

REVIEW

Endoscopic resection of colorectal polyps in patients on antiplatelet therapy: an evidence-based guidance for clinicians

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ABSTRACT

Due to the rising prevalence of coronary heart disease, endoscopists are more frequently performing a polypectomy in patients on antiplatelet therapy (APT) and dual antiplatelet therapy (DAPT). Despite the availability of several guidelines with regard to the management of antiplatelet drugs during the periprocedure period, there is still variability in the current clinical practice. This may be influenced by the low quality of the evidence supporting recommendations, because most of the studies dealing with APT and polypectomy are observational and retrospective, and include mainly small (< 10 mm) polyps. However, some recommendations can still be made. An estimation of the bleeding and thrombotic risk of the patient should be made in advance. In the case of DAPT the procedure should be postponed, at least until clopidogrel can be safely withheld. If possible, non-aspirin antiplatelet drugs should be withheld 5-7 days before the procedure. Polyp size is the main factor related with post-polypectomy bleeding and it is the factor that should drive clinical decisions regarding the resection method and the use of endoscopic prophylactic measures. Non-aspirin antiplatelet agents can be reintroduced 24-48 hours after the procedure. In conclusion, there is little data with regard to the management of DAPT in patients with a scheduled polypectomy. Large randomized controlled trials are needed to support clinical recommendations.

Key words: Colonoscopy. Colonic polyps. Antiplatelet agents. Polypectomy. Gastrointestinal hemorrhage.

INTRODUCTION

Coronary heart disease (CHD) is a major public health problem in Western countries. Recent statistics show that the prevalence of CHD in the United States (USA) is 6.4% in adults older than 20 years, and projections suggest that the prevalence will increase to 18% by 2030. The overall prevalence of myocardial infarction (MI) in the USA is 2.9%, with an estimated annual incidence of 515,000 new attacks. As a consequence, a huge number of coronary procedures are performed every year (1). Dual antiplatelet therapy (DAPT) is the mainstay of pharmacologic therapy for arterial coronary disease and after a percutaneous coro-

nary intervention with stent insertion (2), with the objective of reducing the risk of arterial occlusion and stent thrombosis. Although this is a matter of ongoing debate (3), the recommended length of DAPT following a stent placement is still 12 months (4). Therefore, endoscopists can expect to encounter increasingly more patients on DAPT.

Polypectomy is one of the most frequent endoscopic procedures performed in clinical practice. With the implementation of colorectal cancer screening programs, the number and complexity of polypectomy procedures have increased (5). The periendoscopic management of the antiplatelet therapy is challenging as the risk of bleeding when treatment is administered in a peri-procedural manner must be balanced against the thrombotic risk that the interruption of DAPT carries. Despite the fact that several guidelines on antiplatelet therapy and endoscopy have been published (6,9), and that some authors have given expert opinions with regard to this problem (10,11), there is still a great amount of uncertainty among practice clinicians and endoscopists about the periendoscopic management of patients treated with antiplatelet agents (12). Several survey studies have shown a huge variability in the percentage of physicians performing a polypectomy or endoscopic mucosal resection (EMR) on patients undergoing clopidogrel monotherapy and DAPT (13) as well as the appropriate time to restart the administration of antiplatelet agents (14,15). This situation is common even regarding aspirin, as shown in a very recent report that reviewed colonoscopy preparation instruction sheets of 317 endoscopy units in the USA. In about 50% of cases, instructions went against most of the guideline recommendations (16). This variability in clinical practice may be related to the low quality of evidence supporting guidelines (Table I), as well as the lack of evidence on some key points.

Polypectomy can be a complex procedure and clinical decisions involving different medical areas have to be taken prior to and during the procedure. Unlike other published reviews, the whole process of the polypectomy on a

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patient undergoing APT or DAPT therapy will be covered, including the evaluation of bleeding and thrombotic risk, the periprocedural management of drugs, and the use of endoscopic techniques to minimize the risk of bleeding. Our aim is to give the endoscopist performing a polypectomy a practical framework to daily practice.

MECHANISM OF ACTION OF ANTIPLATELET AGENTS

Two recent reviews have covered this topic (17,18), therefore we will only mention this briefly, commenting

only on commercially available oral drugs. Platelets circulate in an inactive state, but they activate rapidly following interaction with the exposed subendothelial tissue. Activation releases several mediators (arachidonic acid, thromboxane A₂) and granular contents. The most important of those is ADP, a platelet agonist that interacts with the P2Y₁ and P2Y₁₂ platelet receptors. P2Y₁ and P2Y₁₂ activation drives aggregation of platelets, a process also mediated by fibrinogen. Finally, the exposure of damaged tissues also induces local formation of thrombin, which contributes to the platelet activation process via the PAR-1 receptor (19). Due to these mechanisms, platelets are an active part of normal hemostasis, but they also take part in atherothrom-

