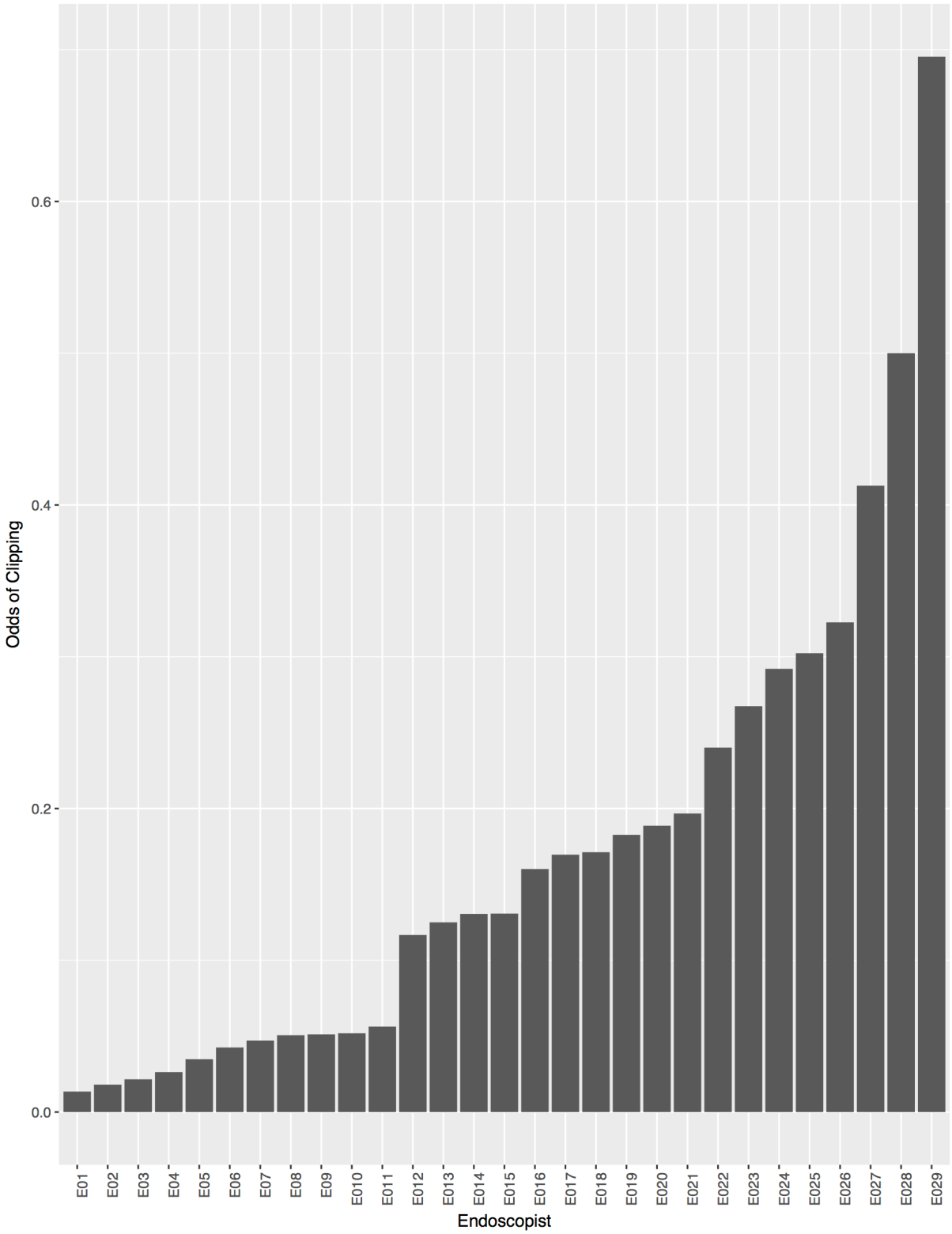

Figure 3.5. Inter-endoscopist variability in prophylactic clipping; odds of clipping for all polyps < 10 mm prophylactically clipped, based on final multivariable model.

Table 3.1. Endoscopist and patient characteristics according to clipped or unclipped status, for 5,739 colonoscopies involving polypectomy.

