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**Anticoagulation and antiplatelet management in gastrointestinal endoscopy: A review of current evidence**

Chan A *et al*. Anticoagulation and antiplatelet in gastrointestinal endoscopy

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**Abstract**

The role of endoscopic procedures, in both diagnostic and therapeutic purposes, is continually expanding and evolving rapidly. In this context, endoscopists will encounter patients prescribed on anticoagulant and antiplatelet medications frequently. This poses an increased risk of intraprocedural and delayed gastrointestinal bleeding. Thus, greater importance on optimal pre, peri and post-operative management of anticoagulant and antiplatelet use is important to minimise the risk of post-procedural bleeding, without increasing the risk of a thromboembolic event, as a consequence of therapy interruption. There are currently position statements and guidelines from the major gastroenterology societies available to assist endoscopists with an evidenced-based systematic approach to anticoagulant and/or antiplatelet management in endoscopic procedures, to ensure optimal patient safety. However, since the publication of these guidelines, there has been emerging evidence not previously considered in the recommendations, that may warrant changes to our current clinical practices. Most notably, and divergent from current position statements, is growing concern regarding the use of heparin bridging therapy during warfarin cessation and its associated risk of increased bleeding. Suggestive that this practice should be avoided. Also, there is emerging evidence that anticoagulant and/or antiplatelet therapy may be safe to be continued in cold snare polypectomy for small polyps (< 10 mm).

**Key Words:** Endoscopy; Anticoagulants; Antiplatelets; Antithrombotics; Bleeding; Gastrointestinal

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**Core Tip:** The current position statements and guidelines from the major gastroenterology societies have provided endoscopists with an evidenced-based systematic approach to pre, peri and post-operative management of patients on anticoagulant and antiplatelet agents in the context of both low and high-risk endoscopic procedures. While there is sufficient evidence on the index bleeding risk in common endoscopic procedures in in the absence of anticoagulant and/or antiplatelet agents, the evidence surrounding bleeding risk while on anticoagulant and/or antiplatelet agents is variable among different publications and still evolving. In this review, we have summarised the available evidence, provided an overview, and described our recommended practical application of anticoagulant and antiplatelet management in common endoscopic procedures. Finally, we have compared our recommendations against the current guidelines from the major gastroenterology societies to assimilate a new working reference, and to highlight any knowledge gaps and directions for future research.

**INTRODUCTION**

Contemporary management of patients with atrial fibrillation (AF), venous thromboembolism (VTE) and acute coronary syndromes (ACS) requires the use of an expanding range of anticoagulant and antiplatelet agents. Similarly, the type and range of endoscopic procedures has evolved rapidly, and screening for neoplasia has increased the frequency of procedures per se. In this context, endoscopists will encounter patients prescribed on anticoagulant and antiplatelet medications frequently, and thus an informed and systematic approach to pre, peri and post-operative management is of great importance.

The major risk of anticoagulant and antiplatelet therapy is gastrointestinal bleeding, especially within the first 30 d following an endoscopic procedure[1]. Optimal management involves minimising the risk of post-procedural bleeding (PPB) on one hand, without significantly increasing the risk of a thromboembolic event on the other. Thromboembolic events [including stroke, myocardial infarction (MI) or pulmonary embolism] often have serious, irreversible consequences compared to gastrointestinal bleeding, which if detected early and managed appropriately is of minor consequence. The old wisdom that the brain or heart cannot be replaced, whilst blood or fluid can be readily transfused holds true.

In recent years, a wealth of literature relating to anticoagulant and antiplatelet use has emerged, including a number of position statements and guidelines from the major gastroenterology societies in Europe, the United States of America and Asia. These documents, along with the research studies from which they are based, should logically form the basis of future recommendations. The purpose of this review therefore is to firstly evaluate the index bleeding risk associated with common endoscopic procedures in the absence of anticoagulant and/or antiplatelet use. We then aim to consider the major research studies relating to anticoagulant and antiplatelet use in this context, and to compare the available evidence against the relevant major guidelines mentioned, to assimilate a new working reference, and to highlight any knowledge gaps and directions for future research.

**SEARCH STRATEGY**

We performed a structured literature review using Ovid Medline, considering articles from January 1, 2011 to January 1, 2020, with the intention of identifying relevant research potentially not included in recent guidelines[2-4]. Medical Subject Headings (Supplementary material) were formulated relating to the anticoagulant and antiplatelet agents of interest [aspirin, thienopyridine (clopidogrel, prasugrel, ticagrelor), warfarin, direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban), heparin bridging therapy (HBT)], all relevant endoscopic procedures, and “bleeding” rates. Case reports, abstracts, commentaries, letters, and editorials were not considered. Relevant articles were retrieved and reviewed, with data tabulated (Tables 1-56)

**ENDOSCOPIC PROCEDURES AND ITS RISK OF POST-PROCEDURE BLEEDING IRRESPECTIVE OF ANTICOAGULANT AND ANTIPLATELET THERAPY**

A summary of relevant studies evaluating the index bleeding risk according to endoscopic procedure type, in the absence of antiplatelet or anticoagulant use, is outlined in Tables 1-16.

**DIAGNOSTIC ENDOSCOPIC PROCEDURES**

***Diagnostic endoscopy and colonoscopy with biopsy (Table 1)***

Endoscopic biopsy is a minimally invasive procedure that is commonly undertaken during diagnostic endoscopies and colonoscopies to diagnose a range of conditions (*e.g.*, neoplasia, coeliac disease, *Helicobacter pylori)*. The risk of PPB is low, ranging from 0.12%-0.98% in published studies[5-7].

***Diagnostic ± therapeutic push or device assisted enteroscopy/balloon enteroscopy (Table 2)***

Double balloon enteroscopy (DBE) allows for detailed and direct visualisation and assessment (diagnostic) of the small bowel and application of endoscopic intervention. The risk of PPB associated with DBE is at 0.5%, but increases with therapeutic intervention[8,9]. Wang *et al*[9] recorded 7 episodes of PPB in 1531 DBEs (0.5%), and all were associated withtherapeutic polypectomy*.* There were no reported incidences of PPB in the studies in diagnostic-only DBE.

***Endoscopic ultrasound ± fine needle aspiration (Table 3)***

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with 22G FNA needle is the gold standard diagnostic tool for pancreatic and upper gastrointestinal tract lesions. A 22G FNA needle is generally preferred, but the procedure can also be performed with either 19G or 25G needles. The reported risk of PPB varies according to needle gauge, ranging from 2.1% with 25G needles to 4.3% with 22G needles[10-17]. Of note, both the study by Vilmann *et al*[13] and Inoue *et al*[17] observed an associated immediate/intraprocedural bleeding risk of 0.7%-1%. However, in both studies, the bleeding was self-limited and did not require any further endoscopic intervention. Published data on use of 19G needles is more limited compared to the data available on both 22G and 25G needles. 19G needles are more rigid than its smaller gauge counterparts, making adequate positioning of the endoscope and manipulation more technically difficult[18]. However, successful use of 19G needles has been shown to yield superior diagnostic accuracy and better diagnostic tissue acquisition compared to the 22G and 25G needles[18,19]. There were no reported incidences of PPB in any of the studies[18-20], although two studies observed an associated immediate/ intraprocedural bleeding risk of 1.0%-1.8%[19,20] with 19G needle use.

***Endoscopic retrograde cholangiopancreatography (diagnostic) (Table 4)***

With advancements in imaging modalities, such as magnetic resonance cholangiopancreatography, the role for diagnostic only endoscopic retrograde cholangiopancreatography (ERCP) is rare, and ERCP is mainly an interventional procedure (endoscopic sphincterotomy, papillotomy, biliary stone removal and insertion of biliary stents). Diagnostic ERCP rarely causes PPB, a rate of 0.3%-1.66% is reported[21-25]. In all of the studies, PPB was most commonly observed in diagnostic ERCPs when sphincterotomy was required to obtain better access. Sphincterotomy was found to be a significant risk factor associated with up to a five-fold increased risk of PPB[21,23-25] and will be discussed further in the “ERCP with sphincterotomy” section (Table 9).

**THERAPEUTIC ENDOSCOPIC PROCEDURES**

***Conventional polypectomy/hot snare polypectomy (Table 5)***

Conventional polypectomy, also referred to as hot snare polypectomy (HSP), uses electrosurgical current through a polypectomy snare and is the standard practice for polyp resection and prevention of colorectal cancer. It has been associated with a colorectal cancer mortality reduction over 30 years. Numerous published studies have identified the overall risk of PPB post conventional polypectomy to be around 0.05%-3.0%[26-42]. Larger polyp sizes (> 10 mm), polyps located in caecum and ascending colon, and pedunculated polyps are all associated with an additional increased risk of overall PPB[33,36,41,43].

***Cold snare polypectomy and endoscopic mucosal resection (Tables 6 and 7)***

Aside from conventional polypectomy (HSP), other polypectomy techniques are often utilised, specifically cold snare polypectomy (CSP) and endoscopic mucosal resection (EMR), with the chosen method often dependent on polyp characteristics. Hot biopsy forceps (HBF), which are insulated monopolar electrocoagulating forceps and allows for biopsy and electrocoagulating tissue simultaneously[44], was previously used for polypectomy of diminutive polyps. It has now fallen out of favour due to its poorer *en-bloc* resection rate and increased rate of significant injury to the pathology tissue compared to CSP[45]. Given HBF is no longer commonly practiced; it will not be a focus for this review and will not be discussed further.

The European Society of Gastrointestinal Endoscopy (ESGE) clinical guidelines[46] recommends the use of CSP technique for removal of diminutive polyps ≤ 5mm and sessile polyps 6-9 mm in size because of its superior safety profile. Studies have shown that CSP is superior to HSP in resection of polyps ≤ 10 mm, with a shorter procedure time[27] and no statistically significant difference in complete resection rate[27,39] or delayed bleeding rates[27,37-40].The risk of delayed PPB in CSP is shown to be very low with no incidences (0%) observed in any of the studies[27,37-39,47,48]. This is comparable to HSP with an incidence rate of 0%-0.5% for polyps ≤ 10 mm[27,37-40]. However, there is an increased risk of immediate/intraprocedural PPB in CSP for small polyps (< 10 mm), with three studies[27,39,48] showing an intraprocedural bleeding rate of 2.7%-9.1%, compared to 1%-3.5% in HSP[27,39].

Conventionally, HSP (for polyps > 10 mm in size) and EMR (for polyps > 20 mm in size, particularly if sessile) have been the standard of care in the removal of these larger polyps, as it is considered more efficacious in minimising the risk intraprocedural bleeding. The ESGE clinical guideline on colorectal polypectomy and EMR[46] still recommends HSP as the preferred technique for polyps 10-19 mm in size and EMR for polyps ≥ 20 mm. This is due to its ability to cauterise the resected tissue, while also providing additional ablation to the residual tissue promoting complete haemostasis[40]. The risk of intraprocedural and delayed PPB with EMR in polyps < 10 mm is 1.7%[48] and 0%-1.7%[48,49], respectively. Risk of delayed PPB is higher with increasing polyp size. So *et al*[50] found an incidence of 6.3% in polyps with a mean size of 34 mm.

Recent publications suggest that HSP carries a higher risk of both PPB and perforation compared to CSP in polyps > 10 mm, likely due to the thermal injury of the intestinal wall. A study of resection specimens indicates that the higher risk of delayed bleeding was caused by more extensive arterial injury in the submucosal, deep submucosa and muscularis propria layers at HSP[40]. In contrast, the removal of polyps > 10 mm by CSP does not cause PPB, with no evidence of bleeding in 6 studies[40,51-55]. There was one reported incidence of delayed PPB that developed in a patient in the study by Hirose *et al*[54] but this patient was on warfarin for AF and so was not included in the final analysis. This is compared to a delayed PPB incidence rate of 3.5%, as published in a study by Ket *et al*[40] in the removal of polyps > 10 mm by HSP. There was limited published data on the time to PPB in patients undergoing HSP in the available studies. The study by Ket *et al*[40] reported the time to PPB in their patient cohort to be between 2 to 7 d post endoscopic procedure. While, the study by Sewitch *et al*[29] had only 1 complication of PPB (0.05%) which occurred 3 wk post polypectomy. However, this was thought to be more likely in the setting to the follow-up treatment than to the index colonoscopy. A potential limitation is the majority of the studies were retrospective studies which may have missed subsequent bleeds due to inadequate period of follow-up post procedure.

***Endoscopic submucosal dissection (Table 8)***

The practice of endoscopic submucosal dissection (ESD) is often required for the resection of large gastrointestinal lesions *en bloc*, and (compared to CSP and EMR) is associated with a significantly higher risk of PPB between 2.7% to 6.6%[56-63] irrespective of the location of the lesion. This increased risk also translates to a higher risk of immediate/intraprocedural bleeding, reportedly 6.1% in a study by Chen *et al*[63].

***ERCP with sphincterotomy (Table 9)***

Endoscopic sphincterotomy has now become a standard intervention during ERCP for therapy of pancreaticobiliary diseases but is commonly associated with complications such as PPB. The risk of bleeding post ERCP with sphincterotomy is between 0.45%-9.9%[21,64-71]. The timing of PPB varies between studies, with Bae *et al*[69] finding that the majority of its cases (95 out 108 patients) were from immediate/intraprocedural bleeding. Similarly, Masci *et al*[21] observed a higher occurrence of immediate/ intraprocedural bleeding of 1.1%, compared to only a 0.7% rate of delayed PPB. This is in contrast to the findings from Patai *et al*[66], which found a higher occurrence of delayed PPB of 6.3%, compared to only a 2.7% rate of immediate/ intraprocedural bleeding.

***Ampullectomy (Table 10)***

Endoscopic ampullectomy allows for a minimally invasive nonsurgical intervention option for the treatment of ampullary adenomas, however is associated with significant risk of PPB between 4.9% to 30%[72-79]. The considerably high incidence of PPB of 30% observed in the study by Hopper *et al*[72] was in resections of larger sized ampullary adenomas (between 40-60 mm), but also was limited by having a small sample size of 10. Close monitoring post endoscopic ampullectomy is important.

***Endoscopic dilatation (Table 11)***

Endoscopic dilatation provides an alternative to surgical intervention, reducing morbidity and prolonging the surgery-free intervals, in patients with symptomatic gastrointestinal strictures. Data from patients with eosinophilic oesophagitis who required dilatation found that PPB was rare (0%-0.3%)[80-84].