Table I. Comparison of guidelines on antiplatelet therapy and endoscopy

Guideline	Low-risk procedure	High-risk procedure		Resumption
		Low-risk condition	High-risk condition	
UK 2008 (9)	ASA/clopidogrel continued (Evidence IV. Recommendation C)	<ul style="list-style-type: none"> – ASA continued – Clopidogrel discontinued 7 days before the procedure (consider substitute for ASA) (Evidence IIb. Recommendation B) 	<ul style="list-style-type: none"> – Liaison with cardiologist – ASA continued – Discontinue clopidogrel 7 days before the procedure if > 1 month after insertion of a BMS or if > 12 months after insertion of a DES (Evidence III, Recommendation B) 	On the day after the procedure
ASGE 2009 (7)	ASA/thienopyridines continued (Low quality evidence)	<ul style="list-style-type: none"> – Consider continuing ASA – Discontinue thienopyridines 7-10 days before the procedure – Consider continuing ASA with DAT or starting it with thienopyridine monotherapy (Low quality evidence) 	<ul style="list-style-type: none"> – Continue ASA – Consider postponing the procedure – Consider thienopyridine discontinuation 7-10 days before the procedure – Consider continuing ASA with DAT or starting it with thienopyridine monotherapy (Low quality evidence) 	“As soon as deemed safe”
ESGE 2011 (6)	Continue antiplatelet agents including DAT (Recommendations B to D)	<ul style="list-style-type: none"> – Discontinue ASA if: EUS-FNA of cysts, EMR/ESD, ampullary resection, sphincterotomy + papillary large-balloon dilation – Discontinue thienopyridine (clopidogrel 5 days before, prasugrel 7 days before) and substitute for ASA (Recommendations B to D) 	<ul style="list-style-type: none"> – Delay endoscopy or discuss with cardiologist temporary cessation of thienopyridines – Maintain ASA (Recommendations C to D) 	“Shortly after the procedure”
JGES 2014 (8)	<p><i>Endoscopy without biopsy: continue ASA/APT</i></p> <p><i>Endoscopy with biopsy: continue if monotherapy. If DAPT decisions case-by-case (Recommendations B to C1)</i></p>	<ul style="list-style-type: none"> – ASA can be withdrawn 3-5 days before – Stop thienopyridine (Recommendations C1) 	<ul style="list-style-type: none"> – Continue ASA – Stop thienopyridine 5-7 days before the procedure – Replacement with ASA or cilostazol (Recommendations C1) 	“As soon as hemostasis is confirmed after the procedure”
SEED 2015 (17)	Continue ASA/clopidogrel	<ul style="list-style-type: none"> – Consider continuing ASA – Clopidogrel discontinued 7 days before the procedure (consider substitute for ASA) 	<ul style="list-style-type: none"> – Continue ASA – Clopidogrel discontinued 5 days before 	24 hours after the procedure except in high bleeding risk situations

ASA: Acetylsalicylic acid; BMS: Bare-metal stent; DES: Drug-eluting stent; APT: Antiplatelet therapy; DAPT: Dual antiplatelet therapy.

basis development because of their ability to adhere to an injured blood vessel wall. The uncontrolled progression of the process of adhesion, activation and aggregation can lead to intravascular thrombus formation, vascular occlusion and ischemia.

Antiplatelet drugs are designed to interfere with some steps of the activation and aggregation process, thus reducing the risk of thrombosis. Aspirin and P2Y₁₂ inhibitors, especially thienopyridines ticlopidine, clopidogrel and prasugrel, are the most prescribed oral drugs to prevent cardiac problems. Ticagrelor and vorapaxar are two drugs recently added to our antiplatelet armory (4,20-22) (Table II). Aspirin irreversibly inactivates platelet and megakaryocyte COX-1, blocking TXA₂ synthesis both in the platelets already in circulation and in the newly released ones. Therefore, even though aspirin has a plasma half-life of 15-20 min, the pharmacodynamics effect persists for seven to nine days until a significant pool of new platelets is released from the bone marrow. Ticlopidine, clopidogrel and prasugrel block the platelet ADP receptor P2Y₁₂ inhibiting ADP-induced platelet aggregation. These three drugs are administered as prodrugs that undergo hepatic CYP450 system metabolism to generate the active drug. The use of ticlopidine has become almost obsolete due to concerns about bone marrow toxicity. Clopidogrel induces a permanent inhibition of the P2Y₁₂ receptor, and platelet function does not recover until 7-10 days after the last dose of the drug. There are variable levels of P2Y₁₂ inhibition in patients treated with clopidogrel. High-on-treatment platelet reactivity (HPR) has been described in about one third of patients (Table II), and it is related with a higher risk of thrombosis. Prasugrel has a more rapid onset of action than clopidogrel and produces a more consistent and predictable platelet response. Platelet function recovery usually returns 7 to 10 days after cessation of the drug (23). Ticagrelor is a cyclopentyltriazolopyrimidine that induces a reversible

inhibition binding directly, without previous metabolism, to the P2Y₁₂ receptor (24). The rate of platelet recovery after interrupting treatment with ticagrelor is faster than that of clopidogrel, but it still requires 4-5 days for platelet reactivity. Vorapaxar is a protease-activated receptor (PAR-1) antagonist that inhibits thrombin.

