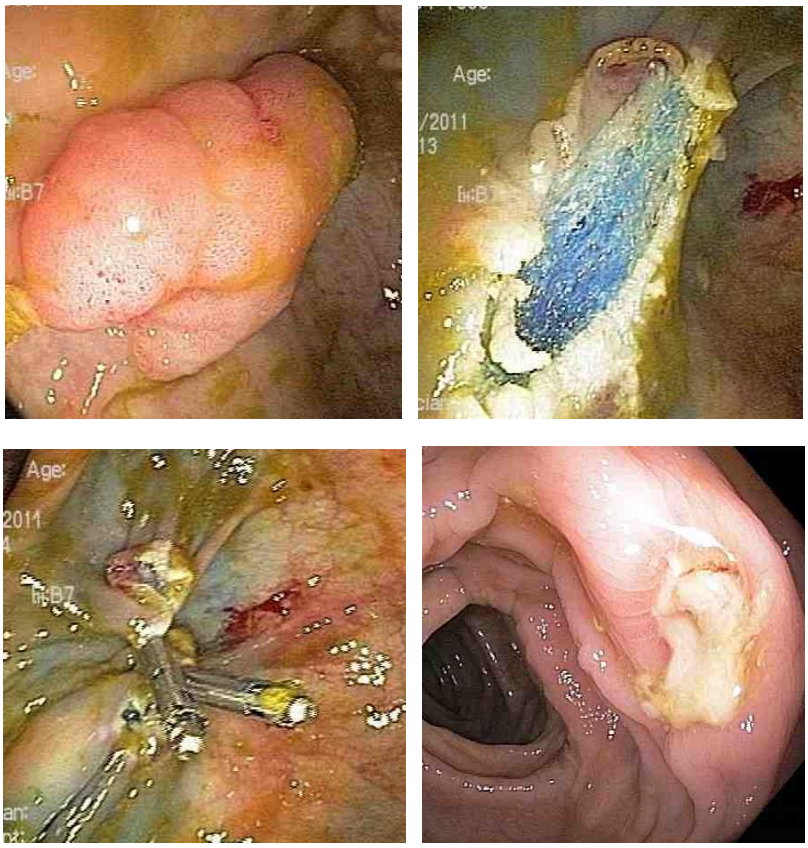
Prevention of Postpolypectomy Bleeding after Colonoscopy



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This is to acknowledge that Annie Feagins, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns that are directly or indirectly related to this program. Unrelated to this program, Dr. Feagins has been a consultant for Pfizer. Dr. Feagins will not be discussing off label uses in her presentation.

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Purpose & Overview

This presentation reviews the complications of colonoscopy with a focus on bleeding after polypectomy. At a minimum, colon cancer screening is recommended for all adults reaching the age of 50 years old and is most commonly accomplished with colonoscopy. Polyps are the precursor to colon cancer and removal of polyps has been associated with a reduced risk of colon cancer. However, while the majority of colonoscopies are performed without complication, hemorrhage can occur in between 1-6% of patients. This presentation reviews the clinical presentation, risk factors, and prevention strategies for postpolypectomy bleeding.

Educational Objectives

1. To understand the risk factors for post-polypectomy bleeding
2. To understand the importance of managing anticoagulation during the periprocedural period in order to reduce the risk of hemorrhage
3. To explore possible endoscopic treatment options that may reduce the risk of hemorrhage

Introduction

Colon cancer is the third leading cause of new cancer diagnoses and of cancer deaths in the United States. Patients with colon cancer diagnosed at an early, localized stage have a 90% 5-year survival, whereas those who have advanced tumors with distant metastases have only a 10% 5-year survival. Fortunately, colon cancer typically develops slowly over a period of years from the uncensored growth of adenomatous polyps, which can be detected and removed readily by colonoscopy. If these polyps are removed during colonoscopy, then most colon cancers can be prevented.[1-4] Therefore, organizations such as the American Cancer Society and the VA recommend routine screening of asymptomatic adults for colon cancer. Recent guidelines recommend one of several options for screening:

(a) yearly non-invasive stool based testing (i.e. high sensitivity gFOBT, FIT, or stool DNA)

(b) flexible sigmoidoscopy alone or in combination with stool testing every 5 years

(c) CT colonography every 5 years

(d) colonoscopy alone every 10 years

Irrespective of the interval and method that is chosen for screening, the standard of care for a positive test is to perform a colonoscopy to remove any polyps so identified.

Complications of Colonoscopy

While colonoscopy with removal of any polyps discovered during the procedure is used widely to reduce the risk of developing colorectal cancer, colonoscopy is not without risk. Life-threatening complications of polypectomy include perforation and bleeding.[5]

Table 1: Common complications of colonoscopy. Of note, risk reported is for all patients presenting for colonoscopy.