***Colonic, enteral, and oesophageal stenting (Tables 12-14)***

Endoscopic placement of self-expandable metallic stent (SEMS), or other various types of stents, is commonly indicated in patients with gastrointestinal obstructive disease secondary to malignancy. It plays an important role in either temporary bridging to surgery, or palliative management in patients with incurable disease[85]. For endoscopic colonic SEMS placement, the risk of PPB is estimated to range from 0.3%-3.7% in several publications[85-88].

A study by Costamagna *et al*[89] reported a similar rate of PPB, compared to colonic stenting, of 3% post endoscopic duodenal stent insertion.

However, oesophageal stent insertion for oesophageal obstruction has been reported to be associated with higher risk of PPB compared to both colonic and duodenal stenting, of 1.7%-10.4% in two retrospective studies[90,91]. Liu *et al*[91] defined massive PPB, as bleeding that required > 3 units of packed red blood cells and which was complicated by haemorrhagic shock. Massive bleeding was observed in 54 out of 519 of their patients (10.4%) and was associated with fatality within 24 h. Independent risk factors contributing to an increased risk of bleeding (from highest to lowest risk) include: The presence of accompanying tracheal stent insertion, previous history of radiotherapy and oesophageal fistulae[91].

***Endoscopic cystogastrostromy (Table 15)***

Endoscopic drainage of contained pancreatic fluid collections (pseudocysts) as a result of acute or chronic pancreatitis, trauma or obstruction, is traditionally considered first-line management over surgical drainage[92-95]. Varadarajulu *et al*[96] reported no significant difference in outcomes of treatment success, complication rates, and need for re-intervention between endoscopic *vs* surgical drainage. Although there were significant benefits in the length of hospital stay post endoscopic cystogastrostomy [median stay of 2 d, compared to 6 d in the surgical group (*P* < 0.001)]. Endoscopic cystogastrostomy is however associated with a significant risk of PPB of between 2.9%-9.5%[92-97].

***Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion (Table 16)***

The endoscopic placement of percutaneous endoscopic gastrostomy (PEG)/ percutaneous endoscopic jejunostomy (PEJ) has a PPB rate of 0%-2.7%[98,99].

**ENDOSCOPIC PROCEDURES AND ITS RISK OF POST-PROCEDURE BLEEDING ACCORDING TO EACH ANTICOAGULANT AND ANTIPLATELET AGENT**

A summary of the relevant studies evaluating the bleeding risk associated with each anticoagulant and antiplatelet agent for common endoscopic procedures, is outlined in Tables 17-56.

**Acetylsalicylic acid (ASPIRIN) MONOTHERAPY**

Acetylsalicylic acid, also known as aspirin, acts by irreversibly inhibiting the cyclooxygenase 1 and 2 enzyme system, resulting in reduction of thromboxane A2 synthesis leading to inhibition of platelet aggregation[100].

Antiplatelet therapy, with aspirin, is first line for secondary prevention of ACS, non-cardioembolic ischaemic stroke and transient ischaemic attack. In a meta-analysis of randomised-controlled trials of aspirin therapy for secondary MI and stroke prevention, there was a 34% reduction in non-fatal MI and a 25% reduction in non-fatal strokes when on long-term aspirin therapy[101].

Interruption of aspirin, in cases of elective endoscopic procedures, is associated with a three-fold increased risk of cardiovascular or cerebrovascular event, with 70% of events occurring within the first 7 to 10 d of withholding antiplatelets[102]. Therefore, withholding aspirin therapy needs to be carefully considered.

***Diagnostic endoscopy and colonoscopy with biopsy (Table 17)***

Continuing aspirin monotherapy in diagnostic endoscopies and colonoscopies with biopsy is associated with an overall low risk of PPB of 0.4%-0.95% in multiple published studies[5-7,103-105]. There is minimal additive risk in continuing aspirin, as the bleeding risk in patients not using any antiplatelet agent is similar between 0.12%-0.98% (Table 1).

Continuing aspirin without interruption is considered safe in diagnostic endoscopy and colonoscopy with biopsy for patients with indication for aspirin and this recommendation concurs with previous position statements.

***EUS ± FNA (Table 18)***

The risk of PPB in EUS ± FNA while on continuous aspirin is low. In two recent studies there were no reported incidences of PPB[17,106]. In the study by Inoue *et al*[17], aspirin monotherapy was either continued, in patients considered to be at high-risk of thromboembolism secondary to drug withdrawal, or withheld 3 d before the procedure. There were no incidences of PPB in either subgroup. However, one case of immediate/intraoperative bleeding occurred in the continued aspirin group (1.6%).

Continuing aspirin in EUS ± FNA is safe and is recommended, to avoid the risk of a thromboembolic event. This concurs with previous position statements.

***Polypectomy (Table 19)***

The risk of PPB following endoscopic polypectomy in patients on aspirin monotherapyhas been considered by a number of groups, who performed randomised controlled trials (RCT). Aspirin use is associated with a three- to six-fold increased relative risk of PPB post endoscopic polypectomy[31], although the absolute risk of PPB is overall still low at 0.6%-5.5%[31,32,41]. Three other studies assessed the risk of PPB when aspirin was withheld at least 3-7 d before the procedure and the associated risk of PPB as a result, was reported to be 0.6%-4.2%[41,43].

The risk of PPB on aspirin monotherapy, either when continued or withheld before the procedure, is overall low at 0.6%-5.5%[31,32,41,43,107-109] and has a similar absolute risk of bleeding when not on any anticoagulant or antiplatelet agents of 0.05%-3.0% (Table 5). Thus, continuation in all cases is recommended. This concurs with previous position statements.

***CSP (Table 20)***

There is emerging evidence that aspirin monotherapy in CSP is safe and is not associated with an increased risk of PPB. All three studies[110-112] observed no incidences of PPB when aspirin monotherapy was continued. However, two of the studies[111,112] did observe incidences of immediate/intraprocedural bleeding, of 2.2% in the study by Won *et al*[112] to 9.8% in the study by Arimoto *et al*[111]. However, the study by Arimoto *et al*[111] failed to quantify the percentage of immediate/intraprocedural PPB cases who were on continuous aspirin compared to thienopyridine therapy. Therefore, it is unclear the exact risk of immediate bleeding on aspirin monotherapy alone. Despite this, the reported absolute risk of immediate/intraprocedural bleeding on continued aspirin monotherapy is similar to the risk when not on any anticoagulant or antiplatelet agents (2.2%-9.8% *vs* 2.4%-9.1%, respectively) (Table 6).

The bleeding risk with continued aspirin monotherapy has not been shown to significantly increase the risk of bleeding, and continuation in all cases is recommended, which is in accordance with current position statements.

***EMR (Table 21)***

Several studies have examined the effects of Aspirin monotherapy and the risk of PPB in EMR[50,113,114]. A study by Albéniz *et al*[114] prospectively assessed the incidence of PPB post EMR in patients who either continued aspirin monotherapy or had it withheld before EMR. They found that antiplatelet use, either aspirin or thienopyridine monotherapy, before EMR is associated with a two-fold increased relative risk of PPB (OR, 2.51; 95%CI, 2.14-9.63, *P* < 0.001) in lesions ≥ 20 mm. However, the study was limited by not specifying the risk of PPB associated with aspirin monotherapy only.

Another study by So *et al*[50] observed a rate of PPB of 8.2% in EMR of polyps of mean size > 30 mm when on antiplatelet monotherapy. EMR in smaller polyps of < 10 mm was only associated with a 1.35% risk of PPB per polyp resection when on antiplatelet therapy (aspirin monotherapy either continued or withheld 3 d before) in the study by Ono *et al*[113]. Once again, both studies assessed the risk of PPB in both aspirin and thienopyridine monotherapy together and so did not specify the associated risk of aspirin monotherapy alone. Despite this, the risk of PPB is comparable to the absolute risk of bleeding when not on any anticoagulant or antiplatelet agents of respective size (1.35% *vs* 1.7% in polyps ≤ 10 mmand 8.2% *vs* 6.3% in polyps ≥ 20 mm, respectively) (Table 7).

The risk of PPB with aspirin use is comparable in EMR of polyps < 10 mm[113] but the absolute risk is significantly increased in larger polyp resections ≥ 20 mm[50,114]. Continuation of aspirin monotherapy is thus recommended in EMR (< 20 mm) but should be withheld 7 d before in EMRs (≥ 20 mm). This concurs with previous position statements.

***ESD (Table 22)***

Continued aspirin monotherapy is associated with a two-fold increased risk of PPB post ESD[58], with numerous published studies reporting the risk of bleeding to be 2.0%-22.6%[56,57,59,115-119]. This is a considerable increased absolute risk of PPB compared to the risk of bleeding when not on any anticoagulant or antiplatelet agents (2.0%-22.6% *vs* 2.7%-6.6%, respectively) (Table 8).

Given the high risk of PPB in ESD, it is recommended aspirin monotherapy should be withheld 7 d before ESD. This concurs with previous position statements.

***ERCP with sphincterotomy (Table 23)***

Aspirin monotherapy in ERCP with sphincterotomy is associated with an increased risk of PPB of 1.8%-10%[66,68,120,121]. Three studies by Patai *et al*[66], Ikarashi *et al*[68], and Oh *et al*[121] continued aspirin and reported the risk of bleeding in their studies to be 5.8%, 1.8%, and 4.7%, respectively. However, the study by Onal *et al*[120] reported an incidence of PPB of 10.0% even when aspirin monotherapy was given within the last 24 h. There were no reported incidences of PPB in the study by Yamamiya *et al*[122] in either the continued or withholding aspirin 3-5 d before group.

The absolute risk of PPB with continued aspirin use is increased compared to the absolute risk of bleeding when not on any anticoagulant or antiplatelet agents in ERCP with sphincterotomy (1.8%-10% *vs* 0.3%-1.66%, respectively) (Table 9). However, the absolute risk is still low, and therefore we recommend to continue aspirin monotherapy in ERCP with sphincterotomy, but caution is recommended. This concurs with previous position statements.

***PEG/ PEJ insertion (Table 24)***

Aspirin use, whether continued or ceased before PEG/PEJ insertions, has not been shown to be associated with an increased risk of PPB. In two retrospective studies[99,123] there were no reported incidences of PPB when aspirin monotherapy was continued. However, two other studies[98,124] observed a bleeding rate of 1.7%-3.9%. The divergent results may be explained in part by case definition, where Singh *et al*[98] included GI bleeding from any source post PEG insertion (as opposed to bleeding confirmed as caused by PEG insertion).

The absolute risk of PPB post PEG/PEJ insertion on continued aspirin monotherapy is comparable to the overall risk of bleeding when not on any anticoagulant or antiplatelet agents (1.7%-3.9% *vs* 2.7%, respectively) (Table 16). Thus, the overall bleeding risk is low and continuation of aspirin monotherapy in all cases is recommended. This concurs with previous position statements.

**P2Y12 RECEPTOR ANTAGONIST/THIENOPYRIDINE (CLOPIDOGREL, PRASUGREL, TICAGRELOR) MONOTHERAPY**

P2Y12 receptor antagonists includes clopidogrel, ticagrelor and prasugrel. Both clopidogrel and prasugrel are thienopyridines, an active metabolite that irreversibly binds to the P2Y12 receptor and prevents activation of the GPIIb/IIIa receptor, thereby inhibiting platelet aggregation[100]. Platelet aggregation is affected for the life of the platelet. Platelet function returns to baseline 5 to 7 d after withdrawal of clopidogrel. Ticagrelor is a different class of agent that also binds to the P2Y12 receptor but is reversible.

***Diagnostic endoscopy and colonoscopy with biopsy (Table 25)***

Continued thienopyridine monotherapy is considered safe in endoscopic biopsies. In several published studies there were no reported incidences of bleeding[5-7,103-105].

Continued thienopyridine monotherapy is recommended in all cases and this concurs with previous position statements.

***EUS ± FNA (Table 26)***

Data pertaining to PPB secondary to EUS/FNA in patient where thienopyridines are continued is limited. However, two studies from Japan[17,106] assessed the risk of bleeding on thienopyridine monotherapy when withheld 5 d before EUS ± FNA. Both studies did not observe any incidences of PPB. This is compared to an absolute risk of PPB between 2.1%-4.3% reported when not on any anticoagulant or antiplatelet agents (Table 3).

Given the current lack of high-quality evidence assessing the safety of EUS ± FNA on continued thienopyridine, and the moderate risk of PPB associated with EUS ± FNA irrespective of anticoagulant or antiplatelet use, withholding of thienopyridine 5-7 d before is recommended in all cases. This concurs with previous position statements.

***Polypectomy (Table 27)***

The risk of PPB attributed with conventional polypectomy while on thienopyridine has been considered in numerous comparative studies, where the agent was ceased 5-7 d pre-procedure in the control arm. Four studies[28,107,125,126] assessing the risk of PPB on continued thienopyridine reported PPB in 2.4%-3.8%.

Continued thienopyridine is associated with a significant increased risk of immediate/intraprocedural bleeding. The study by Feagins *et al*[125] observed an incidence of immediate bleeding of 7.3%, compared to only 4.7% in their control group. This was a similar finding in a recent RCT by Chan *et al*[126], which reported the risk of immediate bleeding to be 8.5% when on continued thienopyridine, compared to only 5.5% in their control group.

Five other studies[41,107-109,127] looked at the risk of PPB when thienopyridine was withheld 5-7 d before endoscopic polypectomy. They reported a rate of PPB between 0.6%-6.7%. Although the associated risk of PPB is still higher than when not on any anticoagulant or antiplatelet agents, this would be considered safer practice than continuing thienopyridine monotherapy.

The absolute risk of PPB while on thienopyridine, either when continued or when withheld 5-7 d before, is slightly increased compared to the rate of bleeding when not on any anticoagulant or antiplatelet agents (0.6%-6.7% *vs* 0.05%-3%, respectively) (Table 6).

As highlighted, there is emerging evidence to suggest the risk of delayed PPB is not greatly increased while on continued thienopyridine monotherapy, however given the associated high risk of immediate/intraprocedural bleeding, temporary cessation between 5-7 d before is recommended. This concurs with previous position statements.

***CSP (Table 28)***

There is emerging evidence to suggest that thienopyridine monotherapy may be safely continued in CSP for polyps ≤ 10 mm. Two studies[110,111] reported no incidences of PPB after CSP while on continued thienopyridine monotherapy. However, both studies were small retrospective studies. Larger, RCTs, are still required before this could be safely recommended as standard practice.

Given the current paucity of high-quality evidence, withholding thienopyridine 5-7 d before CSP is recommended and concurs with previous position statements. However, with larger studies evaluating the safety of continued thienopyridine monotherapy in CSP, amendments to future position statements may be indicated.