ESTIMATING THE RISK OF POST-POLYPECTOMY BLEEDING

Polypectomy is considered by all guidelines as a procedure with a high risk of bleeding (6-9,17). Postpolypectomy bleeding (PPB) is usually classified as immediate bleeding, produced during the procedure, and delayed bleeding, which usually occurs up to 14 days after the procedure. There is a wide variability in the reported incidence of PPB across different studies, most likely due to the definition of bleeding, inclusion of early or delayed bleeding, and the characteristics of the resected polyps. For instance, the English National Bowel Cancer Screening Programme reported a 1.14% bleeding rate, but immediate bleeding was not considered (25). By contrast, the Munich Polypectomy study, which registered any immediate bleeding that led to an intervention during the procedure as a complication, reported a bleeding rate of 8.6% (26). Overall, polypectomy increases the risk of bleeding by a factor of 11 (25). When focused on immediate bleeding, incidence has been reported to be 2.8% in a multicenter study (27), while the largest series assessing delayed bleeding reported an incidence ranging between 0.6 and 2.8% (28-31). A meta-analysis including studies in which colorectal lesions larger than 20 mm were treated with endoscopic resection has been published. Combined data of adverse events in 6,442 patients showed a bleeding rate of 6.5% (95% confidence interval [CI] 5.9%-7.1%) (32). Severe

Table II. Characteristics of commercially available oral antiplatelet agents used in coronary syndromes

Drug	Mechanism	Characteristics	Duration of effect (days)	Recommended interval (days) if discontinuation
Aspirin	Irreversible COX1 inhibition	HPR	5	7-10
Ticlopidin	P2Y12 irreversible receptor blocker	Bone marrow toxicity	10	10-14
Clopidogrel	P2Y12 irreversible receptor blocker	Prodrug thienopyridine CYP2C19 metabolism HPR	3-10	5
Prasugrel	P2Y12 irreversible receptor blocker	Prodrug thienopyridine Non-CYP2C19 metabolism Contraindicated in the case of a stroke	5-10	7
Ticagrelor	P2Y12 reversible receptor blocker	Triazolopyrimidine Active drug	3-4	5
Vorapaxar	PAR-1 reversible antagonist	Contraindicated in the case of a stroke or intracranial hemorrhage	14-28	NA

HPR: High on-clopidogrel platelet reactivity; PAR-1: Protease-activated receptor; NA: Not available.

bleeding requiring transfusion, surgery or prolonged hospitalization fortunately seemed rare (25).

Patient-, polyp-, and technique-related risk factors

Patient-related delayed bleeding factors have been described, such as age (33,34), the presence of diverticulosis (35), and hypertension (36), but the results are contradictory (31). Factors related to immediate bleeding have also been described, such as age, and cardiovascular or chronic renal disease (27). There is little evidence to suggest that cirrhosis is a risk factor, but one small retrospective study found no increase of bleeding risk in patients with Child-Pugh A cirrhosis (37).

There are some known polyp-related risk factors for PPB. Polyp size larger than 10 mm is a consistently reported risk factor (25,26,28-30). In the aforementioned Munich Polypectomy Study, about 50% of polyps were 10 mm or larger (26). In an additional study, with every 1-mm increase in polyp size, the risk of PPB increased by 9% (31). Other important risk factors include polyp location such as the right colon or cecum (28,25). Some studies have suggested that polyp morphology (pedunculated and flat lesions) may be related with immediate bleeding (27).

Technical issues also influence bleeding rates. For instance, the use of pure cutting current instead of blended or coagulation current increases the risk of immediate PPB (27). The use of a non microprocessor-controlled current has been related with delayed bleeding in wide field EMR (38). Other studies have suggested that the experience of the endoscopist (28,39) or the number of procedures performed by an institution may be influential variables for PPB. The occurrence of immediate PPB during the procedure has been related to delayed PPB in some large series (30,38). Regarding the resection modality, EMR carries higher rates of PPB than conventional polypectomy, both for immediate and delayed bleeding. A recent Spanish study on EMR of lesions ≥ 20 mm showed a rate of

delayed PPB of 3.7% (33). Size is also related with PPB in EMR, with an incidence of 11.3% for immediate and 6.2% for delayed bleeding in lesions larger than 20 mm (38), and an incidence equivalent to that of conventional polypectomy for lesions < 10 mm (40). The rate of delayed PPB in colonic ESD seems to be around 2%, lower than that of EMR of large lesions (41). A European multicentric study showed a 13% rate of delayed PPB, but this study included only rectal lesions (42). Location in the rectum seems to be a risk factor for delayed PPB (43). Other studies have shown that cecal location is also a risk factor for PPB (44).