Complication	Risk
Cardiopulmonary complications (related to sedation)	0.9%
Perforation	<0.1%
Hemorrhage	0.1 – 0.6%
Post-polypectomy electrocoagulation syndrome	0.003 - 0.1%
Death	0.07 - 0.007%

Post-Polypectomy Bleeding

Post-polypectomy bleeding (PPB) can be observed by the colonoscopist immediately after polyp removal (termed immediate post-polypectomy bleeding), or bleeding can occur at some time point after the colonoscope has been removed (termed delayed post-polypectomy bleeding). Immediate post-polypectomy bleeding is thought to be due to

inadequate cauterization of the polyp vessels during polypectomy and occurs in 1-2% of polypectomies.[6] Immediate bleeding typically is controlled readily during the colonoscopy with various hemostatic techniques including hemoclipping.[7-9] Delayed bleeding is thought to be due to the sloughing of the eschar of the cautery-induced ulcer, with exposure and penetration of an underlying vessel. Clinically important delayed post-polypectomy bleeding has been defined as rectal bleeding that requires hospitalization, blood transfusion, repeat colonoscopy or surgery to treat the bleeding site.[5] Bleeding severity has been categorized as mild, moderate, or severe depending on the need for blood transfusion and on whether the bleeding can be controlled colonoscopically or whether angiographic or surgical intervention is required to control the hemorrhage.[10] Delayed bleeding has been reported to occur as late as 29 days after the colonoscopy, but most occurs within 7-10 days.[11] Studies have found the rates of post-polypectomy bleeding to range from 0.3% to 6.1% depending on study design.[5]

Risk Factors for Delayed Post-Polypectomy Bleeding: Polyp related factors

One of the major risk factors for post-polypectomy bleeding is polyp size. In a study investigating pedunculated polyps, the post-polypectomy bleeding rate (immediate or delayed) for 98 polyps that were 1 to 1.9cm in size was 3.1%, whereas post-polypectomy bleeding occurred in 15.1% of 66 polyps sized 2cm or greater.[12] In a retrospective study of 9,336 colonic polypectomies, a multivariate analysis of risk factors for immediate post-polypectomy bleeding found polyp size greater than 1 cm to be a significant risk factor for bleeding, with an odds ratio of 2.38.[13] Moreover, another study with a case-control design evaluating delayed post-polypectomy bleeding found that for every 1mm increase in polyp diameter, the risk of hemorrhage increased by 9%.[14] Increased risk for post-polypectomy bleeding has also been associated with the morphology of the polyp including pedunculated polyps or laterally spreading tumors.[14]

Risk Factors for Delayed Post-Polypectomy Bleeding: Patient related factors

The use of anticoagulants, even when stopped periprocedurally, has also been associated with an increased risk of immediate and delayed post-polypectomy bleeding.[13-16] Co-morbid disease, specifically coronary artery disease, renal disease and diabetes mellitus have also been associated with an increased risk of post-polypectomy bleeding.

With an aging population and the increasing use of anticoagulants, physicians are often faced with the dilemma of how to manage a patient's anticoagulants when needing to undergo either elective or emergent procedures. The American Heart Association estimates that 83.6 million American adults have some form of cardiovascular disease, including approximately 15.4 million with coronary artery disease (CAD) and 6.8 million with strokes.[17] Patients with coronary artery and cerebrovascular disease are at risk for arterial thrombi and generally are treated with antiplatelet agents like thienopyridines (clopidogrel, prasugrel),[18] whereas patients at risk for arterial embolism (e.g. those with

atrial fibrillation) and venous thrombi (e.g. those with deep venous thrombosis and pulmonary embolism) are treated with anticoagulants like warfarin or direct oral anticoagulants (DOACs) (See table 2). With so many patients at risk for thrombi or embolism, endoscopic evaluations often are indicated for patients taking antiplatelet agents or anticoagulants. When considering endoscopy, the risks of stopping these drugs, and thus precipitating thrombotic events, must be carefully weighed against the risks of continuing these agents during endoscopic procedures that can be complicated by bleeding, particularly procedures with high bleeding risk interventions like polypectomy. It must also be kept in mind that while polypectomy does carry a risk for hemorrhage, many of the patients who are undergoing colonoscopy for colon cancer screening or surveillance will not require a polypectomy during their colonoscopy, but we will not have this knowledge until the procedure is completed.

Table 2: Anti-platelet and anticoagulants used to treat thrombotic diseases that may be encountered in patients presenting for colonoscopy.

Anticoagulants	**Mechanisms**		**Examples**	
warfarin	inhibits vitamin K-dependent coagulation factor synthesis (II, VII, IX, X, proteins C and S)	DVT/PE treatment, VTE prophylaxis with AFib/flutter/valvular disease, LV thrombus, ischemic stroke	oral: warfarin (Jantoven, Coumadin)	5 days
unfractionated heparin	binds to antithrombin III, catalyzing inactivation of thrombin and other clotting factors	thromboembolism prophylaxis/treatment, PCI, STEMI/ NSTEMI adjunct therapy	IV: heparin	4-6 hours
low molecular weight heparin	binds to antithrombin III and accelerates activity, inhibiting thrombin and factor Xa	DVT prophylaxis, DVT/PE treatment, unstable angina, NQWMI, STEMI adjunct	subcutaneous: enoxaparin (Lovenox), daltaparin (Fragmin)	12 hours
factor Xa inhibitors	selectively bind antithrombin III (fondaparinux) and synthetic selective factor Xa inhibitor	DVT prophylaxis, DVT/PE treatment, thromboembolic prophylaxis with AFib	oral: rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa) subcutaneous: fondaparinux (Arixtra),	1-2 days (CrCl≥50ml/min) 3-5 days (CrCl<50ml/min)
direct thrombin inhibitors	directly, reversibly inhibit thrombin	thromboembolism prophylaxis in AFib, PCI adjunct, DVT prophylaxis	oral: dabigatran (Pradaxa), subcutaneous: desirudin (Iprivask)	1-2 days (CrCl≥50ml/min) 3-5 days (CrCl<50ml/min)