***EMR (Table 29)***

The impact of thienopyridine monotherapy and the associated risk of PPB in EMR has not been directly evaluated in published studies. As per with aspirin monotherapy, the same three studies[50,113,114] examined the incidence of PPB associated with both aspirin and thienopyridine monotherapy, generally withheld 3-5 d before, in the same group (antiplatelet group). Therefore, determining the direct impact of thienopyridine monotherapy can only be estimated.

Albéniz *et al*[114] found that antiplatelet use, either aspirin or thienopyridine monotherapy, before EMR is associated with a two-fold increased relative risk of PPB (OR, 2.51; 95%CI, 2.14-9.63, *P* < 0.001) in lesions ≥ 20 mm. Another study by So *et al*[50] observed a rate of PPB of 8.2% in EMR of polyps of mean size > 30 mm when on either aspirin or thienopyridine monotherapy.

However, the risk of PPB in EMR for smaller polyps of < 10 mm, although still associated with an increased bleeding risk, is not as high when compared to larger polyp resections (≥ 20 mm). The study by Ono *et al*[113] reported a 1.35% risk of PPB per polyp resection when on either aspirin or thienopyridine monotherapy.

Overall, the absolute risk of PPB is increased in thienopyridine use, particularly in lesions ≥ 20 mm in size, compared to the risk of bleeding when not on any anticoagulant or antiplatelet agents, of respective size (1.35%-8.2% *vs* 1.7%-6.3%, respectively) (Table 7).

Given the increased absolute risk of PPB associated with thienopyridine use, withholding thienopyridine monotherapy 5-7 d before is recommended in all cases. This concurs with previous position statements.

***ESD (Table 30)***

Thienopyridine monotherapy is associated with a four-fold increased relative risk of PPB (OR, 4.26, 95%CI, 1.36-13.29, *P* = 0.13)[116] in ESD, with a reported incidence of 3.6%-19.4%[56,57,116,118] even when withheld 5-7 d before.

It is apparent that withholding thienopyridine monotherapy for an extended period of time is required to decrease PPB risk. A study by Oh *et al*[116] compared the risk of bleeding when thienopyridines were withheld at either 0-4 d or 5-7 d before EMR. The two patients in the study who developed PPB (3.6%) both had their thienopyridine ceased on the day of the EMR procedure.

Another study by Igarashi *et al*[56] also assessed the risk of PPB when thienopyridine was withheld on the day of the procedure and found the risk of bleeding to be 5.6%.

Ono *et al*[128] observed the risk of PPB in patients on dual antiplatelet therapy (DAPT) undergoing an ESD, who had aspirin ceased but thienopyridine monotherapy continued. The observed rate of PPB reported was 20%.

The absolute risk of PPB in ESD is high irrespective of whether thienopyridines monotherapy is continued or withheld 5-7 d before the procedure and compared to when not on any anticoagulant or antiplatelet agent (5.6%-20% *vs* 2.7%-6.6%, respectively) (Table 8). In all circumstances, thienopyridine monotherapy should not be continued and withheld 5-7 d before. This concurs with previous position statements.

***ERCP with sphincterotomy (Table 31)***

There are currently limited studies evaluating the risk of PPB associated with thienopyridine use in ERCP with sphincterotomy. One study by Patai *et al*[66] assessed the risk of bleeding on continued thienopyridine and found the incidence of immediate/intraprocedural and delayed PPB to both be at 3.5%.

However, when thienopyridine is withheld 5-7 d before ERCP with sphincterotomy, the risk of bleeding is lower and found to be only 3.0% in one study by Ikarashi *et al*[68] This study was limited by analysing the risk of bleeding associated with thienopyridine, warfarin and DOAC use together. It did not directly analyse the risk thienopyridine has on PPB alone. Another study by Yamamiya *et al*[122] did not observe any incidence of PPB in their study in patients on thienopyridine.

There is an increased absolute risk of PPB with thienopyridine use, when withheld 5-7 d before, compared to when not on any anticoagulant or antiplatelet agents (0%-3% *vs* 0.3%-1.66%, respectively) (Table 9).

Given the increased absolute risk and the current limited evidence on the safety on continuation thienopyridine and risk of bleeding post ERCP, it is recommended that thienopyridines should be withheld 5-7 d before the procedure. This concurs with previous position statements.

***PEG/PEJ insertion (Table 32)***

The estimated risk of PPB post endoscopic PEG/PEJ insertion associated with thienopyridine use, and when withheld 1-3 d before, is reported to be 0%-2.1% in several published studies[99].

The study by Richter *et al*[124] evaluated the associated risk of PPB when thienopyridine monotherapy was continued. It reported a bleeding rate of 4%.

The absolute risk of PPB with thienopyridine use, when continued or withheld before, is increased when compared with the risk of bleeding in patients not on any anticoagulant or antiplatelet agents (2.1%-4% *vs* 2.7%, respectively) (Table 16).

Given the increased absolute risk of PPB when thienopyridine monotherapy is continued, it is recommended that thienopyridine should be withheld 5-7 d before PEG/PEJ insertion. This concurs with previous position statements.

**DAPT**

DAPT of aspirin plus a P2Y12 receptor antagonist (thienopyridine) is most commonly indicated for the management of ACS. In percutaneous coronary intervention (PCI), such as drug eluding stent (DES) or bare metal stent (BMS) insertion, indication to remain on DAPT for a given period is paramount in order to prevent stent thrombosis. The current Cardiac Society of Australia and New Zealand (CSANZ) guidelines[129] on DAPT duration post PCI, recommends patients should remain on DAPT for 12 mo. Risk of stent thrombosis increases after 5 d without antiplatelet therapy with an approximate risk of 40% for MI and death[2]. Emerging evidence that prolonged therapy of up to 3 years for patients with prior MI demonstrates a relative reduction in cardiovascular death (RR: 0.85, 95%CI: 0.74-0.98), and recurrent MI (RR: 0.70, 95%CI: 0.55-0.88). However, there is an associated increase incidence of bleeding events (RR: 1.73, 95%CI: 1.19-2.50) with no improvement in non-cardiovascular death or overall mortality[129]. In patients with a high bleeding risk and low risk for recurrent ischaemic events, a shorter duration of treatment such as 6 mo could be considered, but not ideal. The minimum duration of uninterrupted DAPT should be at least 30 d for BMS, and 3 mo for DES.

***Diagnostic endoscopy and colonoscopy with biopsy (Table 33)***

Continued DAPT in endoscopic biopsy has an overall low risk of bleeding. Three studies[7,104,105] reported no incidences of PPB post biopsy. While the study by Ara *et al*[6] only reported one episode of bleeding post biopsies while on continued DAPT (0.35%). This absolute risk on continued DAPT is comparable to the reported risk of PPB without anticoagulant or antiplatelet agents (0.35% *vs* 0.12%-0.98%) (Table 1).

Overall, DAPT is considered safe and is recommended to be continued in all cases. This concurs with previous position statements.

***EUS ± FNA (Table 34)***

There is currently a scarcity of evidence evaluating the risk of PPB in DAPT users undergoing EUS ± FNA. Although a study by Kawakubo *et al*[106] reported of risk of PPB of 3.6% in patients undergoing EUS ± FNA, when thienopyridine was withheld 5 d before and bridged with aspirin monotherapy, in patients initially on DAPT. This is comparable to the absolute risk of PPB of 2.1%-4.3% when not on any anticoagulant or antiplatelet agents (Table 3).

Given the limited evidence regarding the safety of continued DAPT, it is recommended that thienopyridine should withheld 5-7 d before with bridging aspirin monotherapy (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

***Polypectomy (Table 35)***

The risk of PPB is reportedly significantly increased in patients on continued DAPT undertaking endoscopic polypectomy. A study by Singh *et al*[28] reported a three-fold increased relative risk of PPB when DAPT is continued (OR: 3.69; 95%CI, 1.60-8.52, *P* = 0.002), with the rate of PPB on continuation DAPT between 0.85%-6%, as found in several published studies[28,30,41,109].

The study by Kishida *et al*[41] considered the risk of bleeding when either, both aspirin and thienopyridine were withheld (before 2012), or only thienopyridine withheld and bridged with aspirin monotherapy. In this study, the incidence of PPB was reported to be 1.8%.

The absolute risk of PPB post polypectomy with withholding thienopyridine and bridging with aspirin monotherapy is comparable to the overall risk of PPB when not on any anticoagulant or antiplatelet agents (1.8% *vs* 0.05%-3.0%, respectively) (Table 5).

Given the high risk of bleeding complications on continued DAPT, it is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

***CSP (Table 36)***

In CSP, there is emerging evidence to suggest the risk on continued DAPT is overall low and estimated to be only around 2.4% in a recent RCT by Won *et al*[112]. However, this study was limited by a small sample size of total 91 patients, and larger, RCTs, are still required before this could be safely recommended as standard practice.

In a retrospective study by Arimoto *et al*[111], they reported no incidences of PPB in their DAPT group. Despite this, uninterrupted DAPT appears to be associated with a significant increased risk of immediate/intraprocedural bleeding between 4.8%-17.8%[111,112]. This is significantly higher compared to the reported rates of immediate/intraprocedural bleeding when not on any anticoagulant or antiplatelet agents (2.4%-9.1%, Table 6).

Given the current paucity in high-quality evidence and significant increased risk of immediate/intraprocedural bleeding, withholding thienopyridine 5-7 d before and bridging with aspirin monotherapy is recommended in CSP (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

***EMR (Table 37)***

Two recent studies[50,113] retrospectively assessed the indirect effects of DAPT use, when thienopyridine was withheld and bridged with aspirin monotherapy before EMR. The study by Makino *et al*[110] observed a risk of PPB per polyp resection of 1.35% when on antiplatelet therapy (monotherapy or DAPT). However, this study was limited by not quantifying the exact risk of PPB on DAPT alone.

Another study by So *et al*[50] found DAPT use was associated with a two-fold increased relative risk of bleeding (OR: 2.14; 95%CI, 0.63-7.32, *P* = 0.226) in lesions ≥ 20 mm, with a reported incidence of PPB of 12.3% post EMR.

The relative and absolute risk of PPB with DAPT is higher compared to the risk of bleeding when not on anticoagulant or antiplatelet agents (1.35%-12.3% *vs* 1.7%-6.3%, respectively) (Table 7).

The risk of PPB associated with DAPT use in EMR is considerably high and precautions should be made to reduce this risk. In lesions < 20 mm, withholding thienopyridine 5-7 d before and bridging with aspirin monotherapy is recommended (unless contraindicated). In lesions ≥ 20 mm withholding both thienopyridine and aspirin is the safest recommendation with regards to bleeding risk.

If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

***ESD (Table 38)***

The absolute risk of PPB in ESD for patients not on anticoagulant or antiplatelet agents is high (2.7%-6.6%, Table 8). DAPT use before ESD is associated with a reported two- to three-fold increased relative risk of bleeding in two studies[116,117], even after withholding thienopyridine 5-7 d before and bridged with aspirin monotherapy only. The study by Sato *et al*[57] found that DAPT use was a significant independent risk factor for PPB than what was reported in the two other studies (OR: 10.33, 95%CI, 6.06-17.59, *P* < 0.001).

Several studies have reported the absolute risk of bleeding post ESD to be 23.1%-67.7%[57,58,116,117]. In the study by Harada *et al*[117] they compared the risk of bleeding with bridging aspirin monotherapy *vs* discontinuation of both thienopyridine and aspirin > 5 d before the procedure, with the reported incidence of PPB in this study, 23.1% and 5.0%, respectively.

Continuing DAPT in ESD is not recommended given the significant increased risk of PPB. Withholding both thienopyridine and aspirin is the safest recommendation with regards to bleeding risk. However, if this cannot be undertaken due to risk of thromboembolism, then withholding thienopyridine 5-7 d before procedure and switching to bridging aspirin monotherapy is otherwise recommended (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

***ERCP with sphincterotomy (Table 39)***

There have been limited published studies assessing the risk of bleeding with DAPT in ERCP with sphincterotomy. Two studies by Mok *et al*[130] and Yamamiya *et al*[122] analysed the incidence of bleeding when DAPT was continued and reported an absolute risk of PPB of 0%-3.6%. This compares to an overall risk of PPB of 0.45%-9.9% in patients not on any anticoagulant or antiplatelet agents (Table 9).

These two studies may suggest that continued DAPT in ERCP with sphincterotomy may be safe. However, evidence is limited due to a lack of large, high-quality studies. For now, it is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy only (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements. This concurs with previous position statements.

***PEG*/*PEJ insertion (Table 40)***

Several studies have found DAPT use to be associated with a 2.5% absolute risk of PPB post PEG/PEJ insertion[98,123]. The study by Lee *et al*[123] ceased DAPT at least 4 d (range 4-10 d) before the PEG procedure. Whereas, the study by Singh *et al*[98] did not clearly specify the DAPT management regime. In the study by Lozoya-González *et al*[99] there were no reported incidences of PPB in any of their patients on DAPT, which was ceased 1-3 d before the PEG procedure. The absolute risk of PPB while on DAPT is comparable to the overall risk of PPB in patients not using anticoagulant or antiplatelet agents (2.5% *vs* 2.7%, respectively) (Table 16).

Given current studies have only evaluated the risk of bleeding when DAPT is ceased before a PEG procedure and which have yielded similar rates of PPB in the absence of anticoagulant or antiplatelet agents. It is recommended that thienopyridine is withheld 5-7 d before and bridged with aspirin monotherapy only (unless contraindicated). If thienopyridine cannot be safely withheld due to contraindications, in the example of a recent PCI insertion within 12 mo, then the procedure should be postponed until it is safe to do so, if possible. This concurs with previous position statements.

**VITAMIN K ANTAGONIST (WARFARIN)**

Warfarin is a vitamin K antagonist, which inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and S[100]. The duration of action of warfarin is 5 d. Current evidence supports the shifting trend that DOACs are more efficacious and safer than warfarin[131]. Furthermore, warfarin needs to be withheld for a longer period and generally HBT is required, further increasing the risk of PPB and the hospitalisation period[132].

Despite the rise in DOAC use, warfarin is still commonly encountered in certain conditions such as mechanical heart valve prosthesis, AF with mitral stenosis, and CKD patients where DOACs are contraindicated. Thus, its management in peri-endoscopic period is still very relevant.