Antiplatelet agents as a risk factor

Most of the studies have not shown an increased risk of PPB in patients taking aspirin (31,45-48). However, evidence is weak, and there is no data available from any randomized trials. Data on clopidogrel are scarce and based mainly on retrospective studies (Table III). In a small study by Frieland et al. (49), the authors did not observe a difference in bleeding rate in polyps smaller than 10 mm. Singh et al. (50) described an odds ratio (OR) of 3.7 (95% CI 1.6-8.5) of PPB in patients undergoing combined treatment with clopidogrel and aspirin/NSAIDs. Feagins et al. (51) showed no increase of PPB risk in patients taking clopidogrel alone (OR 2.63, 95% CI 0.3-22.0). The same group reported the first prospective study assessing both immediate and delayed PPB on patients with and without thienopyridines (clopidogrel or prasugrel). There were no differences in the rate of immediate PPB, but the rate of delayed PPB was higher in the group treated with clopidogrel (5.9% vs 0). However, the real magnitude of the clopidogrel effect is difficult to measure, because all five patients with clinically important bleeding were also taking aspirin, and were also in a poorer state of health than the group without clopidogrel (52). There are two reported studies that include patients taking only clopidogrel, presented as conference abstracts. The first one showed an

Table III. Published studies on the role of clopidogrel on postpolypectomy bleeding

Author	Design	N patients C/NC	N polyps ^a	Size ≥ 10 mm n (%) ^a	Resection n (%) ^a	DAPT n (%) ^a	PPB C/CN n (%)	IPPB n (%) ^a	DPPB n (%) ^a	PPB DAPT n (%) ^a
Frieland 2009 (49)	R/S	60/-	125	3 (2)	CS 91 (73) CF 3 (2)	10 (17)	4 (7)/-	3 (5.0)	1 (1.7)	NA
Singh 2010 (50)	R/C-C	142/1,243	375	12 (8)	CS 33 (23) CF 16 (11)	77 (54)	8 (6.0)/38 (3.0)	3 (2.1)	5 (3.5)	8 (100)
Feagins 2011 (51)	R/C-C	118/1,849	360	17 (14)	CS 9 (3) CF 255 (71)	93 (79)	1 (0.8)/6 (0.3)	NA	1 (0.8)	1 (100)
Feagins 2013 (52)	P/C-C	219/297	865	34 (15)	CS 37 (4) CF 558 (64)	192 (88)	21 (10.0)/14 (4.7)	16 (7.3)	5 (2.3)	5 (23.8) ^b

R: Retrospective; P: Prospective; S: Series of patients; C-C: Case control; C: Clopidogrel; NC: No APT; CS: Cold snare; CF: Cold forceps; DAPT: Dual antiplatelet therapy; PPB: Post-polypectomy bleeding; IPPB: Immediate post-polypectomy bleeding; DPPB: Delayed post-polypectomy bleeding; NA: Not available. ^aPercentage from patients on clopidogrel therapy. ^bThese five patients were those with delayed bleeding.

increased risk of both immediate and delayed PPB (53), and the second one showed no difference regarding the PPB rate, but clipping was routinely applied after polypectomy in patients on clopidogrel (54). A meta-analysis on the risk of PPB in patients on clopidogrel therapy showed a pooled relative risk (RR) of 4.66 (95% CI 2.37-9.17) for delayed PPB (55), whereas the relative risk (RR) for immediate PPB was considered as non-significant. These results have been confirmed in a recent meta-analysis that showed a higher rate of delayed bleeding in patients on clopidogrel (OR = 9.7, 95% CI 3.1-30.8) (56).

However, these studies and meta-analysis have some limitations. First, PPB is a rare event and prevalence rates are too low to accurately discriminate the concomitant effect of aspirin. Second, the reported rate of PPB falls well within the ranges reported for the general population not undergoing antiplatelet therapy. Third, most of the polyps resected in these studies are below 10 mm in size (Table III), and as previously mentioned, size is one of the most important risk factors for PPB. Therefore, although some authors (56) and guidelines (6,7) recommend it, the quality of the evidence supporting a systematic withdrawal of clopidogrel in patients undergoing colonoscopy and polypectomy is poor.