Variable	Proportions for clipped procedures, n=2,753 (95% CI)	Proportions for unclipped procedures, n=2,986(95% CI)	p-value
Gender (% female)	0.44 (0.42, 0.46)	0.46 (0.44, 0.48)	0.12
Age (mean)	59.47 (59.20, 59.74)	58.34 (58.00, 58.57)	<0.001*
Indication			
Average risk	0.46 (0.44, 0.48)	0.45 (0.43, 0.47)	
Family history	0.23 (0.22, 0.25)	0.35 (0.33, 0.37)	
FIT/FOBT+ stool	0.14 (0.13, 0.16)	0.06 (0.05, 0.07)	
≤ 1 year repeat	0.08 (0.07, 0.09)	0.05 (0.04, 0.06)	<0.001*
1 to 3 year repeat	0.01 (0.01, 0.02)	0.02 (0.01, 0.02)	
> 3 year repeat	0.05 (0.04, 0.06)	0.04 (0.04, 0.05)	
Other (ie: positive imaging)	0.03 (0.02, 0.03)	0.03 (0.02, 0.04)	
Patient medications			
ASA	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	
NSAIDs	0.01 (0.00, 0.01)	0.01 (0.01, 0.01)	0.36
None	0.94 (0.93, 0.95)	0.95 (0.94, 0.95)	
Total number of polyps (mean)	2.34 (2.30, 2.39)	2.11 (2.07, 2.15)	<0.001*
Endoscopist experience			
≤ 5 years	0.26 (0.24, 0.28)	0.28 (0.26, 0.29)	
6 to 10 years	0.29 (0.28, 0.31)	0.20 (0.19, 0.22)	<0.001*
≥ 11 years	0.45 (0.43, 0.46)	0.52 (0.50, 0.54)	
Endoscopist specialty			
Gastroenterology	0.95 (0.94, 0.96)	0.90 (0.88, 0.91)	<0.001*
Surgery	0.05 (0.04, 0.06)	0.10 (0.09, 0.12)	

CI, confidence intervals; FIT, fecal immunohistochemical test; FOBT, fecal occult blood test; ASA, acetylsalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs;
*statistically significant p-value.

Table 3.2. Polyp characteristics according to clipped or unclipped status, for 5,739 colonoscopies including a total of 12,746 polypectomies.

Variable	Proportions for clipped polyps, n=3,115 (95% CI)	Proportions for unclipped polyps, n=9,631 (95% CI)	p-value
Polyp size			
<1 cm	0.38 (0.37, 0.40)	0.76 (0.75, 0.77)	
1 to 1.9 cm	0.43 (0.42, 0.45)	0.21 (0.20, 0.21)	<0.001*
≥ 2 cm	0.18 (0.17, 0.20)	0.03 (0.03, 0.03)	
Polyp shape			
Diminutive	0.02 (0.01, 0.02)	0.28 (0.27, 0.29)	
Pedunculated	0.32 (0.30, 0.33)	0.13 (0.12, 0.14)	
Sessile	0.50 (0.48, 0.52)	0.55 (0.54, 0.56)	<0.001*
Flat	0.16 (0.14, 0.17)	0.04 (0.04, 0.05)	
Residual	0.01 (0.01, 0.01)	0.00 (0.00, 0.00)	
Polyp location			
Rectum	0.07 (0.06, 0.07)	0.14 (0.14, 0.15)	
Sigmoid colon	0.29 (0.27, 0.30)	0.26 (0.25, 0.27)	
Descending colon	0.06 (0.05, 0.07)	0.07 (0.06, 0.07)	
Splenic flexure	0.01 (0.01, 0.02)	0.02 (0.02, 0.02)	<0.001*
Transverse colon	0.11 (0.10, 0.12)	0.14 (0.13, 0.15)	
Hepatic flexure	0.04 (0.04, 0.05)	0.05 (0.04, 0.05)	
Ascending colon	0.22 (0.21, 0.24)	0.20 (0.19, 0.20)	
Cecum	0.18 (0.16, 0.19)	0.10 (0.10, 0.11)	
Polypectomy technique			
Cold biopsy	0.01 (0.00, 0.01)	0.10 (0.09, 0.10)	
Cold snare	0.03 (0.02, 0.04)	0.09 (0.09, 0.10)	<0.001*
Snare with cautery	0.96 (0.96, 0.97)	0.81 (0.80, 0.82)	
Injectate used			
None	0.60 (0.58, 0.61)	0.93 (0.92, 0.94)	
Saline +/- methylene blue	0.35 (0.33, 0.37)	0.07 (0.06, 0.07)	<0.001*
Epinephrine	0.05 (0.05, 0.06)	0.00 (0.00, 0.00)	
Piecemeal resection			
Yes	0.22 (0.21, 0.24)	0.06 (0.06, 0.07)	<0.001*
No	0.78 (0.76, 0.79)	0.94 (0.93, 0.94)	