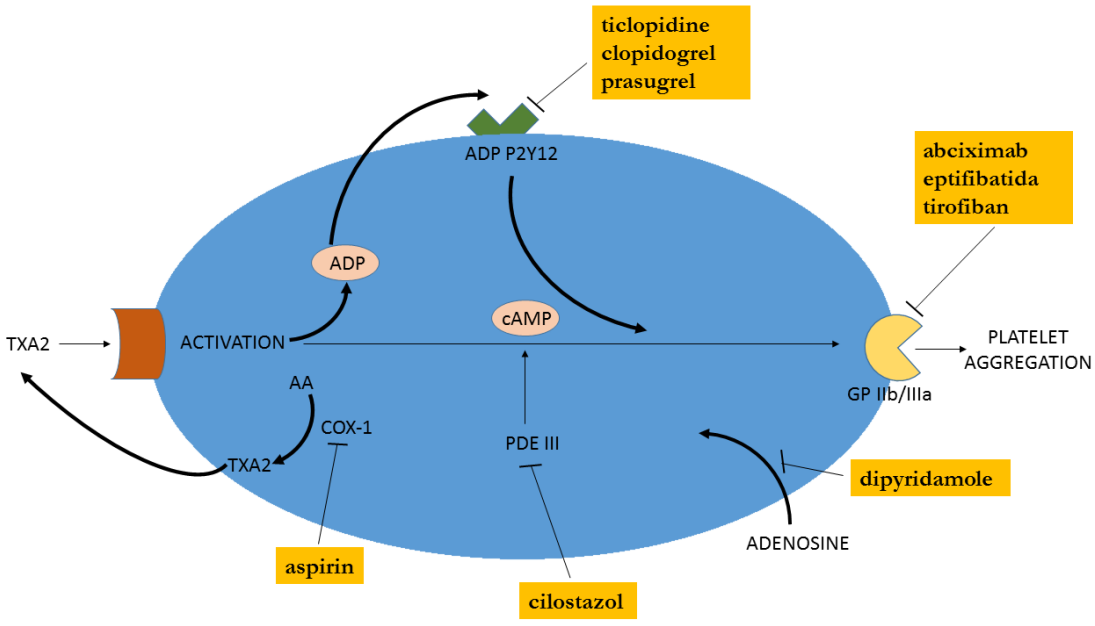
Anti-platelet Agents	Mechanism	Indications	Examples	Recommended time of stopping drug pre-procedure, if indicated
Aspirin	irreversibly acetylates and inactivates cyclooxygenase	primary and secondary cardiovascular protection; cerebrovascular protection	oral: aspirin (Bayer, Ecotrin)	7-10 days, *not recommended to stop if high risk for cardiovascular disease
NSAIDs	reversibly block cyclooxygenase; can be selective (blocking cyclooxygenase-2) or non-selective (blocking both COX-1 and COX-2)	pain, osteoarthritis, rheumatoid arthritis, inflammatory arthritis, dysmenorrhea, fever, anti-inflammatory	oral: ibuprofen (Advil, Motrin), naproxen (Naprosyn), celecoxib (Celebrex), diclofenac, ketoprofen, indomethacin, sulindac, meloxicam, piroxicam	short-half life: ibuprofen, diclofenac, ketoprofen, indomethacin (1 day) intermediate half life: naproxen, sulindac, celecoxib (2-3 days) long half life: meloxicam, piroxicam (10 days)
Dipyridamole	inhibits uptake of adenosine into platelets leading to inhibition of platelet aggregation	thrombotic stroke prevention	oral: dipyridamole (Persantine), aspirin/dipyridamole (Aggrenox)	2 days (7-10 days if being given as Aggrenox, the combination of aspirin and dipyridamole)
Thienopyridines	irreversibly inhibits platelets by blocking their ADP receptors	acute coronary syndrome, thrombotic event prevention	oral: clopidogrel (Plavix), prasugrel (Effient), ticlopidine (Ticlid), ticagrelor (Brilinta)	5-7 days for clopidogrel, 7-9 days for prasugrel, 3-5 days for ticagrelor, 10-14 days for ticlopidine
PAR-1 Antagonist	antagonizes protease-activated receptor-1 (PAR-1), inhibiting platelet aggregation induced by thrombin and thrombin receptor agonist peptide (TRAP)	reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD); used with aspirin and/or clopidogrel	vorapaxar (Zontivity)	40 days
cilostazol	phosphodiesterase type 3 inhibitor, reducing platelet aggregation;	coronary heart disease, coronary	oral: cilostazol (Pletal)	2 days

	suppresses cAMP degradation, producing vasodilation	stents, peripheral arterial disease		