***Diagnostic endoscopy and colonoscopy with biopsy (Table 41)***

Continuation of Warfarin therapy in diagnostic endoscopies and colonoscopies with biopsy is considered safe and overall is not associated with an increased risk of gastrointestinal bleeding. Four prospective and one retrospective study did not report any incidences of PPB while on continued warfarin monotherapy[6,7,104,105].

The study by Kono *et al*[105] observed PPB in one case on continued warfarin, however this patient was also on an antiplatelet agent that would have increased the overall risk of bleeding significantly. In this case, endoscopic haemostasis was required with a good clinical outcome.

Overall, continuing warfarin therapy is considered safe in endoscopic biopsies in all cases. This concurs with previous position statements.

***EUS ± FNA (Table 42)***

Withholding warfarin at least 4 d before EUS ± FNA without HBT does not appear to increase the risk of PPB compared to the absolute risk of bleeding when not on any anticoagulant or antiplatelet agent (0%-4% *vs* 2.1%-4.3%, respectively) (Table 3).

The study by Inoue *et al*[17] found no incidences of PPB in their cohort of patients who had warfarin ceased 4 d before EUS ± FNA. However, HBT was found to be associated with an increased risk of bleeding without reducing the risk of thromboembolic event related to warfarin interruptionin the study by Kawakubo *et al*[106]. In this study there was one case (4%) of PPB in a patient on HBT after EUS ± FNA. There were no reported PPB in the warfarin cessation without HBT group, and no thromboembolic events occurred in either the warfarin cessation or HBT group.

We recommend withholding warfarin 5 d before EUS ± FNA based on current evidence available. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

***Polypectomy (Table 43)***

Warfarin use is associated with a high-risk of PPB in endoscopic polypectomy, irrespective of whether warfarin is withheld with or without HBT before the procedure. The study by Horiuchi *et al*[133] reported a 14% risk of PPB with continued warfarin use. However, when warfarin is withheld 3-5 d before the procedure, the absolute risk of bleeding is reported to be 0.7%-13.5%, according to several studies[1,41,107,108,127].

HBT is indicated in patients with high-thromboembolic risk patients as per current guidelines[2-4]. However, HBT has been shown to be associated with higher risk of bleeding without significantly reducing the risk of a thromboembolic event. A study by Yanagisawa *et al*[1] compared the risk of PPB and thromboembolic event in its analysis and found withholding warfarin with HBT, compared to withholding warfarin without HBT, yielded a higher rate of PPB (21.7% *vs* 13.7%, respectively) without providing significant difference in the prevention of a thromboembolic event. Two cases of a thromboembolic event were reported in this study. However, this occurred in both groups, one in the HBT group and the other in the withholding warfarin without HBT.

Another study by Lin *et al*[107] also associated HBT with a ten-fold increased relative risk of PPB in their cohort (OR: 10.3, *P* = 0.0001), with the incidence of bleeding on HBT reported at 14.9% compared to only 0.7% in the warfarin discontinuation without HBT. Similarly, there was no differences in the rate of thromboembolic event in both groups. No thromboembolic events occurred in the study.

Warfarin use is associated with an absolute increased risk of bleeding in endoscopic polypectomies irrespective of whether warfarin is withheld. The risk of bleeding while on warfarin, even when withheld 3-5 d before polypectomy, compared to not being on any anticoagulant or antiplatelet agent is significantly increased (0.7%-13.5% *vs* 0.05%-3.0%, respectively) (Table 5). Emerging evidence also suggests that HBT is associated with a significantly increased risk of PPB without reducing the risk of thromboembolic event in high-risk patients.

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before the procedure. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

***CSP (Table 44)***

There is emerging evidence that continuing warfarin therapy in CSP for polyps ≤ 10 mm does not increase the risk of PPB. It is theorised the reason for bleeding after polypectomy is due to submucosal vessel damage from electrocautery. CSP does not involve electrocautery and may decrease the risk of bleeding[133].

Three recent studies looking at the bleeding risk without warfarin cessation uniformly reported no incidences of PPB[110,111,133]. However, there is an associated increased risk of immediate/intraprocedural bleeding when on continued warfarin of 5.7%-9.8%[111,133].

Given the current lack of high-quality evidence evaluating the safety with continuing warfarin in CSP, withholding warfarin 5 d before should still be practiced. This concurs with previous position statements. However, with larger studies evaluating the safety of continued warfarin therapy in CSP being currently undertaken, amendments to future position statements may be needed.

***EMR (Table 45)***

Warfarin use in EMR is associated with over a four-fold increased relative risk of bleeding (OR: 4.54, 95%CI, 2.14-9.63, *P* < 0.001)[114]. The rate of PPB on warfarin therapy when ceased at least 3-5 d before EMR is between 10%-16.7%, as reported in two retrospective studies[50,113]. This represents an increased absolute risk of bleeding on warfarin therapy compared to the risk when not on any anticoagulant or antiplatelet agents (10%-16.7% *vs* 0%-1.7%, respectively) (Table 7).

This risk of bleeding is further increased with concurrent HBT use. HBT is considered to be a significant risk factor for PPB (OR: 5.00, 95%CI, 1.11-22.50, *P* = 0.036)[50]. From several small studies, the overall risk of PPB is significantly increased when on HBT in EMR, reported to be 9.8%-35.7%[50,113,134,135].

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before EMRs. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

***ESD (Table 46)***

The risk of PPB in warfarin users in ESD is reported to be 3.2%-10.0% when withheld 3-5 d before the procedure[56-58,115,118]. This is similar to the absolute risk of PPB without anticoagulant or antiplatelet agents (3.2%-10% *vs* 2.7%-6.6%, respectively) (Table 8). HBT continues to be a significant independent risk factor for PPB with a four- to ten-fold increased relative risk of bleeding as estimated in some studies[57,115,132], with a reported incidence of PPB of 10.8%-31.6%[56,57,115,132,136].

Continuing warfarin, as an alternative to HBT, was assessed in two studies[61,136] and was found to have similar risk of PPB compared to when warfarin is withheld 3-5 d before the procedure (7.7%-9.1%*vs* 3.2%-10.0%, respectively). It has been suggested that continuation of warfarin may be a safer alternative to HBT in patients of high-risk of thromboembolism. However, further larger studies are required before this can be safely recommended.

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before ESD. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

***ERCP with sphincterotomy (Table 47)***

Warfarin is associated with a high risk of PPB in ERCP with sphincterotomy. Three studies analysing the incidence of PPB while withholding warfarin with HBT reported a bleeding rate of 4.0%-8.0%[68,137,138]. The study by Muro *et al*[138] reported the risk of bleeding on continued warfarin was slightly higher at 8.3%. This compares to an overall risk of PPB of 0.45%-9.9% in patients not using anticoagulant or antiplatelet agents (Table 9).

Continuing warfarin and/or withholding warfarin with HBT is associated with an overall high-risk of PPB in ERCP with sphincterotomy. To minimise the risk of PPB, it is recommended that warfarin be discontinued 5 d before ERCP with sphincterotomy. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

***PEG/PEJ insertion (Table 48)***

Use of warfarin in PEG/PEJ insertion is a significant independent risk factor for PPB (OR: 7.26, 95%CI, 2.23-23.68, *P* = 0.001)[123]. The study by Singh *et al*[98] reported an incidence of PPB of 5.4% in the group who had warfarin withheld without HBT, and the absolute risk increases to 7.9% with HBT. However, the study by Lozoya-González *et al*[99] reported no incidences of PPB in either group.

Warfarin is a well-established risk factor for bleeding in PEG/PEJ insertion compared to the absolute risk of PPB without anticoagulant or antiplatelet agents is (5.4%-7.9% *vs* 2.7%, respectively) (Table 16).

To minimise the risk of PPB, it is recommended that warfarin be withheld 5 d before the procedure. HBT is associated with increased risk of bleeding and should be considered carefully in patients. Our recommendation of avoiding HBT in patients who are at high-risk of thromboembolic event differs from previous position statements.

**DOAC/(DABIGATRAN, RIVAROXABAN AND APIXABAN)**

DOAC is a collective term for direct thrombin inhibitors (dabigatran) and other direct factor Xa inhibitors (rivaroxaban and apixaban)[139-141]. DOACs offer an alternative to warfarin in management of patients with AF and VTE. More recently DOACs have replaced warfarin as the preferred first line therapy of choice, due its noninferiority at low doses (dabigatran 110 mg BD, rivaroxaban 20 mg daily, apixaban 2.5 mg BD), but superiority at higher doses (dabigatran 150 mg BD, apixaban 5 mg BD), over warfarin in prevention of stroke and thromboembolic events, without increasing the risk of major bleeding in patients with nonvalvular AF[139-141]. DOACs also have other significant logistical benefits over warfarin. Unlike warfarin, DOACs have set doses which do not require regular monitoring with international normalisation ratio blood tests. Due to their shorter half-lives, they also have a faster onset and offset of action compared to warfarin. However, both dabigatran at high dose (150 mg BD) and rivaroxaban are associated with higher rates of gastrointestinal bleeds compared to warfarin[139,140], and reversibility currently remains a significant safety concern with DOACs. Only dabigatran currently has an available antidote in idarucizumab. This is expected to change with ongoing trials and emerging evidence of antidotes for the other DOACs.

Optimal timing of DOAC cessation should take into consideration the time of maximum effect, half-life and the excretion of the agent. To minimise the risk of PPB, DOACs should be stopped for at least 2 half-lives in all high-risk endoscopic procedures[3]. Both rivaroxaban and apixaban have a relatively short time to maximum effect (2-4 h for rivaroxaban and 1-3 h for apixaban). Rivaroxaban has a half-life between 8-9 h [creatinine clearance (CrCl) > 50 mL/min] and 9-13 h (CrCl > 30-50 mL/min), with 66% of the agent excreted by the kidneys. Whereas apixaban has a half-life between 7-8 h (CrCl > 50 mL/min) and 8-15 h (CrCl 30-50 mL/min), with 25% excreted by the kidneys. Dabigatran was the first DOAC and has a time of maximum effect of 1.25-3 h and its half-life is between 12-14 h (CrCl ≥ 80 mL/min) to 22-35 h (CrCl < 30 mL/min). More cautious peri-endoscopic management is required for dabigatran as the timing of discontinuation is mostly dictated by the patient’s CrCl with 80% of the agent excreted by the kidneys[3].

***Diagnostic endoscopy and colonoscopy with biopsy (Table 49)***

There has been no documented increased risk of PPB in endoscopic biopsies while on continued DOAC therapy from several published studies. Four studies all observed no incidences of bleeding post biopsy in their continued DOAC group[5-7,105]. This is compared to an already established low risk of PPB when not on any anticoagulant or antiplatelet agents (0.12%-0.98%, Table 1).

DOAC is considered safe to be continued in endoscopic biopsy procedures in all cases. This concurs with previous position statements.

***EUS ± FNA (Table 50)***

There is currently a paucity of large studies analysing the risk of bleeding while on DOAC therapy in EUS ± FNA. Only one study by Kawakubo *et al*[106] analysed the PPB risk when DOAC therapy was withheld 48 h before the procedure with HBT. There were no reported incidences of bleeding in this study. The absolute risk of PPB in EUS ± FNA is reported to be 2.1%-4.3% when not on any anticoagulant or antiplatelet agent (Table 3).

Given the absolute risk of bleeding while on no anticoagulant or antiplatelet agents is considerable and there is currently limited evidence of the bleeding risk with DOAC use, it is still recommended that DOACs should be withheld at least 48 h before. This concurs with previous position statements.

***Polypectomy (Table 51)***

DOAC use in polypectomy is associated with a significant increased relative risk of PPB (OR: 17.8, *P* < 0.001) as reported in the study by Yanagisaw *et al*[1]. In this study, the incidence of bleeding in their DOAC group, when DOAC therapy is withheld 24-48 h before the procedure, was 13.8%. The rates of bleeding were similar amongst the different DOAC classes, of dabigatran, rivaroxaban and apixaban, with reported rates of 11.1%, 13.2% and 13.3%, respectively. Another study by Beppu *et al*[134] also observed DOAC use was associated with a ten-fold increased relative risk of bleeding (OR: 10.2, 95%CI, 2.7-38.3, *P* = 0.0006).

In several other studies that withheld DOAC therapy 24-48 h before the procedure (median 5 d in one study[108]), reported an overall incidence of bleeding of 0.6%-13.8%[1,41,108,127]. However, both the study by Kishida *et al*[41] and Amato *et al*[108] analysed the risk of bleeding when on either DOAC or warfarin therapy together and not as separate agents. This limits the accuracy of the direct effect DOAC therapy has on the risk of bleeding, however regardless, it can be interpreted that DOACs are associated with a significant increased risk.

DOAC use represents a significant increased absolute risk of bleeding compared to when not on any anticoagulant or antiplatelet agents (0.6%-13.8% *vs* 0.05%-3.0%, respectively) (Table 5). It is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl >50) before polypectomy to minimise the risk of bleeding. This concurs with previous position statements.

***CSP (Table 52)***

Similar with warfarin, there is emerging evidence from small studies that suggest continuation of DOAC therapy in CSP of polyps ≤ 10 mm is considered safe and does not significantly increase the risk of bleeding[110,111]. This is due to the hypothesis that there is minimal damage to the submucosal vessel in CSP because electrocautery is not involved[133].

The study by Makino *et al*[110] only observed two cases of bleeding post CSP (1.2%). One patient was on dabigatran and the other patient was on apixaban. In the study by Arimoto *et al*[111] there were no reported incidences of PPB. However, this study did report complications of immediate/intraprocedural bleeding in 11.9% of cases. All cases were adequately controlled with endoscopic haemostasis and did not require further intervention with blood transfusion, admission, and/or surgery.

Although emerging evidence suggests continued DOAC therapy may be safe in CSP of polyps ≤ 10 mm, until larger studies evaluating the safety of continued DOAC therapy in CSP is undertaken, it is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) before CSP to minimise the risk of bleeding. This concurs with previous position statements.

***EMR (Table 53)***

Most published studies analysing the risk of PPB in EMR in DOAC users have done so by grouping both warfarin and DOAC monotherapy use together under the umbrella term of “anticoagulant.” The risk of bleeding in EMR while on anticoagulant therapy (either warfarin or DOAC) is reported between 5.5%-16.7%[50,113].

However, the risk of bleeding with DOAC use may be overall lower compared to warfarin therapy. In the study by Ono *et al*[113], the risk of bleeding when DOAC has been withheld one day before EMR was reported to be only 6.5% per polyp. While another study by Fujita *et al*[135] observed an incidence of 2.3% of PPB in their DOAC group when ceased the morning of EMR.