CI, confidence intervals; *statistically significant p-value.

Table 3.3. Predictors of prophylactic clipping (versus not prophylactically clipping) following polypectomy, from univariable logistic regression.

Variable	OR	95% CI	p-value
Male gender (versus female)	1.09	0.98, 1.21	0.09
Age (per increased year of age)	1.021	1.014 1.028	<0.001*
Year of procedure (per sequential year, relative to 2008)	1.66	1.61, 1.72	<0.001*
Indication			
Average risk (reference)	1.00	N/A	N/A
Family history	0.65	0.58, 0.74	<0.001*
FIT/FOBT+	2.24	1.86, 2.71	<0.001*
≤ 1 year repeat procedure	1.62	1.29, 2.01	<0.001*
1 to 3 year repeat procedure	0.75	0.50, 1.14	0.18
> 3 year repeat procedure	1.03	0.80, 1.33	0.82
Other (ie: positive imaging)	0.84	0.61, 1.15	0.27
Presence of antiplatelet medications (versus none)	3.69	1.67, 8.13	0.001*
Presence of ASA (versus none)	1.12	0.87, 1.44	0.37
Presence of NSAIDs (versus none)	0.54	0.26, 1.12	0.10
Number of polyps (per additional polyp, relative to one)	1.167	1.120, 1.217	<0.001*
Endoscopist experience			
≥ 11 years (reference)	1.00	N/A	N/A
6 to 10 years	1.69	1.48, 1.92	<0.001*
< 5 years	1.09	0.96, 1.24	0.17
Endoscopist specialty			
Gastroenterology (reference)	1.00	N/A	N/A
Surgery	0.47	0.38, 0.57	<0.001*
Size			
< 1 cm (reference)	1.00	N/A	N/A
1 to 1.9 cm	4.17	3.80, 4.57	<0.001*
≥ 2 cm	11.81	10.13, 13.76	<0.001*
Location			
Rectal (reference)	1.00	N/A	N/A
Left-sided	2.07	1.77, 2.43	<0.001*
Right-sided	2.96	2.52, 3.48	<0.001*
Shape			N/A
Sessile (reference)	1.00	N/A	<0.001*
Diminutive	0.07	0.06, 0.10	<0.001*
Flat	3.96	3.43, 4.56	<0.001*
Pedunculated	2.65	2.40, 2.93	<0.001*
Residual	2.61	1.53, 4.45	<0.001*
Polypectomy technique			
Cold biopsy (reference)	1.00	N/A	N/A
Cold snare	4.54	2.80, 7.37	<0.001*
Snare with cautery	16.92	10.96, 26.13	<0.001*
Injectate used			
None (reference)	1.00	N/A	N/A
Saline +/- methylene blue	8.23	7.37, 9.18	<0.001*
Epinephrine	22.75	15.75, 32.88	<0.001*
Piecemeal resection (versus en-bloc resection)	4.30	3.82, 4.84	<0.001*

OR, unadjusted odds ratio; CI, confidence intervals; FIT, fecal immunohistochemical test; FOBT, fecal occult blood test; ASA, aminosalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs; Right-sided = transverse colon, hepatic flexure, ascending colon, cecum or "right colon"; *statistically significant p-value.

Table 3.4. Independent predictors of prophylactic clipping (versus not prophylactically clipping) following polypectomy, from final multivariable logistic model with collinear variables removed – statistically significant terms only.