Bleeding Risk of Antiplatelet Agents

Aspirin irreversibly acetylates and inactivates platelet cyclooxygenase, thereby inactivating platelets for the duration of their lifespan, 7-10 days. Nevertheless, based on several retrospective studies[14-16], guidelines agree that aspirin can be safely continued during colonoscopy with polypectomy without concern for a significant increase in bleeding.[13,19,20] Similarly, NSAIDs, which reversibly block cyclooxygenase, have generally short-acting effects on bleeding. As is the case for aspirin, guidelines agree that stopping NSAIDs prior to diagnostic or therapeutic endoscopic procedures is not mandatory.[10,21] A number of retrospective studies investigating the potential role for NSAIDs in the risk of both immediate and delayed PPB have all found that NSAIDs do not significantly increase that risk.[14,16,22]

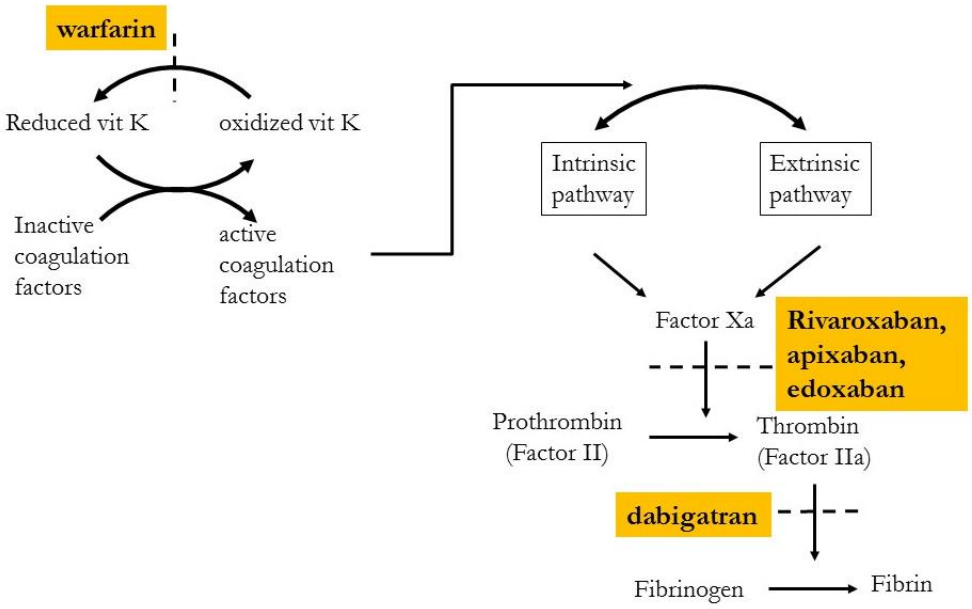
The thienopyridines inhibit platelet function by blocking adenosine diphosphate (ADP), which interferes with the platelets' ability to aggregate. In patients with CAD, especially in the setting of coronary stents, thienopyridines are most frequently given in combination with aspirin, termed dual anti-platelet therapy. For patients who are continued on thienopyridines during polypectomy, retrospective studies have now estimated the risk of a clinically important PPB at 0.9 – 2.1%.[23,24] A recent, prospective study of patients who had polypectomies while on uninterrupted thienopyridine therapy found the rate of PPB to be 2.4%.[5] Although some patients who experienced PPB required transfusion (2 of 5 patients) and/or repeat colonoscopy (3 of 5 patients) to treat their bleeding, no patient required angiography or surgery and none died. Not surprisingly, all of the patients who experienced clinically significant delayed PPB were taking both clopidogrel and concomitant aspirin.



Bleeding Risk of Anticoagulants

Warfarin is a commonly used anticoagulant that works by inhibiting vitamin K-dependent coagulation factor synthesis. In many countries outside of the US, other similar vitamin K antagonists (VKAs) are used commonly including acenocoumarol and phenprocoumon. These drugs are used for treatment of a variety of disorders including deep vein thrombosis, pulmonary embolism, ischemic stroke, and prophylaxis of arterial thromboembolism from atrial fibrillation, flutter and cardiac valvular disorders. A retrospective cohort study that specifically focused on the use of periprocedural anticoagulation, found that delayed PPB occurred in 2.6% of patients who discontinued warfarin prior to colonoscopy, compared to 0.2% of patients not taking any anticoagulation($p=0.005$).[15] Furthermore, a case control study found that resuming anticoagulation (heparin or warfarin) within 1 week of polypectomy increased the risk of delayed PPB more than 5-fold (OR 5.2, CI 2.2-12.5, $p<0.001$).[14] Moreover, patients who are bridged with heparin while their warfarin is interrupted are at higher risk for bleeding compared to patients who are on warfarin but are not bridged (20% vs 1.4%, bridged vs not bridged, respectively).[25] If the procedure is low risk for bleeding, the VKA may be continued during endoscopy. Specifically, mucosal biopsy is safe to perform during endoscopy for patients on warfarin whose INR is in the therapeutic range.[26] A few studies have evaluated performing polypectomy for patients on therapeutic warfarin, although this has not been the standard for most practices. One group reviewed their experience of removing small (<10mm) polyps while on therapeutic warfarin and reported a delayed PPB rate of 0.8%.[27] However, current guidelines recommend for high risk procedures like polypectomy, warfarin should be discontinued.