There is currently limited evidence analysing the risk of bleeding on continued DOAC therapy in EMR. Given this paucity of evidence and to minimise the risk of PPB, it is recommended that DOAC therapy should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) before EMR. This concurs with previous position statements.

***ESD (Table 54)***

ESD in patients on DOAC is associated with an elevated relative risk of PPB, despite withholding therapy at least > 24 h before, compared to when on no anticoagulant or antiplatelet agents in multiple publications[56-58,60,61,132]. The absolute risk of bleeding is, 5.6%-45.5% *vs* 2.7%-6.6%, respectively (Table 8). There have been no studies reporting the rate of PPB on continued DOAC therapy.

The study by Yoshio *et al*[132] reported PPB in five cases on DOAC therapy (45.5%). All five cases were in patients on rivaroxaban. There were no observed cases of PPB in the dabigatran or apixaban group.

HBT is generally not recommended when withholding DOAC therapy, however the study by Kono *et al*[58] analysed the risk of bleeding with HBT during both DOAC and warfarin interruption and observed an incidence of PPB in 29% of cases.

Given the high risk of PPB in ESD procedure associated with DOAC therapy, it is recommended that DOACs should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT in order to minimise the risk of bleeding. This concurs with previous position statements.

***ERCP with sphincterotomy (Table 55)***

Two recent small retrospective studies analysing continued DOAC therapy in ERCP with sphincterotomy reported no incidences of PPB in their studies[122,138]. The risk of bleeding when DOAC therapy was withheld with HBT was also compared in the study by Muro *et al*[138] and found that HBT was a significant risk factor for bleeding. The incidence of PPB in this study was reported in 6.5% of cases. This absolute risk of bleeding when DOAC therapy is withheld compares to the overall risk when not on any anticoagulant or antiplatelet agents (6.5% *vs* 0.45%-9.9%, respectively) (Table 9).

These two small studies may suggest that continued DOAC in ERCP with sphincterotomy may be safe. However, until larger, randomised controlled studies adequately evaluate the risk of bleeding it is still recommended that DOACs be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT before ERCP with sphincterotomy to minimise the risk of bleeding. This concurs with previous position statements.

***PEG/PEJ insertion (Table 56)***

Limited data is available that considers the risk of PPB in PEG/PEJ insertion while on DOAC therapy. One study by Lee *et al*[123] evaluated the risk of bleeding while on either warfarin or DOAC monotherapy. It observed a seven-fold increased relative risk of PPB associated with warfarin or DOAC use (OR: 7.26, 95%CI, 2.23-23.68, *P* = 0.001). However, this study was limited by not specifying the bleeding risk directly related to DOAC therapy use, nor did it specify whether DOAC therapy was continued or withheld before the procedure.

Given the significant increased risk of PPB when on anticoagulant therapy and limited data considering DOAC use, in this context it is recommended that DOACs should be withheld at least 24-48 h (72 h for dabigatran; in CrCl > 50) without HBT. This concurs with previous position statements.

**DISCUSSION**

The current position statements and guidelines from the major gastroenterology societies have provided endoscopists with evidenced-based systematic approaches to pre, peri and post-operative management of patients on anticoagulant and antiplatelet agents in the context of both low and high-risk endoscopic procedures. While there has been sufficient evidence on the index risk of bleeding in common endoscopic procedures in the absence of anticoagulant and/or antiplatelet use, the evidence surrounding bleeding risk while on anticoagulant and/or antiplatelet agents is still evolving.

It is well established that anticoagulant and antiplatelet therapy is associated with an increased risk of PPB in endoscopic procedures. The reported risk will vary depending on endoscopic procedure and the study in which the data was published, but overall, the rate is similar over various publications and has been emphasised in this review. This variability may be explained by the different approaches taken by each study, the patient and geographical demographics, and the technical competency of the proceduralists.

There is no doubt temporary interruption of anticoagulant and antiplatelet therapy, compared to continuation therapy, reduces the risk of PPB in endoscopic procedures. However, this needs to be carefully considered against the risk of thromboembolic event and the potential serious irreversible consequences that comes with anticoagulant and antiplatelet interruption. Careful timing of anticoagulant and antiplatelet interruption to minimise the risk of PPB, while avoiding unnecessary increased risk of thromboembolic event, is of utmost importance. The aim of this review is to provide an evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of both low and high-risk endoscopic procedures for all endoscopists, as outlined in Figures 1 and 2.

This article has reviewed and considered the last 10 years of originally published literature and has found the evidence largely agrees with the current position statements and guidelines from the major gastroenterology societies in anticoagulant and antiplatelet agent management in endoscopic procedures. However, as highlighted earlier, there is emerging evidence that calls attention to some discrepancies in the current recommendations.

For example, current position statements and guidelines[2-4] advise warfarin should be bridged with HBT in all patients with high risk of thromboembolic event undergoing high-risk endoscopic procedures. Peri-endoscopic management with HBT is now becoming a controversial management decision with regards to its efficacy and safety. Numerous studies highlighted in this review have demonstrated that the use of HBT is associated with a 2- to 3-fold increased risk of PPB[7,41,142], while being non-superior in thromboembolic event prevention, compared to warfarin cessation without HBT[1,107,143,144]. This heightened risk of PPB associated with HBT has been shown in a range of endoscopic procedures, including EMR, ESD, polypectomy, EUS ± FNA and ERCP with sphincterotomy. However, this is still emerging evidence and further larger studies directly looking at the safety of HBT compared to warfarin cessation without HBT, specifically evaluating the risk of PPB and the efficacy in thromboembolic prevention, is still very much needed. We currently recommend that HBT use should be considered carefully in all patients undergoing an endoscopic procedure despite current guidelines from major gastroenterology societies still advising for HBT in patients undergoing high-risk endoscopic procedures.

In addition, current position statements and guidelines[2-4] considers CSP for polyps < 10 mm as a high-risk procedure and advises anticoagulant and antiplatelet therapy be ceased before the procedure. However, the risk of PPB on continued antiplatelet therapy of aspirin or thienopyridine (either as monotherapy or DAPT) in CSP for polyps < 10 mm has been reported to be overall low in small retrospective studies[111,113]. Even on continuation DAPT, the risk of PPB is only estimated to be around 2.4% as reported in a small RCT by Won *et al*[112]. Therefore, continuing antiplatelet therapy in CSP for polyps < 10 mm may be possible in some circumstances. There is also no significantly increased risk of PPB shown when anticoagulant therapy (DOAC or warfarin) is continued in CSP for polyps < 10 mm[110,111,133]. However, this is still emerging evidence and has only been captured in a few retrospective studies and one small RCT. Further larger studies directly looking at the safety of continuation therapy is still needed. Furthermore, although the risk of PPB is not significantly increased, uninterrupted anticoagulant and antiplatelet therapy in CSP for polyps < 10 mm has shown to be associated with a significantly increased risk of immediate/intraprocedural bleeding, estimated at around 4.8%-17.8% when on DAPT[111,112], 11.9% when on a DOAC[111] and 5.7%-9.8% when on warfarin[111,133]. Given the current paucity of high-quality evidence and significant increased risk of immediate/intraprocedural bleeding, until more substantial evidence becomes available to verify the safety of continuation therapy, we recommend all anticoagulant and antiplatelet therapy be ceased before CSP for polyps < 10 mm, in accordance to the current position statements and guidelines.

**CONCLUSION**

This review largely agrees with the current position statements and guidelines from the major gastroenterology societies on the recommendations on anticoagulant and antiplatelet management in endoscopic procedures. Although, it has also highlighted some emerging discrepancies that requires further exploration in future guidelines, such as the 2- to 3-fold increased risk of PPB with HBT, and that anticoagulant and antiplatelet therapy may be safe to be continued in CSP for polyps < 10 mm.

In the meantime, we recommend strict endoscopic practice in accordance with the current major Gastroenterology guideline recommendations[2-4] be applied. Although in certain situations, anticoagulant and antiplatelet management may need to be considered on a case by case basis and tailored to the individual. Consultation with a cardiologist or haematologist is advised in these instances to ensure optimal patient safety.

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**Figure Legends**



**Figure 1 An evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of high-risk endoscopic procedures for all endoscopists.** ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; UGI: Upper Gastrointestinal; CrCl: Creatinine clearance; HBT: Heparin bridging therapy; INR: International normalisation ratio; PPB: Post-procedural bleeding; ERCP: Endoscopic retrograde cholangiopancreatography; PEG: Percutaneous endoscopic gastrostomy; PEJ: Percutaneous endoscopic jejunostomy; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; VTE: Venous thromboembolism; CAD: Coronary artery disease; AF: Atrial fibrillation; PCI: Percutaneous coronary intervention; DES: Drug eluding stent; BMS: Bare metal stent; CVA: Cerebrovascular accident; TIA: Transient ischaemic attack; HTN: Hypertension; DM: Diabetes mellitus; CCF: Congestive cardiac failure; ACS: Acute coronary syndrome.



**Figure 2 An evidence-based framework for safe clinical application of anticoagulant and antiplatelet management in the context of low-risk endoscopic procedures for all endoscopists.** ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; DOAC: Direct oral anticoagulant; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; VTE: Venous thromboembolism; CAD: Coronary artery disease; AF: Atrial fibrillation; PCI: Percutaneous coronary intervention; DES: Drug eluding stent; BMS: Bare metal stent; CVA: Cerebrovascular accident; TIA: Transient ischaemic attack; HTN: Hypertension; DM: Diabetes mellitus; CCF: Congestive cardiac failure; ACS: Acute coronary syndrome.

**Table 1 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Fujita *et al*[5] | 2015 | Japan | Retrospective | 3671 | Endoscopic biopsy | No medications | Incidence of PPB 0.98% |
| Ara *et al*[6] | 2015 | Japan | Prospective | 3758 | Endoscopic biopsy | No medications | Incidence of PPB 0.12% |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 263 | Endoscopic biopsy | No medications | No incidence of PPB |

PPB: Post-procedural bleeding.

**Table 2 Diagnostic ± therapeutic push or device assisted enteroscopy/balloon enteroscopy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Yamamoto *et al*[8] | 2015 | Japan | Prospective | 120 | DBE | No medications | No incidence of PPB |
| Wang *et al*[9] | 2020 | Japan | Retrospective | 1531 | DBE | No medications | Incidence of PPB 0.5% |

DBE: Double balloon enteroscopy; PPB: Post-procedural bleeding.

**Table 3 Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative Risk** |
| Song *et al*[18] | 2010 | South Korea | Prospective | 117 | EUS + FNA | No medications | No incidence of PPB |
| Uehara *et al*[10] | 2011 | Japan | Retrospective | 115 | EUS + FNA | No medications | No incidence of PPB |
| Suzuki *et al*[11] | 2012 | United States | Prospective | 20 | EUS + FNA | No medications | No incidence of PPB |
| Lee *et al*[12] | 2013 | South Korea | Prospective | 188 | EUS + FNA | No medications | Incidence of PPB 2.1% (25G group). Incidence of PPB 4.3% (22G group) |
| Vilmann *et al*[13] | 2013 | Denmark | Prospective | 135 | EUS - FNA | No medications | No incidence of PPB |
| Yang *et al*[14] | 2015 | South Korea | Retrospective | 76 | EUS + FNA | No medications | No incidence of PPB |
| Mavrogenis *et al*[15] | 2015 | United States | Prospective | 28 | EUS + FNA | No medications | No incidence of PPB |
| Ramesh *et al*[19] | 2015 | South Korea | Prospective | 100 | EUS + FNA | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.0% |
| Park *et al*[16] | 2016 | Denmark | Prospective | 56 | EUS + FNA | No medications | No incidence of PPB |
| Inoue *et al*[17] | 2017 | Japan | Retrospective | 742 | EUS + FNA | No medications | No incidence of PPB |
| Iwashita *et al*[20] | 2018 | South Korea | Prospective | 110 | EUS + FNA | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.8% |

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

**Table 4 Endoscopic retrograde cholangiopancreatography (diagnostic)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.**  | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Masci *et al*[21] | 2001 | Italy | Prospective | 782 | ERCP (diagnostic) | No medications | Incidence of PPB 1.13% |
| Williams *et al[*22] | 2007 | United Kingdom | Prospective | 5264 | ERCP (diagnostic) | No medications | Incidence of PPB 0.9% |
| Cotton *et al*[23] | 2009 | United States | Retrospective | 11497 | ERCP (diagnostic) | No medications | Incidence of PPB 0.3% |
| Coelho-Prabhu *et al*[24] | 2013 | United States | Retrospective | 1072 | ERCP (diagnostic) | No medications | Incidence of PPB 1.4% |
| Rotundo *et al*[25] | 2020 | United States | Retrospective | 555 | ERCP (diagnostic) | No medications | Incidence of PPB 1.66% (teaching hospital). Incidence of PPB 1.49% (nonteaching hospital) |

ERCP: Endoscopic retrograde cholangiopancreatography; PPB: Post-procedural bleeding.

**Table 5 Conventional polypectomy/hot snare polypectomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Gupta *et al*[26] | 2012 | United Kingdom | Prospective | 1200 | Polypectomy | No medications | Incidence of PPB 0.67% |
| Paspatis *et al*[27] | 2011 | Greece | Prospective | 18 | Polypectomy | No medications | No incidence of PPB |
| Singh *et al*[28] | 2010 | United States | Retrospective | 1243 | Polypectomy | No medications | Incidence of PPB 1% |
| Sewitch *et al*[29] | 2012 | Canada | Prospective | 2134 | Polypectomy | No medications | Incidence of PPB 0.05% |
| Feagins *et al*[30]  | 2011 | United States | Retrospective | 1849 | Polypectomy | No medications | Incidence of PPB 0.32% |
| Pan *et al*[31] | 2012 | New Zealand | Retrospective | 348 | Polypectomy | No medications | Incidence of PPB 0.86% |
| Manocha *et al*[32] | 2012 | United States | Retrospective | 672 | Polypectomy | No medications | Incidence of PPB 3.0% |
| Kim *et al*[33] | 2013 | South Korea | Retrospective | 7447 | Polypectomy | No medications | Incidence of PPB 1.3% |
| Gavin *et al*[34] | 2013 | United States | Prospective | 20085 | Polypectomy | No medications | Incidence of PPB 0.26% |
| Rutter *et al*[35] | 2014 | United Kingdom | Retrospective | 167208 | Polypectomy | No medications | Incidence of PPB 0.65% |
| Choung *et al*[36] | 2014 | South Korea | Retrospective | 5981 | Polypectomy | No medications | Incidence of PPB 1.1% |
| Gómez *et al*[37] | 2015 | United States | Prospective | 18 | Polypectomy | No medications | No incidence of PPB |
| Suzuki *et al*[38] | 2018 | Japan | Prospective | 27 | Polypectomy | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 3.5% |
| Kawamura *et al*[39] | 2018 | Japan | Prospective | 402 | Polypectomy | No medications | Incidence of PPB 0.5% |
| Ket *et al*[40] | 2020 | Australia | Retrospective | 258 | Polypectomy | No medications | Incidence of PPB 3.5% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 5381 | Polypectomy | No medications | Incidence of PPB 0.7% |

PPB: Post-procedural bleeding.