Nevertheless, circumstances may be different for more complex endoscopic therapies such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). A recent randomized controlled trial on the usefulness of prophylactic endoscopic hemostasis described risk factors of PPB in 347 patients during EMR with lesions larger than 2 cm (57). Antiplatelet use was related to clinically significant PPB in a univariate analysis, and there was also a trend when a multivariate analysis was performed. This may be a sample size issue as only 15 patients had continued treatment with antiplatelet agents before the procedure. Aspirin use during EMR was a risk factor for delayed PPB in a recent multicenter study including 1,255 EMRs (33). However, two observational studies, one with 1,387 patients and another with 288, showed conflicting results with regard to the effects of aspirin (38,58). In these four studies there are not enough data on clopidogrel to draw an adequate conclusion. Data about colonic ESD are also scarce. Two observational retrospective studies on a total of 682 patients found no relationship between the use of antithrombotic agents and delayed PPB (43,44). The authors suggest that submucosal vessel coagulation during the ESD procedure prevented delayed bleeding, thus allowing the procedure to be performed without discontinuing aspirin (43).

ESTIMATING THE THROMBOTIC RISK OF PATIENTS WITH CORONARY STENTS

Depending on the patient's characteristics and anatomical issues, PCI with coronary stenting may be chosen as

a therapy for a patient presenting with an acute coronary syndrome. Two types of stents can be placed, bare-metal (BMS) or drug-eluting stents (DES) (59). Thrombosis is the most problematic adverse event after placement of a coronary stent. Overall, it has a relatively low prevalence but it carries a high mortality rate. For instance, in a multicenter prospective observational study on 2,229 patients a stent thrombosis rate of 1.9% was observed, with a mortality rate of 45% (60). Early stent thrombosis is defined as occurring in the first month after stent placement, and thereafter the thrombotic events are considered as late thrombosis. BMS and DES have a different behavior in relation to late thrombosis. BMS have developed complete endothelial coverage 30 days after implantation. However, DES have a maintained high risk of thrombosis during a longer time period that may be related with a delayed endothelialization of the stent (61).

To reduce the stent thrombosis rate, guidelines recommend treatment with DAPT for 12 months after DES and for one month in the case of BMS. Lifetime AAS is prescribed thereafter for both stents (59). However, the duration of DAPT remains controversial. Some studies and a meta-analysis suggest that extending DAPT more than 6 months is no more effective in reducing cardiac events (62,63) but, on the other hand, a randomized controlled trial and two meta-analysis have shown a reduction in the risk of stent thrombosis and major cardiovascular and cerebrovascular events with prolonged DAPT (more than 12 months), perhaps at the expense of an increase in bleeding complications (64-66). The risk of thrombosis is reduced after the introduction of second-generation stents, but it still remains clinically significant (60). Third generation stents are being developed and a shorter duration of DAPT is expected.

Discontinuation of APT carries a high risk of stent thrombosis, cardiovascular events and mortality. In a study that assessed the incidence of thrombosis after a DES implantation in a real clinical setting, the main variable related to stent thrombosis was a premature discontinuation of DAPT (60). A recent prospective observational study showed an adjusted hazard ratio for an early major cardiac adverse event after disruption of treatment of 7.04 (67), and a meta-analysis showed an extremely high risk of major cardiac adverse events after discontinuing APT in patients with coronary stents (OR = 89.78 [29.9-269.6]) (68). Moreover, stent thrombosis usually occurs shortly after discontinuation of the antiplatelet agents. In a prospective observational study in which patients were followed after stent insertion, the hazard ratio for stent thrombosis after disruption of treatment was highest in the first 7 days, and attenuated thereafter (67). Withholding clopidogrel while continuing aspirin reduces, but does not eliminate, the risk of stent thrombosis. In a systematic review, when both agents were withdrawn simultaneously, the median time to thrombosis was 7 days, while if the patient remained on aspirin the median time to an event was 122 days (68).

In summary, elective procedures should be postponed for a minimum of 4-6 weeks for BMS and 6 months after DES implantation, but ideally DAPT should be maintained for 3 months for BMS and 12 months for DES. Afterwards, thienopyridines could be interrupted while aspirin is continued.

MINIMIZING THE RISK OF POST-POLYPECTOMY BLEEDING

Periprocedural management of DAPT

The periprocedural management of DAPT should be individualized in order to avoid fixed recommendations and balance both the bleeding and thrombotic risks. The procedure must be delayed until benefits of performing the polypectomy exceed the risk of halting the DAPT, and consulting a cardiologist should be considered. As previously mentioned, if a BMS was placed, the procedure should be deferred 6 weeks. In the case of DES, guidelines recommend deferring the procedure for the first 6 months, and ideally for 12 months after stent implantation. Clopidogrel therapy should never be withheld within 30 days of stent implantation (2). Guidelines recommend discontinuing clopidogrel and ticagrelor 5 days and prasugrel 7 days before the procedure, maintaining aspirin (17). If the patient is on clopidogrel monotherapy, shifting to aspirin should be considered (7). If an EMR/ESD is scheduled, discontinuation of all antiplatelet agents is recommended provided that the patient is not at a high risk for thrombosis (6), which unfortunately is not the case for patients carrying a coronary stent. Regarding the reintroduction of DAPT, most guidelines suggest that clopidogrel can be initiated within 48 hours after polypectomy, usually the day after the procedure (11,17), when platelet function is expected to be almost completely recovered. The evidence supporting this recommendation is at best of moderate quality, but it is hazardous to discontinue these drugs for longer periods because of the risk of thrombotic events. However, re-initiation can be delayed for 5 days in the case of complex procedures such as piecemeal EMR, due to an increased risk of PPB (38). A delayed reintroduction of prasugrel or ticagrelor may be advisable due to the more rapid onset of action (11).