The direct thrombin inhibitors include dabigatran, desirudin, argatroban and bivalirudin. Similar to warfarin, dabigatran increases the risk of bleeding from all causes. In a post-marketing analysis done by the FDA, the all-cause bleeding rate for dabigatran was similar to that for warfarin.[28] However, there did appear to be a higher incidence of gastrointestinal (GI) bleeding with dabigatran than with warfarin (1.6 versus 1.1 per 100-patient years in the FDA post-market study). The reason for the increased risk of GI bleeding with dabigatran is not clear, but there are several hypotheses. Dabigatran is an inactive prodrug that is absorbed largely in the stomach and proximal small bowel, and then metabolized to the active agent by serum and hepatic esterases. Dabigatran that escapes this proximal gut absorption is converted to active dabigatran in the distal bowel, and then excreted in the feces. It has been proposed that this active drug in the distal bowel may promote GI bleeding more than wafarin, which is not activated in the bowel. There also are reports of dabigatran use being associated with esophagitis and gastric ulceration, and it has been proposed that the drug may cause direct injury to GI mucosae.[29,30] No studies have specifically explored bleeding rates with high-risk endoscopic procedures like polypectomy, but one small Japanese study did find that endoscopic mucosal biopsy appears to be safe for patients taking dabigatran.[26] Moreover, a post hoc analysis of the RE-LY study (the randomized controlled trial that gained dabigatran its FDA approval) found no significant differences in rates of periprocedural bleeding between patients taking warfarin and patients taking dabigatran, but only 8.6% of the procedures were colonoscopies.[31]



The factor Xa inhibitors include rivaroxaban and apixaban (both oral) and fondaparinux (subcutaneous). (see table 2) In a pivotal rivaroxaban trial, overall bleeding rates were similar for patients in the rivaroxaban and warfarin groups, but rates of GI bleeding were higher in the rivaroxaban group.[32] Conversely, intracranial bleeding and fatal bleeding was less common with rivaroxaban than with warfarin. In a study comparing patients taking apixaban with those taking warfarin, overall rates of bleeding were significantly lower for patients in the apixaban group (HR 0.69 with 95%CI 0.60-0.80), while rates of GI bleeding were virtually identical for the two groups (HR 0.89 with 95%CI 0.70-1.15).[33] No studies yet have evaluated the risk of these agents specifically for endoscopy.

Thromboembolic Risks of Interrupting Antiplatelet Agents

The cardiovascular risks associated with stopping aspirin can be high, especially in patients with a prior history of CAD. One study polled 1236 patients who were hospitalized for acute coronary syndromes regarding recent aspirin use.[34] They found that 51 cases of acute coronary syndrome occurred within 1 month of stopping aspirin (4.1% of all cases and 13% of recurrences), with 20% associated with late stent thrombosis (average 15 months after stent placement). Another study found that recent cessation of antiplatelet agents (mostly for elective surgery) in patients with acute coronary syndromes was associated with higher 30 day rates of death or myocardial infarction than in patients who had only a remote history of aspirin use.[35]

Unlike delayed PPB, which usually is managed without surgery and with no long-term consequences, the cardiovascular risks of interrupting thienopyridines include catastrophic complications such as stent thrombosis, myocardial infarction, stroke and death. One study of 2229 patients with drug-eluting coronary stents found that, for patients who had the complication of stent thrombosis, the mortality rate was 45%.[36]

Moreover, non-cardiac surgery within 2-4 weeks of stent placement (with aspirin, clopidogrel, or both stopped for the operation) has been associated with a rate of major cardiovascular events that approaches 30%.[37,38] Therefore, the joint guidelines published by the American College of Gastroenterology (ACG) and the American College of Cardiology (ACC) state that the interruption of platelet antagonists for elective procedures should not be a common occurrence, particularly for patients at high risk for stent thrombosis with its associated high mortality rate.[39]

To date, there have not been any studies that specifically have evaluated the risk of cardiovascular events associated with the interruption of thienopyridine therapy for endoscopic procedures. However, a systematic review of 161 patients with late stent thrombosis found that the practice of continuing aspirin therapy when stopping clopidogrel increased the time to stent thrombosis from 7 days to 122 days, but 6% of the patients who developed a stent thrombosis while taking aspirin did so within 10 days of stopping clopidogrel.[40] Therefore, while the practice of continuing aspirin when clopidogrel is stopped substantially reduces the risk of stent thrombosis, that risk remains substantial. If a high-risk endoscopic procedure must be performed during this period, aspirin therapy should be started or continued while the decision to stop the thienopyridine is weighed carefully by a multidisciplinary team (gastroenterology, cardiology and possibly hematology) along with the patient. Consideration should also be given to performing the procedure on uninterrupted thienopyridines after a careful weighing of risks and benefits. Studies have explored using other short-acting anticoagulants for bridging while off thienopyridines including heparin, glycoprotein IIb/IIIa inhibitors, and short-acting platelet P2Y12 inhibitors, but none have had favorable outcomes to date.