**Table 6 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure**  | **Medication** | **Relative risk** |
| Paspatis *et al*[27] | 2011 | Greece | Prospective | 530 | Polyp size 3-8 mm | CSP | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 9.1% |
| Ichise *et al*[44] | 2011 | Japan | Prospective | 101 | Polyp size < 8 mm | CSP | No medications | No incidence of PPB |
| Gómez *et al*[37] | 2015 | United States | Prospective | 21 | Polyp size < 6 mm | CSP | No medications | No incidence of PPB |
| Choksi *et al*[51] | 2015 | United States | Retrospective | 15 | Polyp size ≥ 10 mm | CSP | No medications | No incidence of PPB |
| Muniraj *et al*[52] | 2015 | United States | Retrospective | 12 | Polyp size ≥ 10 mm | CSP | No medications | No incidence of PPB |
| Piraka *et al*[53] | 2017 | United States | Retrospective | 94 | Polyp size ≥ 10 mm | CSP | No medications | No incidence of PPB |
| Hirose *et al*[54] | 2017 | Japan | Retrospective | 125 | Polyp size ≥ 10 mm | CSP | No medications | No incidence of PPB |
| Tutticci *et al*[55] | 2018 | Australia | Prospective | 163 | Polyp size ≥ 10 mm | CSP | No medications | No incidence of PPB  |
| Zhang *et al*[48] | 2018 | China | Prospective | 212 | Polyp size 6-9 mm | CSP | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 2.7% |
| Suzuki *et al*[38] | 2018 | Japan | Prospective | 25 | Polyp size ≤ 10 mm | CSP | No medications | No incidence of PPB |
| Kawamura *et al*[39] | 2018 | Japan | Prospective | 394 | Polyp size 4-9 mm | CSP | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 7.1% |
| Ket *et al*[40] | 2020 | Australia | Retrospective | 346 | Polyp size 10-20 mm | CSP | No medications | No incidence of PPB |

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

**Table 7 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Zhang *et al*[48] | 2018 | China | Prospective | 203 | Polyp size 6-9 mm | EMR | No medications | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 1.7% |
| So *et al*[50] | 2019 | South Korea | Retrospective | 798 | Mean polyp size 34 mm | EMR | No medications | Incidence of PPB 6.3% |
| Kim *et al*[49] | 2019 | South Korea | Retrospective | 717 | Polyp size ≥ 6 mm to < 20 mm | EMR | No medications | Incidence of PPB 1.7% |

EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

**Table 8 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.**  | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Igarashi *et al*[56] | 2017 | Japan | Retrospective | 722 | Gastric ESD | No medications | Incidence of PPB 4.2% |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 2488 | Gastric ESD | No medications | Incidence of PPB 3.9% |
| Kono *et al*[58] | 2018 | Japan | Retrospective | 814 | Gastric ESD | No medications | Incidence of PPB 5.3% |
| Arimoto *et al*[59] | 2018 | Japan | Retrospective | 783 | Colorectal ESD | No medications | Incidence of PPB 3.3% |
| Yamashita *et al*[60] | 2018 | Japan | Retrospective | 698 | Colorectal ESD | No medications | Incidence of PPB 2.7% |
| Harada *et al*[61] | 2020 | Japan | Retrospective | 286 | Colorectal ESD | No medications | Incidence of PPB 6.6% |
| Manta *et al*[62] | 2020 | Italy | Retrospective | 296 | Gastric ESD | No medications | Incidence of PPB 10.1% |
| Chen *et al*[63] | 2020 | China | Retrospective | 82 | Gastric ESD | No medications | Incidence of PPB 3.7% |

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

**Table 9 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Freeman *et al*[64] | 1996 | United States and Canada | Prospective | 2347 | ERCP + sphincterotomy | No medications | Incidence of PPB 2% |
| Masci *et al*[21] | 2001 | Italy | Prospective | 1662 | ERCP + sphincterotomy | No medications | Incidence of PPB 0.7%. Incidence of immediate PPB 1.1% |
| Tzovaras *et al*[65] | 2012 | Greece | Prospective | 50 | ERCP + sphincterotomy | No medications | Incidence of PPB 2% |
| Patai *et al*[66] | 2014 | Hungary | Prospective | 242 | ERCP + sphincterotomy | No medications | Incidence of delayed PPB 6.3%. Incidence of immediate/intraprocedural bleeding 2.7% |
| Tanaka *et al*[67] | 2015 | Japan | Prospective | 360 | ERCP + sphincterotomy | No medications | Incidence of PPB 9.9% |
| Ikarashi *et al*[68] | 2017 | Japan | Retrospective | 816 | ERCP + sphincterotomy | No medications | Incidence of PPB 2.2% |
| Bae *et al*[69] | 2019 | South Korea | Retrospective | 1121 | ERCP + sphincterotomy | No medications | Incidence of delayed PPB 1.2%. Incidence of immediate/intraprocedural PPB 8.5% |
| Lima *et al*[70] | 2020 | Brazil | Prospective | 2137 | ERCP + sphincterotomy | No medications | Incidence of PPB 2.2% |
| Yan *et al*[71] | 2020 | China | Retrospective | 8477 | ERCP + sphincterotomy | No medications | Incidence of PPB 1.6% |

ERCP: Endoscopic retrograde cholangiopancreatography; PPB: Post-procedural bleeding.

**Table 10 Ampullectomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Hopper *et al*[72] | 2010 | Australia | Prospective | 10 | Ampullectomy | No medications | Incidence of PPB 30% |
| Harano *et al*[73] | 2011 | Japan | Retrospective | 28 | Ampullectomy | No medications | Incidence of PPB 18% |
| Patel *et al*[74] | 2011 | United States | Retrospective | 38 | Ampullectomy | No medications | Incidence of PPB 5.3% |
| Salmi *et al*[75] | 2012 | France | Prospective | 61 | Ampullectomy | No medications | Incidence of PPB 4.9% |
| Laleman *et al*[76] | 2013 | Belgium | Retrospective | 91 | Ampullectomy | No medications | Incidence of PPB 12.1% |
| Attila *et al*[77] | 2018 | Turkey | Retrospective | 44 | Ampullectomy | No medications | Incidence of PPB 6.8% |
| Van Der Wiel *et al*[78] | 2019 | Netherlands | Retrospective  | 87 | Ampullectomy | No medications | Incidence of PPB 12.6% |
| Alali *et al*[79] | 2020 | Canada | Retrospective | 103 | Ampullectomy | No medications | Incidence of PPB 21.4% |

PPB: Post-procedural bleeding.

**Table 11 Endoscopic dilatation**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Schoepfer *et al*[80] | 2010 | United States | Prospective | 207 | Dilatation (EoE) | No medications | No incidence of PPB |
| Ally *et al*[81] | 2013 | United States | Retrospective | 66 | Dilatation (EoE) | No medications | No incidence of PPB |
| Jung *et al*[82] | 2011 | South Korea | Retrospective | 293 | Dilatation (EoE) | No medications | Incidence of PPB 0.3% |
| Dellon *et al*[83] | 2010 | United States | Retrospective | 70 | Dilatation (EoE) | No medications | No incidence of PPB |

EoE: Eosinophilic oesophagitis; PPB: Post-procedural bleeding.

**Table 12 Colonic stenting**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Meisner *et al*[85] | 2011 | Denmark | Prospective | 439 | Colonic stent | No medications | Incidence of PPB 0.5% |
| van Hooft *et al*[86] | 2011 | Netherlands | Prospective | 47 | Colonic stent | No medications | No incidence of PPB |
| Yoon *et al*[87] | 2011 | South Korea | Retrospective | 373 | Colonic stent | No medications | Incidence of PPB 0.3% |
| Gianotti *et al*[88] | 2013 | Italy | Prospective | 81 | Colonic stent | No medications | Incidence of PPB 3.7% |

PPB: Post-procedural bleeding.

**Table 13 Enteral stenting**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Costamagna *et al*[89] | 2012 | Italy | Prospective | 202 | Duodenal stent | No medications | Incidence of PPB 3% |

PPB: Post-procedural bleeding.

**Table 14 Oesophageal stenting**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Oh *et al*[90] | 2014 | South Korea | Retrospective | 1485 | Oesophageal stent | No medications | Incidence of PPB 1.7% |
| Liu *et al*[91] | 2016 | China | Retrospective | 519 | Oesophageal stent | No medications | Incidence of PPB 10.4% |

PPB: Post-procedural bleeding.

**Table 15 Endoscopic cystogastrostromy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Varadarajulu *et al*[92] | 2008 | United States | Retrospective | 20 | ECG | No medications | No incidence of PPB |
| Melman *et al*[97] | 2009 | United States | Prospective | 45 | ECG | No medications | Incidence of PPB 4.4% |
| Johnson *et al*[93] | 2009 | United States | Retrospective | 24 | ECG | No medications | Incidence of PPB 8.3% |
| Varadarajulu *et al*[96] | 2013 | United States | Prospective | 20 | ECG | No medications | No incidence of PPB |
| Saul *et al*[94] | 2016 | United States | Retrospective | 21 | ECG | No medications | Incidence of PPB 9.5% |
| Saluja *et al*[95] | 2019 | India | Retrospective | 35 | ECG | No medications | Incidence of PPB 2.9% |

ECG: Endoscopic cystogastrostomy; PPB: Post-procedural bleeding.

**Table 16 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Singh *et al*[98] | 2012 | United States | Retrospective | 1541 | PEG | No medications | Incidence of PPB 2.7% |
| Lozoya-González *et al*[99] | 2012 | Mexico | Retrospective | 40 | PEG | No medications | No incidence of PPB |

PEG: Percutaneous endoscopic gastrostomy; PPB: Post-procedural bleeding.

**Table 17 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Whitson *et al*[103] | 2011 | United States | Prospective | 280 | Endoscopic biopsy | Aspirin (continued) | Incidence of bleeding 0.4% |
| Ono *et al*[104] | 2012 | Japan | Prospective | 101 | Endoscopic biopsy | Aspirin (continued) | No Incidence of PPB |
| Ara *et al*[6] | 2015 | Japan | Prospective | 3758 | Endoscopic biopsy | Aspirin (continued) | No incidence of PPB |
| Fujita *et al*[5] | 2015 | Japan | Retrospective | 105 | Endoscopic biopsy | Aspirin (continued) | Incidence of PPB 0.95% |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 560 | Endoscopic biopsy | Aspirin (continued) | No incidence of PPB |
| Kono *et al*[105] | 2017 | Japan | Prospective | 221 | Endoscopic biopsy | Aspirin (continued) | No incidence of PPB |

PPB: Post-procedural bleeding.

**Table 18 Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Inoue *et al*[17] | 2017 | Japan | Retrospective | 742 | EUS + FNA | Aspirin either:(1) Continued (high-risk conditions); (2) Ceased 3 d before | No incidence of PPB |
| Kawakubo *et al*[106] | 2018 | Japan | Prospective | 85 | EUS + FNA | Aspirin(continued) | No incidence of PPB |

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

**Table 19 Polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Pan *et al*[31] | 2012 | New Zealand | Retrospective | 145 | Size: 2-40 mm (average size 9.6 mm) | Polypectomy | Aspirin (continued) | Incidence of PPB 5.5% |
| Manocha *et al*[32] | 2012 | United States | Retrospective | 502 | Size: 2-50 mm | Polypectomy  | Aspirin (continued) | Incidence of PPB 3.2% |
| Park *et al*[43] | 2018 | South Korea | Prospective | 3887 | Size: < 10 mm and ≥ 10 mm | Polypectomy | Aspirin (ceased 5-7 d before and restarted 1 d after) | Incidence of PPB 3.4% |
| Lin *et al*[107] | 2018 | United States | Retrospective | 20374 | Size: < 20 mm and ≥ 20 mm | Polypectomy | Aspirin (continuation or cessation N/S) | Incidence of PPB 0.92% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 12876 | Size: < 10 mm and ≥ 10 mm | Polypectomy | Aspirin either: (1) Ceased 3-5 d before (cases before 2012); (2) Continued (cases after 2012) | Incidence of PPB 0.6% |
| Amato *et al*[108] | 2019 | Italy | Prospective | 1504 | Size: ≥ 10 mm | Polypectomy | Aspirin (ceased up to 9 d before) | Incidence PPB 4.2% |
| Watanabe *et al*[109] | 2020 | Japan | Retrospective | 1050 | Size: < 10 mm and ≥ 10 mm | Polypectomy | Aspirin (continued) | Incidence of PPB 4.3% |

PPB: Post-procedural bleeding; N/S: Not stated.