Variable	AOR	95% CI	p-value
Year of procedure (per sequential year, relative to 2008)	1.31	1.27, 1.35	<0.001*
Presence of antiplatelet medications (versus none)	3.04	1.83, 5.05	<0.001*
Number of polyps (per additional polyp, relative to one)	0.735	0.704, 0.768	<0.001*
Size			
< 1 cm (reference)	1.00	N/A	N/A
1 to 1.9 cm	1.91	1.70, 2.13	<0.001*
≥ 2 cm	5.10	4.27, 6.09	<0.001*
Location			
Rectal (reference)	1.00	N/A	N/A
Left-sided	1.73	1.45, 2.07	<0.001*
Right-sided	2.98	2.47, 3.60	<0.001*
Shape			
Sessile (reference)	1.00	N/A	N/A
Diminutive	0.13	0.10, 0.16	<0.001*
Flat	2.65	2.25, 3.11	<0.001*
Pedunculated	2.15	1.90, 2.44	<0.001*
Residual	2.71	1.48, 4.97	0.001*

AOR, adjusted odds ratio; CI, confidence intervals; FIT, fecal immunohistochemical test; FOBT, fecal occult blood test; Right-sided = transverse colon or proximal location; *statistically significant p-value.

Chapter Four – Summary

Synthesis of Results

This dissertation has fulfilled two primary research objectives. The first was an assessment of clinical efficacy of prophylactic clips in the prevention of DPPB, which was achieved through a systematic review and meta-analysis of randomized controlled trials. No benefit of prophylactic clipping in reducing the risk of DPPB was found. The meta-analysis and meta-regressions were ultimately underpowered to show a significant effect of clipping within any high-risk clinical subgroups, and thus, further study is required. However, routine prophylactic clipping of polyps < 10 mm is not efficacious. The second was to assess clinical practice patterns and to determine predictors of current prophylactic clip use in a 'real world' setting. This was accomplished via an in-depth analysis of a large retrospective cohort. We demonstrated several endoscopist-, patient- and polyp-level factors that drive the decision to place a prophylactic clip during polypectomy. Perhaps most importantly, substantial variability was shown between endoscopists across a spectrum of polyps, including those < 10 mm, where pooled data from five randomized controlled trials has confirmed no benefit.

Together, these results present a divergence between current best evidence and observed clinical practice at a large tertiary care endoscopy center which is likely to be found elsewhere. Our findings have important implications. Firstly, additional study is necessary to elucidate potential high-risk clinical subgroups where prophylactic clipping may be of benefit. Secondly, a crucial opportunity now exists for effective knowledge translation and education of endoscopists, endoscopy nurses, resource managers, and health policy decision makers to change clinical practice and reduce unnecessary health expenditure.

Directions for Future Research

Conducting Randomized Trials within Higher-Risk Subgroups

It is clear based on the results of our systematic review and meta-analysis that prophylactic clipping to prevent DPPB is a futile practice when applied across all-comers undergoing polypectomy. However, there may be subgroups that could benefit from prophylactic clipping which our meta-analysis was underpowered (due to a lack of available data) to determine. Nevertheless, important trends have emerged from this work and that of others which will help guide future study in this field.

Larger sized lesions could plausibly benefit from prophylactic clipping. In a retrospective study of over 200 clipped lesions ≥ 20 mm, the DPPB rate was 9.7% in the unclipped group compared to 1.8% in the clipped group.[22] Of note, all lesions in the treatment group were classified as 'fully clipped', indicating full clip closure of the post-polypectomy defect, rather than partial closure or targeted clipping.[22] The authors also reported a significantly increased OR of DPPB of 1.3 per 10 mm increase in lesion size. Overall, the study by Liaquat *et al.* was limited by its retrospective design, use of a historical control group and potential lack of generalizability given that all procedures were performed by a single highly experienced endoscopist.[22] Only one randomized controlled trial has shown a benefit of prophylactic clipping, and similarly enrolled only patients with lesions ≥ 10 mm. The relative risk (RR) of DPPB was 0.21 (95% CI 0.05 to 0.92) following clipping of post-EMR defects within this study.[58] Although our meta-analysis failed to show a benefit of clipping within any of the larger lesion size subgroups, indeed there was a trend toward benefit among those ≥ 10 mm, with a RR of 0.51 (95% CI 0.23 to 1.16). This was not apparent

for lesions ≥ 20 mm, but only 7 bleeding events occurred within this very small subgroup of cases. Overall, it is clear that increasing lesion size is an important predictor of DPPB,[25, 33] and thus larger lesions should be the focus of future randomized trials assessing the efficacy of prophylactic clipping.