Thromboembolic Risks of Interrupting Anticoagulants

The risks of thromboembolic events during warfarin cessation for colonoscopy have not been extensively studied. However, one study by Blacker et al reviewed patients with atrial fibrillation who were on warfarin and were undergoing endoscopy (EGD, colonoscopy or bronchoscopy). They found that in 987 patients undergoing 1,137 procedures, 12 patients experienced strokes within 30 days (1.06%/procedure) as compared to no strokes in 438 patients who did not have their warfarin adjusted. Moreover, the stroke risk was greatest for the patients undergoing more complex procedures or with more co-morbid illness.[41] Similar studies in the setting of direct thrombin inhibitor and factor Xa inhibitor use are lacking.

Bridging Patients Treated with VKAs

Once the decision is made to discontinue the VKA, the risk for thromboembolic disease must be weighed in the decision whether or not to “bridge” the patient with a short-acting anticoagulant such as unfractionated heparin or low molecular weight heparin. Currently, for patients with nonvalvular atrial fibrillation, scores such as the CHADS2 score are used to determine the risk for stroke and to help determine if bridging therapy is needed periprocedurally. It is important to remember that while the goal with interrupting VKA therapy periprocedurally is to reduce the risk of bleeding, patients who are on VKA therapy are still at increased risk for bleeding post-procedure even despite stopping the drug periprocedurally. A retrospective study compared delayed PPB in patients who interrupted their warfarin to patients who were not on warfarin and found significantly

higher rates of bleeding in those who used warfarin despite it being stopped for the procedures (OR=11.6, 2.6% vs 0.2%, CI 2.3-57.3, p=0.005).[15] Moreover, a recent randomized controlled trial found that patients with nonvalvular atrial fibrillation who were randomized to bridging with LMWH or no bridging for elective procedures found that rates of major bleeding were higher in those who were bridged (3.2% versus 1.3%, p=0.005) with no difference in periprocedural thromboembolic events (0.3% versus 0.4%).[42] However, similar data are lacking for indications other than nonvalvular atrial fibrillation and these data should not be extrapolated to higher risk conditions.

When to Consider Delaying Colonoscopy

For high thromboembolic risk conditions, consideration should be given to postponing the procedure, particularly if the treatment duration of the antiplatelet agent or anticoagulant may soon be reached (e.g., waiting for completion of 6 months of warfarin for a provoked DVT or waiting 6-12 months after placement of a drug eluding coronary stent(DES)). Moreover, the urgency of the procedure needs to be weighed into the timing of the procedure. For example, postponing referral of a patient for a screening or surveillance procedure until 12 months of dual antiplatelet therapy (for a patient with a DES) is ideal while waiting only 6 months of therapy after a DES may be preferred for a symptomatic patient with iron deficiency anemia.

While the highest risk period for stent thrombosis is within the first 30 days after stent placement, it is now well accepted that there remains a substantial protracted risk for delayed stent thrombosis, particularly in patients with DES.[40,43] For bare metal stents (BMS), the highest risk period is within the first 4 weeks after stent placement. However, for DES, which undergo delayed endothelialization, high risk for stent thrombosis continues for at least 6 months, with a lower but considerable risk for late thrombosis extending 12 to 24 months.[39] For patients with DES, elective procedures should be postponed for at least the first 12 months, when discontinuation of antiplatelet therapy would be especially hazardous. Patients with BMS should have elective procedures postponed at least 1 month. For patients with BMS and a recent acute coronary syndrome, procedures should be delayed for the first 12 months.

When to Restart Antiplatelet Agents or Anticoagulants

After making the decision to discontinue an antiplatelet agent or anticoagulant in preparation for an endoscopic procedure, the next important decision is when to restart the agent after the procedure. Risk of bleeding with prompt resumption must be weighed against the thromboembolic risk of holding the drug after the procedure. Unfortunately, the guidelines provide no clear consensus. For thienopyridines, the JACC/ACG guidelines recommend restarting “as soon as possible” and the ASGE recommends timing based on weighing the risks of thromboembolic disease with holding the medication and risks of bleeding based on the procedure performed with restarting immediately. All of these recommendations are based on opinion, as there are no definitive data to guide these decisions. When restarting a thienopyridine, another contentious issue is whether reloading of the drug (to obtain quicker therapeutic levels) is necessary. When restarting clopidogrel in its usual oral dose (75mg per day), it takes 5-10 days to reach maximal platelet inhibition, compared to 12 to 15 hours if the patient is given a 300-600mg loading dose. The JACC/ACG guideline recommends that the

decision regarding the need for reloading should be tailored to the patient's thromboembolic risk. Studies of patients having percutaneous intervention for CAD did not reveal significant differences in adverse outcomes, including bleeding, between patients who received loading doses of thienopyridimes and those who received standard dosing.[44] No comparable data are available for endoscopic procedures.