Endoscopic prevention of PPB

Polypectomy in this setting should be performed by an experienced endoscopist, both in resection techniques and in the management of complications. Immediate PPB is more common with cutting or blended current, while delayed bleeding is more common with coagulation current (69). Immediate PPB after cold forceps or cold snare is nearly always clinically insignificant. Therefore, pol-

ypectomy with cold forceps is recommended for polyps < 3 mm and cold snare can be used for polyps up to 7-10 mm (70). Blended current should be used for larger lesions.

Several prophylactic methods aimed to reduce the rate of PPB have been described, but there are no studies specifically focused in patients undergoing DAPT or P2Y₁₂ inhibitor therapy. In fact, patients treated with APT are excluded in most of the studies summarized. Epinephrine injection was the most frequently applied prophylactic method in a survey among American endoscopists (71). However, reports on the efficacy of epinephrine *versus* saline for prevention of PPB show variable results with some efficacy in preventing immediate bleeding (72-74). Prophylactic placement of hemoclips at the resection site has been advocated as a method to reduce the rate of PPB, but the published evidence supporting this practice is also weak. To the present date, there are three randomized controlled trials published. Shioji et al. (75) compared the incidence of delayed PPB in a group assigned to receive prophylactic hemoclippping and a group with no hemoclippping. They found no difference between groups, although the median size of polyps was < 8 mm, a size with a reduced probability of bleeding. Quintanilla et al. (76) focused on prophylactic hemoclippping of large (> 10 mm) pedunculated polyps. This trial had to be prematurely stopped due to an increased risk of mucosal burns and perforation in the hemoclippping group, without finding any reduction in PPB rates. The most recent study was focused on the role of clipping closure of a mucosal defect after EMR or ESD of 1 to 4 cm colorectal lesions (77). The authors showed a significant reduction in delayed PPB with clipping (1.1% vs 6.9%), a result that suggests clipping may be worthwhile after the resection of flat and large polyps. This suggestion is also supported by the results of a retrospective study evaluating the outcomes of patients with resected lesions larger than 20 mm, which found a significant reduction in PPB rates in the clipped group. In fact, not clipping was a risk factor for delayed PPB (OR 6.0; 95% CI 2.0-18.5) (78). A retrospective case-control study has been recently published, showing no significant difference in the rate of delayed PPB between patients who had prophylactic clipping and those who had not (79). However, there were only four cases of PPB, and the decision of placing hemoclips was not defined prospectively. Prophylactic clipping could be cost-effective in some instances, such as patients undergoing antiplatelet and anticoagulant therapy (80), and EMR performed in patients at high risk of PPB (33).

Some studies have compared the use of a detachable snare before polypectomy with other hemostatic methods. Di Giorgio et al. (81) showed that both detachable snare and adrenaline were better than no hemostatic method in reducing PPB, mainly for lesions larger than 20 mm. No difference was found between both methods. Ji et al. (82) found no differences regarding bleeding rates after the resection of pedunculated polyps between detachable snare and hemoclips.

Two meta-analyses have been published. The first included only randomized controlled trials in which early and late bleeding were distinguished. The authors showed that any prophylactic measure reduced the risk of immediate PPB (OR = 0.34 [0.20-0.58]), but had no significant effect on delayed PPB (OR = 0.37 [0.11-1.28]). The use of multiple prophylactic measures reduced even further the early bleeding rate (83). The second included only studies focused on the effect of several prophylactic methods on PPB of polyps larger than 10 mm. The application of any hemostatic method reduced PPB rate when compared to no method at all (RR = 0.32; 95% CI 0.20-0.52). The injection of adrenaline alone also reduced the risk of bleeding, and the pooled risk was reduced with mechanical hemostasis compared to adrenaline injection (RR = 0.28; 95% CI 0.14-0.57). Applying two hemostatic methods also reduced the risk when compared to one method alone. The authors suggested considering mechanical prophylaxis or two methods of prophylaxis in patients at high risk of PPB. However, in this study no clear distinction between immediate and delayed bleeding was made (84). A main drawback of both meta-analyses is that the influence of polyp morphology (pedunculated vs sessile) could not be assessed because most of the included studies did not report data on bleeding rates by polyp morphology. Finally, a recent randomized trial tested the use of prophylactic endoscopic coagulation or large submucosal vessels to prevent bleeding after wide-field EMR. The authors showed that submucosal vessels were more numerous and larger in the mucosal defect after EMR of distal lesions while bleeding was more frequent in proximal lesions. Endoscopic coagulation did not reduce the incidence of PPB after wide-field EMR (57). However, whether this is the case with regard to patients taking antiplatelet agents is not known as only a few patients were on ATP therapy.