It is less clear whether antiplatelet medications such as aspirin or clopidogrel have an effect on DPPB rates. Previous studies have inconsistently associated the presence of antiplatelet medications with increases in DPPB. Even more scarce is evidence for the effect of anticoagulant medications, including traditional oral anticoagulants (OACs, such as warfarin) and direct anticoagulants (DOACs, such as dabigatran, rivaroxaban and apixaban). A 2008 case-control study of nearly 5,000 polypectomies showed no increase in DPPB in patients on ASA, with an OR of 1.1.[27] However, this same study showed an OR of 5.2 of DPPB in patients who had resumed OAC following polypectomy versus those in whom these medications were held following the index procedure.[27] Conversely, a prospective study of over 300 lesions showed that ASA use was associated with DPPB, with an OR of 6.3.[30] In a large prospective study of over 1,000 patients, use of 'any antithrombotic agent within 7 days' was associated with clinically significant DPPB in the authors' univariable analysis, but not in the final multivariable model.[23] It is thus paramount that future randomized trials assessing clipping efficacy are designed specifically to address the effect of these medications. Particular attention must be paid to several factors, including: ongoing use during the procedure, use of dual or triple agents, timing of resumption of anticoagulant medications following the procedure, and the effect of DOACs, a scarcely studied group of medications to date within this setting.

Another important clinical subgroup in which prophylactic clipping deserves additional study is right-sided polyps. Right-sided polyp location has been found to be an independent risk factor for DPPB in two retrospective studies.[34, 81] It is known that the relative wall thickness of the right colon (cecum, ascending and proximal transverse colon) is less than that of the left colon.[34, 35] As such, submucosal injection needs to be more precise in the right colon to expand the correct tissue plane, and there is thus a greater chance for variability in endoscopist skill level and/or experience to influence resection outcomes.[82] Furthermore, the morphologic (and histologic) profile of right-sided lesions can be different from that of left-sided lesions.[83] Sessile serrated adenomas are more common in the right colon, and are flatter with indistinct borders compared with traditional adenomas. Incomplete resection rates are higher with sessile serrated adenomas than with traditional adenomas,[84] suggesting that a more refined endoscopic skill set is required to expertly detect and resect these polyps. For these reasons, clipping these defects shut may be beneficial, especially in cases performed by low-volume endoscopists or those inexperienced in EMR.

The influence of polyp morphology on the efficacy and effectiveness of prophylactic clipping also requires clarification. Mechanical hemoprophylaxis, including placement of prophylactic clips, may be efficacious in preventing bleeding following polypectomy of pedunculated lesions with large stalks, within which vascular supply is usually limited to a single or few larger blood vessel(s).[66] Use of a detachable loop, alone or in combination with clipping, has been shown to decrease post-polypectomy bleeding from pedunculated polyps ≥ 20 mm.[67, 68] Clip use alone in this setting has yet to be studied. Future trials ought to consider this issue, acknowledging that employing a single or multiple clips on a thick stalk

can be technically challenging or even unfeasible and that use of multiple clips adds hundreds of dollars to the procedure. Finally, although flat or sessile laterally spreading lesions (LSLs) can be effectively treated by wide-field EMR (WF-EMR),[85] the rate of DPPB following this inject and resect technique is higher compared to conventional polypectomy. DPPB following WF-EMR has ranged from 3-16% depending on how many high-risk features relating to the patient and/or lesion are present.[25] As referenced previously, full clip closure of EMR defects may be effective in preventing DPPB,[22] although successfully completing this intervention is often extremely difficult and even impossible for very large post-EMR defects. In contrast, partial closure has not appeared to yield the same benefit, trending in fact towards an increased risk of bleeding.[47] This issue is therefore another challenge that needs careful consideration when planning future RCTs.