**Table 20 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Makino *et al*[110] | 2018 | Japan | Prospective | 33 | Size: ≤ 10 mm | CSP | Aspirin (continued) | No incidence of PPB |
| Arimoto *et al*[111] | 2019 | Japan | Retrospective | 501 | Size: ≤ 10 mm | CSP | Aspirin (continued) | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 9.8% |
| Won *et al*[112] | 2019 | South Korea | Prospective | 43 | Size: ≤ 10mm | CSP | Aspirin (continued) | No incidence of PPB. Incidence of immediate/intraprocedural bleeding 2.2% |

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

**Table 21 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Ono *et al*[113] | 2019 | Japan | Retrospective | 1734 | Size: Median size 8.5-9.5 ± 5 mm | EMR | Aspirin (continuation or ceased 3 d before) | Incidence of PPB per polyp resection 1.35% (*P* = 0.81) on antiplatelet therapy (study limited by not differentiating between aspirin *vs* thienopyridine) |
| So *et al*[50] | 2019 | South Korea | Retrospective | 399 | Size: Mean lesion size 34 mm | EMR | Aspirin (ceased day of procedure or 0-4 d before or ceased 5-7 d before or ceased 8-14 d before procedure) | Incidence of PBB 8.2% (either aspirin or thienopyridine monotherapy) |
| Albéniz *et al*[114] | 2020 | Spain | Prospective | 1034 | Size: ≥ 20 mm (mean size 30.5 mm) | EMR | Aspirin (cessation dependent on comorbidities) | Study expressed risk of PPB on antiplatelet monotherapy as OR: 2.51, 95%CI: 0.99-6.34, *P* < 0.001 (either aspirin or thienopyridine monotherapy) |

OR: Odds ratio; EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

**Table 22 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Igarashi *et al*[56] | 2017 | Japan | Retrospective | 367 | Gastric ESD | Aspirin (continued) | Incidence of PPB 12.1% |
| Furuhata *et al*[115] | 2017 | Japan | Retrospective | 15 | Gastric ESD | Aspirin (continued or ceased 3-5 d before) | Incidence of PPB 6.7% |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 211 | Gastric ESD | Aspirin (continued) | Incidence of PPB 5.7% |
| Kono *et al*[58] | 2018 | Japan | Retrospective | 23 | Gastric ESD | Aspirin (continued) | Incidence of PPB 21.7% |
| Arimoto *et al*[59] | 2018 | Japan | Retrospective | 26 | Colorectal ESD | Aspirin (continued) | No incidence of PPB |
| Oh *et al*[116] | 2018 | South Korea | Retrospective | 94 | Gastric ESD | Aspirin either: (1) Ceased 0-4 d before; (2) Ceased 5-7 d before | Incidence of PPB 12.8% |
| Harada *et al*[117] | 2019 | Japan | Retrospective | 56 | Gastric ESD | Aspirin (continued) | Incidence of PPB 10.7% |
| Nam *et al*[118] | 2019 | South Korea | Retrospective | 31 | Gastric ESD | Aspirin (ceased 7 d before) | Incidence of PPB 22.6% |
| Horikawa *et al*[119] | 2019 | Japan | Retrospective | 50 | Gastric ESD | Aspirin (continued) | Incidence of PPB 2.0% |

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

**Table 23 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Onal *et al*[120] | 2013 | Turkey | Prospective | 35 | Sphincterotomy | Aspirin (within 24 h) | Incidence of PPB 10% |
| Patai *et al*[66] | 2014 | Hungary | Prospective | 87 | Sphincterotomy | Aspirin (continued) | Incidence of delayed PPB 5.8%. Incidence of immediate/intraprocedural bleeding 4.6% |
| Ikarashi *et al*[68] | 2017 | Japan | Retrospective | 1113 | Sphincterotomy | Aspirin (continued) | Incidence of PPB 1.8% |
| Oh *et al*[121] | 2018 | United States | Prospective | 256 | Sphincterotomy | Aspirin (continued) | Incidence of PPB 4.7% |
| Yamamiya *et al*[122] | 2019 | Japan | Retrospective | 76 | Sphincterotomy | Aspirin either: (1) Continued (low-risk conditions); (2) Ceased 3-5 d before (high-risk conditions) | No incidence of PPB in either continuous or cessation group |

PPB: Post-procedural bleeding.

**Table 24 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Richter *et al*[124] | 2011 | United States | Retrospective | 990 | PEG | Aspirin (continued) | Incidence of PPB: (1) ≤ 48 h post-PEG 2.2%; (2) > 48 h post-PEG 1.7% |
| Singh *et al*[98] | 2012 | United States | Retrospective | 1541 | PEG | Aspirin (continued) | Incidence of PPB 3.9% |
| Lozoya-González *et al*[99] | 2012 | Mexico | Retrospective | 27 | PEG | Aspirin (ceased 1-3 d before) | No incidence of PPB |
| Lee *et al*[123] | 2013 | South Korea | Retrospective | 151 | PEG | Aspirin (continued) | No incidence of PPB |

PEG: Percutaneous endoscopic gastrostomy; PPB: Post-procedural bleeding.

**Table 25 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Whitson *et al*[103] | 2011 | United States | Prospective | 350 | Endoscopic biopsy | Thienopyridine (continued) | No incidence of PPB |
| Ono *et al*[104] | 2012 | Japan | Prospective | 101 | Endoscopic biopsy | Thienopyridine (continued) | No incidence of PPB |
| Ara *et al*[6] | 2015 | Japan | Prospective | 3758 | Endoscopic biopsy | Thienopyridine either: (1) Continued; (2) Ceased 5-7 d before | No incidence of PPB in either group |
| Fujita *et al*[5] | 2015 | Japan | Retrospective | 28 | Endoscopic biopsy | Thienopyridine (continued) | No incidence of PPB |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 560 | Endoscopic biopsy | Thienopyridine (continued) | No incidence of PPB |
| Kono *et al*[105] | 2017 | Japan | Prospective | 221 | Endoscopic biopsy | Thienopyridine (continued) | No incidence of PPB |

PPB: Post-procedural bleeding.

**Table 26 Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Inoue *et al*[17] | 2017 | Japan | Retrospective | 742 | EUS + FNA | Thienopyridines (ceased 5 d before) | No incidence of PPB  |
| Kawakubo *et al*[106] | 2018 | Japan | Prospective | 30 | EUS + FN | Thienopyridines (ceased 5 d before) | No incidence of PPB |

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding.

**Table 27 Polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Singh *et al*[28] | 2010 | United States | Retrospective | 142 | Size: < 5 mm or ≥ 10 mm | Polypectomy | Thienopyridine (continued) | Incidence of PPB 3.5% |
| Feagins *et al*[30] | 2011 | United States | Retrospective | 118 | Size: < 20 mm and > 20 mm (average 7 mm) | Polypectomy | Thienopyridine (continued) | No incidence of PPB |
| Feagins *et al*[125] | 2013 | United States | Prospective | 219 | Size: Average 5.2 mm | Polypectomy | Thienopyridine (continued) | Incidence of PPB 2.4% |
| Lin *et al*[107] | 2018 | United States | Retrospective | 20374 | Size: < 20 mm or ≥ 20 mm | Polypectomy | Thienopyridine (ceased 5-7 d before) | Incidence of PPB 0.84% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 12876 | Size: < 10 mm or ≥ 10 mm | Polypectomy | Thienopyridine (ceased 5-7 d before) | Incidence of PPB 0.6% |
| Amato *et al*[108] | 2019 | Italy | Prospective | 1648 | Size: ≥ 10 mm | Polypectomy | Thienopyridine (ceased 6 d before) | Incidence of PPB 4.2% |
| Chan *et al*[126] | 2019 | China (Hong Kong) | Prospective | 216 | Size: < 10 mm or ≥ 10 mm (mean size 4.7 mm) | Polypectomy | Thienopyridine (continued) | Incidence of PPB 3.8% |
| Yu *et al*[127] | 2019 | United States | Retrospective | 6443 | N/S | Polypectomy | Thienopyridine (cessation timing N/S) | Incidence of PPB 0.9% |
| Watanabe *et al*[109] | 2020 | Japan | Retrospective | 45 | Size: < 10 mm or ≥ 10 mm | Polypectomy | Thienopyridine (cessation timing N/S) | Incidence of PPB 6.7% |

N/S: Not stated;PPB: Post-procedural bleeding.

**Table 28 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Makino *et al*[110] | 2018 | Japan | Prospective | 24 | Size: ≤ 10 mm | CSP | Thienopyridine (continued) | No incidence of PPB |
| Arimoto *et al*[111] | 2019 | Japan | Retrospective | 516 | Size: ≤ 10 mm | CSP | Thienopyridine (continued) | No incidence of PPB |

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

**Table 29 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Ono *et al*[113] | 2019 | Japan | Retrospective | 1734 | Size: Median size 8.5-9.5 ± 5 mm | EMR | Thienopyridines (ceased 3-5 d before) | Incidence of PPB 1.35% |
| So *et al*[50] | 2019 | South Korea | Retrospective | 399 | Size: Mean lesion size 34 mm | EMR (and ESD) | Thienopyridines either: (1) Ceased day of procedure; (2) 0-4 d before; (3) Ceased 5-7 d before; (4) Ceased 8-14 d before | Incidence of PBB 8.2% |
| Albéniz *et al*[114] | 2020 | Spain | Prospective | 1034 | Size: ≥ 20 mm (mean size 30.5 mm) | EMR | Thienopyridines (ceased 5 d before) | Study expressed risk of PPB on antiplatelet monotherapy as OR: 2.51, 95%CI: 0.99-6.34, *P* < 0.001 (either aspirin or thienopyridine monotherapy) |

OR: Odds ratio; EMR: Endoscopic mucosal resection; PPB: Post-procedural bleeding.

**Table 30 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Igarashi *et al*[56] | 2017 | Japan | Retrospective | 90 | Gastric ESD | Thienopyridines either: (1) Continued until day of; (2) Ceased 3-7 d before | Incidence of PPB 5.6% (continued). Incidence of PPB 12.5% (ceased) |
| Ono *et al*[128] | 2017 | Japan | Prospective | 10 | Gastric ESD | Thienopyridines (continued) | Incidence of PPB 20% |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 19 | Gastric ESD | Thienopyridines(ceased 5-7 d before) | No incidence of PPB |
| Oh et al[116] | 2018 | South Korea | Retrospective | 56 | Gastric ESD | Thienopyridines either: (1) Ceased 0-4 d before; (2) Ceased 5-7 d before | Incidence of PPB 3.6% |
| Nam *et al*[118] | 2019 | South Korea | Retrospective | 31 | Gastric ESD | Thienopyridines(ceased 7 d before) | Incidence of PPB 19.4% |

ESD: Endoscopic submucosal dissection; PPB: Post-procedural bleeding.

**Table 31 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Patai *et al*[66] | 2014 | Hungary | Prospective | 29 | Sphincterotomy | Thienopyridine (continued) | Incidence of delayed PPB 3.5%. Incidence of immediate/intraprocedural bleeding 3.5% |
| Ikarashi *et al*[68] | 2017 | Japan | Retrospective | 1113 | Sphincterotomy | Thienopyridine (ceased 5-7 d before) | Incidence of delayed PPB 3.0%. (study categorised cessation of thienopyridine, warfarin and DOAC into the same “discontinuation” group) |
| Yamamiya *et al*[122] | 2019 | Japan | Retrospective | 76 | Sphincterotomy | Thienopyridine (either continued or ceased 5-7 d or switched to aspirin monotherapy before) | No incidence of PPB in either continuous or cessation group |

PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

**Table 32 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Richter *et al*[124] | 2011 | United States | Retrospective | 990 | PEG | Thienopyridines(continued) | No incidence of PPB ≤ 48 h post-PEG. Incidence of PPB > 48 h post-PEG 4% |
| Singh *et al*[98] | 2012 | United States | Retrospective | 143 | PEG | Thienopyridines (ceased on average 2.2 d before) | Incidence of PPB 2.1% |
| Lozoya-González *et al*[99] | 2012 | Mexico | Retrospective | 24 | PEG | Thienopyridines (ceased 1-3 d before) | No incidence of PPB |
| Lee *et al*[123] | 2013 | South Korea | Retrospective | 81 | PEG | Thienopyridines (continued) | No incidence of PPB |

PPB: Post-procedural bleeding; PEG: Percutaneous endoscopic gastrostomy.

**Table 33 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Ono *et al*[104] | 2012 | Japan | Prospective | 101 | Endoscopic biopsy | DAPT (continued) | No Incidence of PPB |
| Ara *et al*[6] | 2015 | Japan | Prospective | 3758 | Endoscopic biopsy | DAPT either: (1) Continued; (2) Ceased before | Incidence of PPB on DAPT (continued) 0.35%. No incidence of PPB with DAPT (cessation) |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 277 | Endoscopic biopsy | DAPT (continued) | No incidence of PPB |
| Kono *et al*[105] | 2017 | Japan | Prospective | 221 | Endoscopic biopsy | DAPT (continued) | No incidence of PPB |

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 34** **Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Kawakubo *et al*[106] | 2018 | Japan | Prospective | 85 | EUS + FNA (for solid lesions only). Pancreatic cysts excluded | DAPT (ceased thienopyridine 5 d before and bridged with aspirin monotherapy) | Incidence of PPB 3.6% |

EUS: Endoscopic ultrasound; FNA:Fine needle aspiration;DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 35 Polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Singh *et al*[28] | 2010 | United States | Retrospective | 77 | Size: < 5 mm to ≥ 10 mm | Polypectomy | DAPT (continued) | Incidence of delayed PPB 5.2% |
| Feagins *et al*[30] | 2011 | United States | Retrospective | 118 | Size: < 20 mm and > 20 mm | Polypectomy | DAPT (continued) | Incidence of PPB 0.85% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 6382 | Size: < 10 mm or ≥ 10 mm | Polypectomy | DAPT either: (1) Ceased 7 d before (before 2012); (2) Bridged with aspirin monotherapy (after 2012) | Incidence of PPB 1.8% |
| Watanabe *et al*[109] | 2020 | Japan | Retrospective | 50 | Size: < 10 mm or ≥ 10 mm | Polypectomy | DAPT (various timing of agent continuation or switching strategies) | Incidence of PPB 6% |

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 36 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Arimoto *et al*[111] | 2019 | Japan | Retrospective | 516 | Size: ≤ 10 mm | CSP | DAPT (continued) | No incidence of PPB |
| Won *et al*[112] | 2019 | South Korea | Prospective | 91 | Size: ≤ 10 mm | CSP | DAPT (continued) | Incidence of PPB 2.4% |

CSP: Cold snare polypectomy; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 37 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Ono *et al*[113] | 2019 | Japan | Retrospectively | 825 | Size: Median size ranged from 8.5-9.5 ± 5 mm | EMR | DAPT (thienopyridines ceased and aspirin monotherapy continued) | Incidence of PPB per polyp resection 1.35% (aspirin/thienopyridine/DAPT) |
| So *et al*[50] | 2019 | South Korea | Retrospective | 399 | Size: Mean lesion size 34 mm | EMR and ESD | DAPT (varying patterns of agent continuation or switching strategies) | Incidence of PPB 12.3% |

EMR: Endoscopic mucosal resection; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding; ESD: Endoscopic submucosal dissection.