For patients on warfarin who were not bridged, the guidelines recommend restarting warfarin within 24 hours. For patients who were bridged with heparin, warfarin should be restarted the evening of the procedure, while heparin should be resumed as soon as possible after the procedure and stopped once the INR has become therapeutic. However, adjustment to these guidelines may be necessary on a case by case basis in the setting of high risk bleeding procedures, such as large polypectomies as one case-control study even found that resuming warfarin within 7 days of polypectomy was a risk factor for PPB.[14] There are no data to guide the timing of drug resumption for patients on a direct thrombin inhibitor or a factor Xa inhibitor. The ASGE recommends the agent should ideally be restarted within 24 hours if adequate hemostasis achieved, otherwise bridging should be considered for those at high thromboembolic risk if the agent is being held based on the bleeding risk for the intervention that was performed.

Risk Factors for Delayed Post-Polypectomy Bleeding: Physician related factors

Numerous factors in the technique of polypectomy may also affect the risk of post-polypectomy bleeding. These include techniques such as whether the endoscopist uses cautery or not while performing snare polypectomy (term "hot snare" or "cold snare"), the type of electrocautery used (pure "cut" or pure "coagulation" or a mixture of the two), as well as the use of hemoclips to close defects after polypectomy.

Prophylactic Hemoclips

Hemoclips have become available to colonoscopists only within the past decade. The hemoclip is a device that is passed through the channel of the colonoscope to apply a metal clip that can seal the mucosal defect left by polypectomy and stop hemorrhage. The clips are <u>not</u> reusable, and each clip deployed costs approximately $150-200 (depending on the type of clip and the manufacturer). It is now common practice to use hemoclips for a variety of indications including achieving endoscopic hemostasis, prevention of bleeding prior to polypectomy, intraluminal marking for fluoroscopic procedures, anchoring of jejunal feeding tubes, and closure of recognized perforations after polypectomy.[45] However, there are few published data to support the common practice of prophylactic hemoclipping after polypectomy to prevent bleeding, and there are no clear guidelines on when or how to perform prophylactic hemoclipping.

Despite the widespread clinical practice of prophylactic hemoclipping, only two randomized trials have evaluated its efficacy.[46,47] In the first study, patients who underwent polypectomy (of any size) were randomized to prophylactic placement of a hemoclip after polypectomy or to no treatment. Although the investigators found no significant difference in post-polypectomy bleeding rates between patients who had hemoclips placed prophylactically and those who did not, this study has been criticized

because most of the polyps removed were small. The average size of those polyps was only 7 mm, and patients with polyps >3 cm were excluded. Such small polyps are unlikely to bleed, and are not routinely hemoclipped in clinical practice. In the second study, investigators evaluated the use of hemoclips placed on the stalks of large (1cm or larger) pedunculated polyps ***prior*** to polypectomy. The study was stopped early due to higher rates of complications in the group receiving the hemoclips, particularly mucosal burns thought to occur due to transmission of the current from the snare coming in contact with the hemoclip during polypectomy. Lastly, a large retrospective study has been performed that evaluated the rate of PPB in patients with large polyps (2cm or larger) who received or did not receive prophylactic hemoclipping after polypectomy.[48] This study evaluated the practice of a single endoscopist who early in the study period did not routinely perform hemoclipping and compared that to his practice in the later half of the study period where he did routinely place hemoclips prophylactically. This study did find a significantly lower rate of PPB in the patients who received prophylactic hemoclipping (9.7% versus 1.8%). Given this controversial data, the efficacy of the common practice of prophylactic hemoclipping large polypectomy sites remains unclear.

We conducted a retrospective review of the medical records of patients who underwent elective colonoscopy at our VA Hospital between July 2008 and December 2009.[49] We identified patients who had polypectomy sites prophylactically hemoclipped (i.e. a hemoclip was placed even though the colonoscopist did not observe acute bleeding) as our study cohort. Patients who had polypectomy without prophylactic hemoclipping comprised the control group. To minimize confounding due to differences between the groups in conditions that might contribute to delayed hemorrhage, controls were matched to study patients based on polyp characteristics (size, number, morphology, and technique of polyp removal) and anticoagulant use. The primary outcome was delayed post-polypectomy bleeding (within 30 days of polypectomy). We identified 185 patients (mean age 64 years) who had prophylactic clipping of polypectomy sites. These 185 patients had hemoclips placed on a total of 237 polyps. The average polyp size was 12.5 mm, 73% were sessile, and 86% were removed with hot snare (Table 1). We identified 1896 total control patients who had polypectomy without hemoclipping, and matched the 185 patients in the study cohort to 185 control patients. After matching, there were no significant differences between the hemoclip group and the control group in age, frequency of co-morbidities (including coronary artery disease, lung disease, diabetes, and renal disease) (Table 2) or polyp characteristics (Table 3). There were 3 delayed post-polypectomy bleeds in the 185 patients that had prophylactic hemoclipping (1.6%), and 1 delayed post-polypectomy bleed in the 185 matched control patients (0.5%, p=0.62). For the patients who experienced PPB in the prophylactically clipped group, one patient was on the combination of aspirin and warfarin, one was on clopidogrel alone, and one was on aspirin alone. For the one PPB in the control group, this patient was on no anticoagulants or anti-platelet agents (Table 4). In conclusion, we found no significant difference in the low rate of delayed post-polypectomy bleeding between patients who had prophylactic hemoclipping of polypectomy sites and a well-matched control group of patients who had polypectomy without prophylactic clipping. Interestingly, numerically, there were more bleeds in the group that underwent prophylactic hemoclipping, though this did not reach statistical significance. Although our study is limited by its small size

and retrospective nature, these data call into question the expensive practice of prophylactic hemoclipping.