Ultimately, a RCT is the only study design that can determine efficacy by controlling for both known as well as unknown confounders. However, RCTs are often conducted within study environments that are challenging to replicate in everyday practice, which can lead to potential questions surrounding external validity and applicability. Furthermore, given the low overall event rate of DPPB, a large number of patients is required to demonstrate any potential efficacy of prophylactic clipping. A large RCT is underway that addresses multiple high risk factors for DPPB given it is only enrolling laterally spreading lesions (LSLs) ≥ 20 mm undergoing EMR in the proximal colon.[86] We eagerly anticipate completion of this trial so that its results can be used to update our meta-analysis.

Performing a Large Propensity-Matched Cohort Study

We have established that the decision to prophylactically clip during polypectomy is

influenced by a number of endoscopist-, patient-, and polyp-related variables. Propensity-matched methods can control for these known confounders. A propensity score is the calculated probability of being assigned to a certain treatment (in this case, being prophylactically clipped versus not being clipped) conditional on these variables.[87] Generation of propensity scores and subsequent matching between cohorts allows one to appropriately analyze a large retrospective dataset by ensuring a similar distribution of covariates across the treated and untreated groups, in a fashion similar to prospective randomized trials.[88] In so doing, one is able to reduce the risk of confounding by indication. A limitation of this design is the inability to control for unknown confounders that only a RCT study design can accomplish.

The primary data collected for this thesis work will contribute to a larger retrospective data bank of clipped and unclipped patients (numbering over 10,000 patients) permitting a full propensity-matched study on the effectiveness of clipping in the prevention of DPPB. Databases linkage will be performed, and medical record reviews will be conducted on all emergency room visits and inpatient admissions identified that are possibly related to the index procedures. In so doing, all adverse events, including DPPB following colonoscopy, will be formally identified and confirmed. After linking the post-polypectomy adverse events with the 'clipped' and 'non-clipped' cohorts, outcomes between the two cohorts will be compared. To examine the independent association between the use of prophylactic endoscopic clips and DPPB, multivariate logistic regression models will be employed to adjust for potential confounding effects of known confounders.

Propensity score analysis will be then employed to generate a cohort with a balanced

distribution of covariates between individuals who were prophylactically clipped and those not clipped. Clipped and unclipped subjects will then be matched based on propensity scores.[89-91] Comparisons will then be made between the clipped and unclipped groups. Based on our large cohort size, we estimate approximately 200 cases of DPPB, a number which would be unfeasible within even a large RCT. The performance of such a study will be crucial not only in determining the overall effectiveness of prophylactic clipping in a 'real life' cohort, but also in establishing the clinical subgroups in which clipping may be beneficial. Collectively, this large propensity-matched cohort study will complement both the present and future randomized controlled literature.

Knowledge Translation and Policy Change

There are several methods and challenges associated with the conversion of scientific and clinical research findings into care that ultimately benefits patients. This overall process has been coined "knowledge translation" (KT), but one must appreciate that KT is extremely broad and can have diverse definitions and significance depending on its contextual application.[92] Nevertheless, it is crucial to gain an understanding of these concepts prior to implementing any plan that ultimately targets clinical practice change. The translational process can generally be summarized in two phases (Figure 4.1); the first involves progression from basic research or innovation to clinical research, while the second involves incorporation of clinical research findings into clinical practice.[3, 93] Given the nature of our research, it is the second phase on which we are currently focused.

It is well established that a substantial time lag typically exists between publication of relevant results and their ultimate incorporation into clinical practice.[3, 94] Though this phenomenon is well recognized within the pharmaceutical and public health research fields,[94] it has been more scarcely studied when it comes to interventions or procedures involving medical or surgical devices.[95] While it is clear that innovations with unequivocal benefit and/or cost savings see faster and easier implementation,[96] far less is known regarding the barriers to translation when it comes to reversing a currently common but generally ineffective and costly practice, such as prophylactic clipping. Thus, it is essential to first publish the results of this dissertation in order to disseminate the findings herein as quickly as possible. The next logical step would be the presentation of these results locally to all practitioners who perform colonoscopy. This target group would include members of the Divisions of Gastroenterology and General Surgery as well as their respective training programs. Informing soon-to-be independent practitioners is anticipated to be highly effective through instilling evidence-based practice from the outset. Finally, in addition to physicians, it will also be important to educate endoscopy room nurses, given their collaborative role in the provision of care and use of medical devices in the endoscopy unit.