In summary, the evidence is weak and there are no studies specifically in patients on APT, but probably prophylactic measures should be applied when performing a polypectomy on patients under APT, mainly if the size is larger than 10 mm. In the case of polyps larger than 20 mm, postpolypectomy clipping is probably advisable.

MANAGING A BLEEDING COMPLICATION IN A PATIENT WITH CORONARY ARTERY DISEASE ON DAPT

When bleeding develops during polypectomy, epinephrine injection is the most frequently used hemostatic method. One small study on patients with bleeding peptic ulcers showed an increase of serum concentration of epinephrine after injection. The clinical implications of this finding are not known (85). However, cardiac monitoring during the procedure and perhaps the use of other mechanical hemostatic methods may be advisable in these patients. One study has suggested that snare tip coagulation for bleed-

ing during wide-field EMR may be effective to achieve hemostasis, but in this study only 4% of patients were on clopidogrel therapy (86).

Another important decision is how to manage antiplatelet agents if PPB occurs. Since polypectomy is usually a scheduled procedure, clopidogrel therapy will most likely have been stopped and the patient will be only on aspirin therapy. Should aspirin also be stopped? This decision should be carefully evaluated keeping in mind that most of early re-bleeding is treatable by endoscopic methods but thrombosis can have fatal consequences. Probably in most cases aspirin interruption will not be necessary, but following expert recommendations, if there is a major bleeding complication and endoscopic hemostasis is difficult to achieve, all antiplatelet agents should be withheld for 3-5 days (87).

If aspirin has been stopped, when should it be reintroduced? Studies on endoscopic therapy of bleeding peptic ulcers have shown that early reintroduction of aspirin after endoscopic therapy may increase re-bleeding rates but reduce mortality attributable to cardiovascular events (88). Therefore, early reintroduction of APT is advisable.

CONCLUSION

The number of patients on antiplatelet therapy (APT) or dual antiplatelet therapy (DAPT) who are scheduled for colonoscopy with polypectomy is expected to increase steadily. In spite of the fact that there are several practice guidelines, there is still a great amount of uncertainty among endoscopists about the peri and intraprocedural management of these patients. The available evidence to support recommendations is weak, as studies on this topic are mainly observational and retrospective, most polyps included are small and variable definitions of bleeding are used. Therefore, dealing with polypectomy in patients on dual antiplatelet therapy in daily practice is a matter of concern for clinicians. In spite of this, with the available data, some practical recommendations can be made (Fig. 1):

- An estimation of the bleeding and thrombotic risk of the patient should be made in advance. Liaison with a cardiologist is advised. In the case of DAPT the procedure should be postponed, if possible, at least until clopidogrel can be safely withheld.
- An experienced endoscopist, with expertise in treating bleeding complications and in applying prophylactic measures, should perform the procedure.
- Generally speaking, if possible, non-aspirin antiplatelet drugs should be withheld some days before the procedure (Table II). Aspirin should be maintained. In very special circumstances, polypectomy could be performed under clopidogrel therapy or DAPT, but not in patients on other non-aspirin agents due to the lack of safety data. Ideally, if an EMR or ESD is scheduled, all antiplatelet agents should be stopped