We performed a national survey of gastroenterologists who practice at VA medical centers using SurveyMonkey® online software.[50] An invitation to participate in the survey was sent to 718 gastroenterologists identified as gastroenterologists in the VA system throughout the United States. A total of 144 gastroenterologists responded to the survey (Table below). No trainees were invited to take the survey. Despite the lack of data to support their use, the practice of placing hemoclips for prophylaxis of bleeding was common among the responding gastroenterologists. In patients with large polyps removed piecemeal, 46% of gastroenterologists reported that they would prophylactically place a hemoclip after polypectomy (either for fear of bleeding or perforation, or both). In patients on uninterrupted clopidogrel therapy, 39% of responding gastroenterologists would place a hemoclip prophylactically after the removal of a polyp >1cm in size. Moreover, even in patients who had held their clopidogrel for 7 days prior to colonoscopy, 32% of respondents would place a hemoclip after polypectomy for polyps >1 cm. Lastly, in patients who had held their warfarin for colonoscopy, 41% of gastroenterologists would place a clip prophylactically after 1cm or larger polypectomy. Interestingly, 67% of the respondents believe that placing hemoclips prophylactically after polypectomy reduces the risk of delayed PPB despite the fact that 87% of the respondents also reported that they knew there were no data in the literature to support this notion.

Table 2. Polypectomy techniques and prophylaxis for patients with large polyps (A) on anticoagulation and (B) not on anticoagulation

(A)	Leave polyp intact	Hot snare, single piece	Cold snare, single piece	Cold forceps, piece meal	Hot snare, prophylactic hemoclip	Cold snare, prophylactic hemoclip	Cold forceps, prophylactic hemoclip
Uninterrupted clopidogrel, polyp >1 cm	63 (43.8%)	17 (11.8%)	1 (0.7%)	2 (1.4%)	57 (39.6%)	4 (2.8%)	0
Clopidogrel held for 7 days, polyp>1 cm	0	90 (62.5%)	4 (2.8%)	3 (2.1%)	41 (28.5%)	6 (4.2%)	0
Warfarin withheld for 5 days, >1 cm polyp	0	76 (52.8%)	5 (3.5%)	3 (2.1%)	49 (34%)	11 (7.6%)	0
(B)	**Polypectomy with hot snare only**	**Hemoclip at stalk base prior to hot snare**	**Endoloop at stalk base prior to hot snare**	**Polypectomy with hot snare with hemoclipping afterwards at base**	**Epinephrine into stalk and then hot snare afterwards**		
Large (>10 mm) pedunculated polyp with thick stalk	74 (51%)	7 (5%)	18 (13%)	17 (12%)	28 (19%)		

Given the need for a definitive trial to clarify the utility of hemoclips for prophylaxis of post-polypectomy bleeding, we are currently performing a randomized controlled trial of prophylactic hemoclipping for patients with large (1cm or larger) polyps removed during colonoscopy. Our hypothesis for the study is that the prophylactic placement of hemoclips does NOT reduce the risk of PPB. We therefore designed our study as an equivalence study comparing polyps randomized to hemoclip placement to those not treated with hemoclips. Patients are included regardless of anticoagulation use with a planned subgroup analysis for these patients.

As of November 2016, we have enrolled 5648 patients into this study. Of these, 632 had polyps at least 1 cm in size and were able to be randomized into the study. Twenty of these patients are still in their 30 day follow-up period and 2 were lost to follow-up. Of the remaining 610 patients, 308 were randomized to the “hemoclip placement” group and 302 were randomized to the “no hemoclip placement” group.

An interim analysis for safety is being performed currently and no difference was found in PPB rates between those who received prophylactic hemoclips and those who did not (9/308 (2.9%) versus 10/302 (3.3%), p=0.82 for patients receiving hemoclips versus those who did not respectively). Subgroup analyses also revealed no significant differences between the groups in rates of important delayed PPB for patients using antiplatelet or anticoagulant medications; similarly, there were no significant differences between the groups in rates of important delayed PPB related to polyp morphology or polyp removal techniques. We are anxiously awaiting the ongoing efforts of this study and the final outcome.

Conclusions

While colonoscopy is generally a safe procedure, post-polypectomy bleeding is an important complication of colonoscopy. A number of risk factors contribute to the risk of post-polypectomy bleeding and include polyp related factors (particularly size of the polyp), patient related factors (especially the use of anticoagulants and antiplatelet agents), and physician (or technique) related factors. The referring physician as well as the gastroenterologist performing the colonoscopy should be well aware of the risks of associated anticoagulation use and carefully counsel their patients regarding interrupting or continuing their use during colonoscopy. The use of hemoclips placed prophylactically after polypectomy has become widespread but without clear evidence to support their use and we look forward to randomized trial data to guide our use of these devices.

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