The results of future definitive studies will be important in dictating the overall message regarding prophylactic clipping on a larger, yet more refined scale. Our planned propensity-matched study will help determine whether prophylactic clipping is effective, and whether there are subgroups that appear to benefit. This important study will help inform future clinical trials and compliment those currently underway.

A position statement endorsed by the Canadian Association of Gastroenterology (CAG) and the Canadian Association of General Surgeons (CAGS) is a consideration, even at this point given the knowledge gaps that presently exist. All endoscopists should be encouraged to take pause when considering routine prophylactic clipping. Our research strongly points to this being of no benefit and of unnecessary cost to the health care system. As such, this practice should be discouraged. Once further research becomes available a formal clinical practice guideline clearly stating recommendations on the appropriate use of endoscopic devices (including clips) for prophylaxis again DPPB would be valuable. Ultimately, it is the hope that these measures influence policy makers at the institutional, provincial and national levels to consider changing existing policies relating to clipping. These changes could range from reducing the number of clips stocked in endoscopy units to altering the billing fee schedule to ensure there is no external incentive to apply ineffective prophylactic clips.

Conclusions

Post-polypectomy prophylactic clipping does not appear to reduce the overall risk of DPPB. This has been demonstrated through a systematic review and meta-analysis of published randomized controlled trials. Despite this, there is a great deal of variability between endoscopists in terms of their prophylactic clipping practices, and clip use for this purpose remains common. It is now pivotal that this knowledge be disseminated in an effort to alter practice. Simultaneously, additional well-designed and targeted studies are required to elucidate the subgroups within which clipping may be of benefit.

Figures and Tables

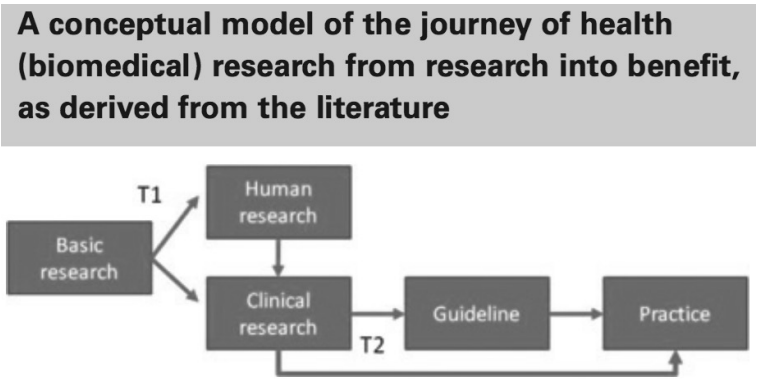

Figure 4.1. Summary of the knowledge translation process.[3]

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Appendices

Appendix A – PRISMA Checklist[2]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**23,24,27**
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.	**24,25**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**26,27**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**27,28**
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.	**27**
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.	**27,28**
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.	**27,28**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**28,96**
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).	**28,29,38**
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.	**29,30**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**95,96,97**
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.	**30**

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**30**
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.	**30**
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).	**30,42**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**30**
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.	**31,38**
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.	**31,32,41**
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).	**42**
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.	**39**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**39**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**40**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**43,44**
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).	**33-37**
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).	**36**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**36,37**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**N/A**

Appendix B – Search Strategy

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

Appendix C – Data Extraction Form

1. Reviewer:_____ 2. Study ID #:_____

3. Lead author name:_____

4. Title:_____

5. Journal:_____

6. Publication year:_____

7. Volume and issue:_____

8. Pages:_____

ELIGIBILITY CRITERIA

9. Reports on original data? Yes No Unclear

10. Endoscopic clips used for prevention? Yes No Unclear

DATA

11. Baseline data

	Clipped Group	Non-clipped Group
Sample size (n)		
Mean age (SD)		
Male # (%)	..	..
Polyp size in mm # (%) <5 6-10 11-20 20+	..	..