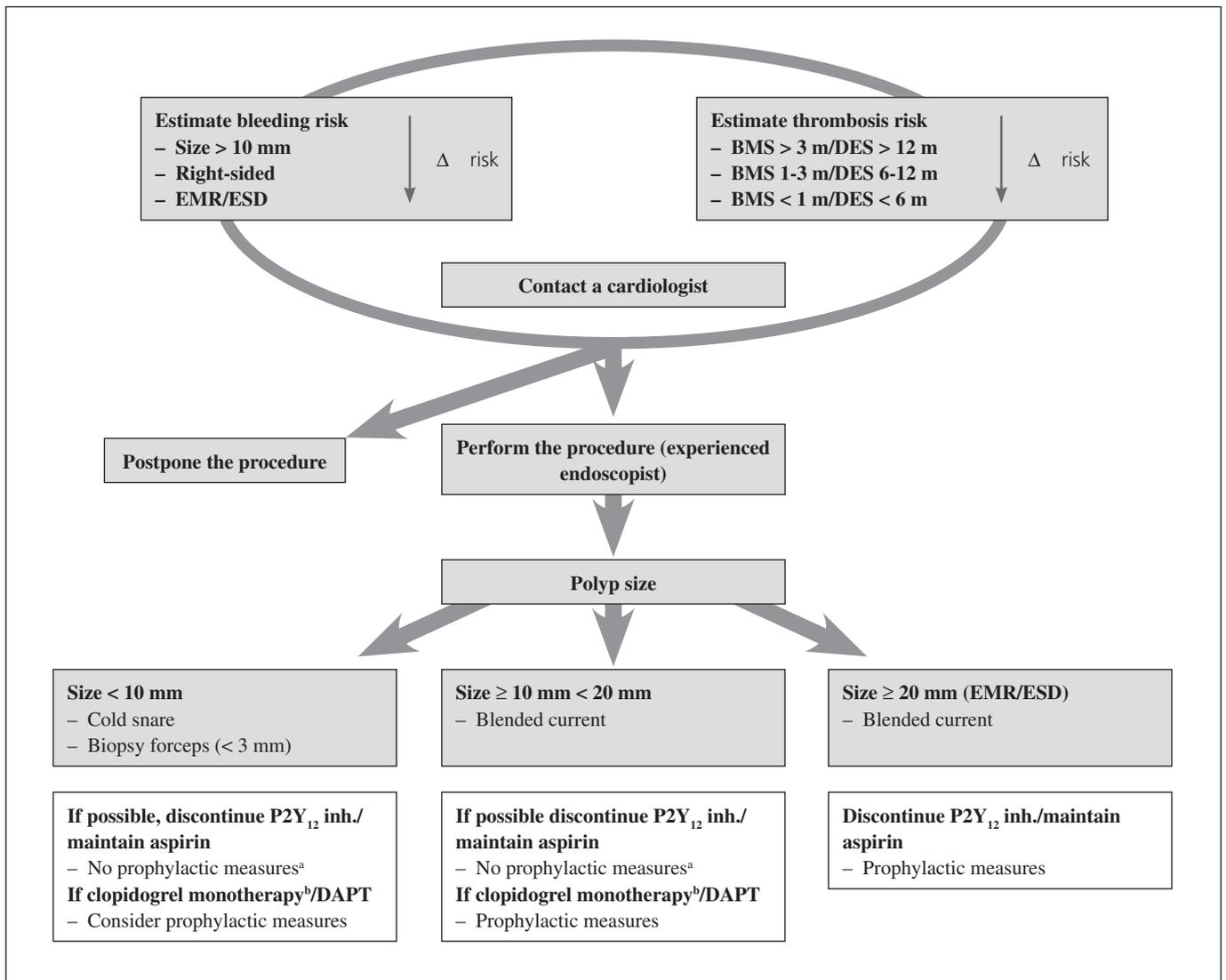


Fig. 1. Proposed algorithm for the management of a patient with DAPT when a polypectomy is scheduled. ^aProphylactic measures: Submucosal injection of diluted adrenaline, loop ligating device, hemostatic clips, ^bbut no other P2Y₁₂ inhibitors. BMS: Bare-metal stent; DES: Drug-eluting stent.

5-7 days before the procedure. However, this is not possible in the case of previous coronary stenting because the patient should be on aspirin in the long-term but performing these procedures in patients on clopidogrel or DAPT should be avoided.

- Polyp size is the main variable related to PPB and it is the main variable that drives clinical decisions. If the polyp is smaller than 10 mm, biopsy forceps (size ≤ 3 mm) or cold snare (size < 10 mm) should be used and no prophylactic measures are usually needed. Prophylactic endoscopic techniques can be considered if the patient is on clopidogrel monotherapy or DAPT. If the polyp is larger than 10 mm, blended current should be used and prophylactic measures should be applied. Submucosal injection of diluted adrenaline should be considered, and post-resection clipping is an option.

- If an EMR or ESD is scheduled for lesions larger than 20 mm, non-aspirin antiplatelet agents should be stopped and the same prophylactic measures used for polyps larger than 10 mm should be applied. Post-procedural instructions including information about potential complications and contact details should be provided to every patient.
- Clopidogrel can be reintroduced 24-48 hours after the procedure; ticagrelor and prasugrel should be reintroduced within 48 hours. In the case of EMR or ESD, reintroduction can be delayed for up to five days.

The quality of the available evidence will probably not improve in the short-term because PPB has a low prevalence, even in patients taking clopidogrel, making the performance of studies large enough to assess the preva-

lence and risk factors for PPB difficult. For instance, in order to detect a 5% difference on PPB prevalence in patients with or without clopidogrel if the overall prevalence of PPB is 6%, 802 patients in each arm would be needed. For the same reason, a well designed randomized controlled trial on PPB endoscopic prevention would be hard to perform. However, an effort must be made to design and implement multicenter studies including sufficient patients to achieve stronger conclusions. Perhaps scientific societies should take the lead in this kind of project with the aim of shedding light on the peri- and intra-procedural management of antiplatelet agents in the polypectomy setting.

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