Macroscopic polyp type # (%) Sessile Flat Pedunculated Diminutive		
Polyp location # (%) Rectum Sigmoid Descending Transverse Ascending Cecum		
Antiplatelet drug use # (%) ASA Clopidogrel Other		
Anticoagulant drug use # (%) Warfarin Novel		
Endoscopist specialty # (%) Gastroenterology Surgery Other		
Average number of clips		

12. Duration of Follow-up_____

13. Outcomes/Results

	Clipped Group	Non-clipped Group
Bleeding Cases # (%)		
Perforation Cases # (%)		

Coagulation syndrome cases # (%)		
Abdominal pain cases # (%)		
Mean procedure time		
Mean case cost (USD)		
Mean follow-up		

STUDY QUALITY

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

Appendix D – Standardized Data Abstraction Forms

53368

ENDOCLIP STUDY FORM
PAGE 1

RHRN ☐☐☐☐☐☐☐☐☐☐

Case ID ☐☐☐☐☐

Age: ☐☐ **Gender:** O Male O Female **Year of Procedure:** ☐☐☐☐

Endoscopist: _____

Exclusion: _____

Indication:
O Average Risk O <=1yr repeat
O Family Hx O 1-3yr repeat
O FIT/FOBT+ O >3yr repeat
O Other/Unsure

MEDICATIONS

OAC: O Warfarin
O Pradaxa (dibigatran)
O Xarelto (rivaroxaban)
O Eliquis (apixaban)

AP: O Plavix (clopidogrel)
O Ticlid (ticlopidine)
O Brilinta (ticagrelor)
O Effient (prasugrel)

MISC: O ASA
O NSAID
O Persantine (dipyridamole)
O Aggrenox (ASA/dipyridamole)

If 'Yes' to any meds, held appropriately prior to procedure? O Yes O No O Unsure

Meds to be resumed after procedure? O Within 48 hours O After 48 hours O Unsure

POLYP#1

Polyp Size:
O <1cm
O 1-1.9cm
O >=2cm
☐☐ mm
O Unknown

Polyp Shape:
O Pedunculated
O Sessile
O Flat
O Diminutive
O Residual
O Unknown

Location:
O RE O SC O DC
O SF O TC O HF
O AC O CE O ICV
O Right Colon O Left Colon
O Appendix

Technique:
O Snare with cautery
O Cold snare
O Cold biopsy
O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication: O Prophylaxis of bleeding (assume this unless perforation mentioned)
O Prophylaxis of perforation
O Treatment of bleeding
O Treatment of perforation
O Laceration/other

53368

POLYP#2 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#3 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

16146

ENDOCLIP STUDY FORM
PAGE 2

RHRN ☐☐☐☐☐☐☐☐☐☐

Case ID ☐☐☐☐☐

POLYP#4 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#5 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

16146

POLYP#6 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#7 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

36008

ENDOCLIP STUDY FORM
PAGE 3

RHRN | | | | | | | | | | |

Case ID | | | | | |

POLYP#8 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → | | mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: | |

Total Number of Clips Fired (if different): | |

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#9 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → | | mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: | |

Total Number of Clips Fired (if different): | |

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

36008

POLYP#10 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#11 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

6220

ENDOCLIP STUDY FORM
PAGE 4

RHRN ☐☐☐☐☐☐☐☐☐☐

Case ID ☐☐☐☐☐

POLYP#12 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#13 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm → ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

6220

POLYP#14 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other

POLYP#15 (if applicable)

Polyp Size:
- O <1cm
- O 1-1.9cm
- O >=2cm
  - ☐☐ mm
- O Unknown

Polyp Shape:
- O Pedunculated
- O Sessile
- O Flat
- O Diminutive
- O Residual
- O Unknown

Location:
- O RE O SC O DC
- O SF O TC O HF
- O AC O CE O ICV
- O Right Colon O Left Colon
- O Appendix

Technique:
- O Snare with cautery
- O Cold snare
- O Cold biopsy
- O Partial removal

Cushion? O Epinephrine O Saline +/- Methylene blue O Other O None O Unsure

Piecemeal? O Yes O No O Unsure

Clipped? O Yes O No O Unsure

Closed? O Yes O No O Unsure

Timing: O Before O After O Both O Unknown

Other: O None O Loop O Thermal O APC O Tattoo O Epinephrine

Number of Clips Applied: ☐☐

Total Number of Clips Fired (if different): ☐☐

Clip Indication:
- O Prophylaxis of bleeding (assume this unless perforation mentioned)
- O Prophylaxis of perforation
- O Treatment of bleeding
- O Treatment of perforation
- O Laceration/other