**Table 38 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 75 (2378) | ESD | DAPT (ceased thienopyridine before and bridged with aspirin monotherapy) | Incidence of PPB 30.7% |
| Kono *et al*[58] | 2018 | Japan | Retrospective | 6 (872) | ESD | DAPT (ceased thienopyridine 7 d before and bridged with aspirin monotherapy) | Incidence of PPB 67.7% |
| Oh *et al*[116] | 2018 | South Korea | Retrospective | 51 (215) | ESD | DAPT either: (1) Ceased 5-7 d before (discontinuation group); (2) Ceased 0-4 d before (continuation group) | Incidence of delayed PPB 27.5% (14/51) |
| Harada *et al*[117] | 2019 | Japan | Retrospective | 59 (597) | ESD | DAPT either: (1) Ceased thienopyridine 5 d before and bridged with aspirin monotherapy (high-risk conditions); (2) DAPT ceased > 5 d before (low-risk conditions) | Incidence of PPB 23.1% (aspirin monotherapy bridging). Incidence of PPB 5.0% (DAPT ceased) |

ESD: Endoscopic submucosal dissection; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 39 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Mok *et al*[130] | 2017 | United States | Prospective | 50 | Sphincterotomy | DAPT (continued) | Incidence of PPB 3.6% |
| Yamamiya *et al*[122] | 2019 | Japan | Retrospective | 76 | Sphincterotomy | DAPT either: (1) Continued; (2) Ceased 5-7 d. And switched to aspirin monotherapy before | No incidence of PPB in either continuous or cessation group |

DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 40 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Lee *et al*[123] | 2013 | South Korea | Retrospective | 40 (1625) | PEG | DAPT (ceased 4 d before) | Incidence of PPB on DAPT 2.5% |
| Singh *et al*[98] | 2012 | United States | Retrospective | 122 (1541) | PEG | DAPT | Incidence of PPB 2.5% |
| Lozoya-González *et al*[99] | 2012 | Mexico | Retrospective | 91 | PEG | DAPT (ceased 1-3 d before) | Incidence of PPB 0% |

PEG: Percutaneous endoscopic gastrostomy; DAPT: Dual antiplatelet therapy; PPB: Post-procedural bleeding.

**Table 41 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Fujita *et al*[5] | 2015 | Japan | Retrospective | 47 | Endoscopic biopsy | Warfarin (continued) | No incidence of PPB. Risk of immediate/intraprocedural bleeding 4.3% |
| Ara *et al*[6] | 2015 | Japan | Prospective | 3758 | Endoscopic biopsy | Warfarin either: (1) Continued; (2) Ceased before | No incidence of PPB on continuous or Warfarin cessation |
| Ono *et al*[104] | 2012 | Japan | Prospective | 101 | Endoscopic biopsy | Warfarin (continued) | No Incidence of PPB |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 277 | Endoscopic biopsy | Warfarin (continued) | No incidence of PPB |
| Kono *et al*[105] | 2017 | Japan | Prospective | 221 | Endoscopic biopsy | Warfarin (continued) | No incidence of PPB when on warfarin monotherapy |

PPB: Post-procedural bleeding.

**Table 42 Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Inoue *et al*[17] | 2017 | Japan | Retrospective | 742 | EUS + FNA | Warfarin (ceased 4 d before) | No incidence of bleeding in either discontinuation warfarin or HBT |
| Kawakubo *et al*[106] | 2018 | Japan | Prospective | 85 | EUS + FNA | Warfarin (ceased 3 d with HBT before) | Incidence of PPB with HBT 4% |

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; PPB: Post-procedural bleeding; HBT: Heparin bridging therapy.

**Table 43 Polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Horiuchi *et al*[133] | 2014 | Japan | Prospective | 35 | Size: ≤ 10 mm | Polypectomy | Warfarin (continued) | Incidence of PPB 14% |
| Beppu *et al*[134] | 2014 | Japan | Retrospective | 20 | Size: ≥ 20 mm and < 20 mm | Polypectomy | Warfarin ± HBT (ceased at least 5 d before) | Incidence of PPB 52.2% |
| Yanagisawa *et al*[1] | 2018 | Japan | Retrospective | 486 | Size: < 10 mm or ≥ 10 mm | Polypectomy | Warfarin ± HBT (ceased 3-5 d before) | Incidence of PPB 13.7%. Incidence of PPB on HBT 21.7% |
| Lin *et al*[107] | 2018 | United States | Retrospective | 427 | Size: < 20 or ≥ 20 mm | Polypectomy | Warfarin ± HBT (ceased 3-5 d before) | Incidence of PPB 0.66% |
| Yu *et al*[127] | 2019 | United States | Retrospective | 3471 | N/S | Polypectomy | Warfarin ± HBT (ceased before procedure) | Incidence of PPB 1.2% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 6382 | Size: < 10 mm or ≥ 10 mm | Polypectomy | Warfarin ± HBT (ceased 3-4 d before) | Incidence of PPB 2.3%. Incidence of PPB with HBT 20% (study did not discern rates between warfarin *vs* DOAC) |
| Amato *et al*[108] | 2019 | Italy | Prospective | n=1504 | Size: ≥ 10 mm | Polypectomy | Warfarin(ceased median 5 d before) | Incidence of PPB 8.5% (anticoagulant monotherapy)(study did not discern rates between warfarin *vs* DOAC) |

PPB: Post-procedural bleeding; HBT: Heparin bridging therapy; DOAC: Direct oral anticoagulant; N/S: Not stated.

**Table 44 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Horiuchi *et al*[133] | 2014 | Japan | Prospective | 35 | Size: ≤ 10 mm | CSP | Warfarin (continued) | No incidences of PPB |
| Makino *et al*[110] | 2018 | Japan | Prospective | 69 | Size: ≤ 10 mm | CSP | Warfarin (continued) | No incidences of PPB. Incidence of immediate/intraprocedural bleeding 5.7% |
| Arimoto *et al*[111] | 2019 | Japan | Retrospective | 501 | Size: ≤ 10 mm | CSP | Warfarin (continued) | No incidences of PPB. Incidence of immediate/intraprocedural bleeding 9.8% |

CSP: Cold snare polypectomy; PPB: Post-procedural bleeding.

**Table 45 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Fujita *et al*[135] | 2018 | Japan | Prospective (non-HBT group). Retrospective (HBT group) | 43/41 | Size: < 10 mm (mean size 7.2-7.8 mm ± 2.2-3.2 mm) | EMR | Warfarin ± HBT (ceased morning of) | No incidence of PPB (non-HBT group). Incidence of PPB 9.8% (HBT group) |
| Ono *et al*[113] | 2019 | Japan | Retrospective | 24 | Size: Median size ranged from 8.5-9.5 ± 5 mm between groups | EMR | Warfarin ± HBT either: Continued; ceased 3 d before procedure | Incidence of PPB (without HBT) 10%. Incidence of PPB (with HBT) 21.4% |
| So *et al*[50] | 2019 | South Korea | Retrospective | 1197 | Size: Mean lesion size 34 mm | EMR | Warfarin either: Ceased day of; 0-4 d before; ceased 5-7 d before; ceased 8-14 d before | Incidence of PPB 16.7% (specific PPB rates between warfarin and DOACs N/S). Incidence of PPB (HBT group) 35.7% |
| Albéniz *et al*[114] | 2020 | Spain | Prospective | 76 | Size: ≥ 20 mm (mean size 30.5 mm) | EMR | Warfarin (ceased 5 d before with HBT) | Increased risk of PPB with anticoagulant use (OR: 4.54, 95%CI: 2.14-9.63, *P* < 0.001). Incidence of PPB not specified in study |

EMR: Endoscopic mucosal resection; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding; N/S: Not stated; OR: Odds ratio.

**Table 46 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Igarashi *et al*[56] | 2017 | Japan | Retrospective | 67 | ESD | Warfarin ± HBT either: (1) Received till day of; (2) Ceased 3-7 d before; (3) HBT 3-7 d before | Incidence of PPB 10.0% (warfarin and DOAC combined). Incidence of PPB 10.8% (HBT group) |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 93 | ESD | Warfarin ± HBT (ceased 3-5 d before) | Incidence of PPB 5.9% (without HBT). Incidence of PPB (with HBT) 30.7% |
| Furuhata *et al*[115] | 2017 | Japan | Retrospective | 253 | ESD | Warfarin ± HBT (ceased 3-4 d before) | Incidence of PPB 7.3% (Warfarin and DOAC combined). Incidence of PPB 28.8% (with HBT) |
| Yoshio *et al*[132] | 2017 | Japan | Retrospective | 97 | ESD | Warfarin ± HBT (ceased 4-5 d before) | No incidence of PPB (without HBT). Incidence of PPB (with HBT) 31.6% |
| Harada *et al*[136] | 2017 | Japan | Prospective | 45 | ESD | Warfarin ± HBT either: (1) Continued; (2) Switched to HBT | Incidence of PPB 9.1% (warfarin continued). Incidence of PPB 21.7% (HBT) |
| Kono *et al*[58] | 2018 | Japan | Retrospective | 872 | ESD | Warfarin ± HBT (ceased 1-3 d before with or without HBT) | Incidence of PPB 6.4% (without HBT). Incidence of PPB 29% (with HBT) (warfarin and DOACs combined) |
| Yamashita *et al*[60] | 2018 | Japan | Retrospective | 650 | ESD | Warfarin with HBT | Incidence of PPB 26.3% (with HBT) |
| Nam *et al*[118] | 2019 | South Korea | Retrospective | 1942 | ESD | Warfarin ± HBT (ceased 7 d before) | Incidence of PPB 3.2% |
| Harada *et al*[61] | 2020 | Japan | Retrospective | 26 | ESD | Warfarin ± HBT either: (1) Continued; (2) Ceased 4-5 d ± HBT before | Incidence of PPB 7.7% |

ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

**Table 47 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Paik *et al*[137] | 2018 | South Korea | Retrospective | 96 | Sphincterotomy | Warfarin with HBT | Incidence of delayed PPB 7.3% |
| Muro *et al*[138] | 2020 | Japan | Retrospective | 149 | Sphincterotomy | Warfarin either: (1) Continued; (2) With HBT | Incidence of PPB 8.3% (warfarin continued). Incidence of PPB 4.0% (with HBT) |
| Yamamiya *et al*[122] | 2019 | Japan | Retrospective | 76 | Sphincterotomy | Warfarin: (1) Continued; (2) With HBT | No incidence of PPB in either continuous or HBT group |
| Ikarashi *et al*[68] | 2017 | Japan | Retrospective | 1113 | Sphincterotomy | Warfarin either: (1) Ceased 4-5 d before; (2) With HBT | Incidence of delayed PPB 3.0% (study categorised cessation of thienopyridine, warfarin and DOAC into the same “discontinuation” group). Incidence of PPB 8.0% (with HBT) |

HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

**Table 48 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Lee *et al*[123] | 2013 | South Korea | Retrospective | 71 | PEG | Warfarin (continuation or cessation details N/S) | Study findings expressed as an OR. Increased risk of PPB with anticoagulant use (OR: 7.26, 95%CI: 2.23-23.68, *P* = 0.001) |
| Singh *et al*[98] | 2012 | United States | Retrospective | 326 | PEG | Warfarin ± HBT | Without HBT group: (1) Incidence of PPB 5.4% (without HBT); (2) Increased risk of PPB without HBT (OR: 1.08, 95%CI: 0.47-2.49, P = 0.860). HBT group: (1) Incidence of PPB with HBT 7.9% (11/140); (2) Increased risk of PPB with HBT (OR: 2.66, 95%CI: 1.18-5.99, *P* = 0.018) |
| Lozoya-González *et al*[99] | 2012 | Mexico | Retrospective | 91 | PEG | Warfarin either: (1) Ceased > 48h with HBT before; (2) Ceased 1-5 d before | No incidence of PPB |

N/S: Not stated; OR: Odds ratio; PEG: Percutaneous endoscopic gastrostomy; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

**Table 49 Diagnostic endoscopy and colonoscopy with biopsy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Fujita *et al*[5] | 2015 | Japan | Retrospective | 5 (7939) | Endoscopic biopsy | DOAC (continued) | No incidence of PPB |
| Ara *et al*[6] | 2015 | Japan | Prospective | 394 (3758) | Endoscopic biopsy | DOAC either: (1) Continued; (2) Ceased before | No incidence of PPB(in both continuous and DOAC cessation group) |
| Yuki *et al*[7] | 2017 | Japan | Prospective | 45 (549) | Endoscopic biopsy | DOAC (continued) | No incidence of PPB |
| Kono *et al*[105] | 2017 | Japan | Prospective | 51 (221) | Endoscopic biopsy | DOAC (continued) | No incidence of PPB |

PPB: Post-procedural bleeding; DOAC: Direct oral anticoagulant.

**Table 50 Endoscopic ultrasound ± fine needle aspiration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Kawakubo *et al*[106] | 2018 | Japan | Prospective | 85 | EUS + FNA | DOAC (ceased 48 h with HBT before) | No incidence of PPB with HBT |

EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

**Table 51 Polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Beppu *et al*[134] | 2014 | Japan | Retrospective | 1 (52) | Size: ≥ 20 mm and < 20 mm | Polypectomy | DOAC (ceased at least 5 d before) | Expressed as OR. Increased risk of PPB with DOAC use (OR: 10.2, 95%CI: 2.7-38.3, *P* = 0.0006) |
| Yanagisaw *et al*[1] | 2018 | Japan | Retrospective | 73 (436) | Size: < 10 mm or ≥ 10 mm | Polypectomy | DOAC (ceased 24-48 h before ± HBT) | Incidence of PPB 13.8% |
| Yu *et al*[127] | 2019 | United States | Retrospective | 1590 (611487) | N/S | Polypectomy | DOAC (ceased before) | Incidence of PPB 0.6% |
| Kishida *et al*[41] | 2019 | Japan | Retrospective | 87 (6382) | Size: < 10 mm or ≥ 10 mm | Polypectomy | DOAC (ceased 24-48 h before) | Incidence of PPB 2.3% (study did not discern rates between warfarin *vs* DOAC) |
| Amato *et al*[108] | 2019 | Italy | Prospective | 1504 | Size: ≥ 10 mm | Polypectomy | DOAC (ceased median 5 d before) | Incidence of PPB 8.5% (study did not discern anticoagulant rates between warfarin *vs* DOACs) |

DOAC: Direct oral anticoagulant; OR: Odds ratio; PPB: Post-procedural bleeding.

**Table 52 Cold snare polypectomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** |  **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Makino *et al*[110] | 2018 | Japan | Prospective | 17 (172) | Size: ≤ 10 mm | CSP | DOAC (continued) | Incidence of PPB 1.2% |
| Arimoto *et al*[111] | 2019 | Japan | Retrospective | 65 (501) | Size: ≤ 10 mm | CSP | DOAC (continued) | No incidence of PPB |

CSP: Cold snare polypectomy; DOAC: Direct oral anticoagulant; PPB: Post-procedural bleeding.

**Table 53 Endoscopic mucosal resection**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Polyp morphology** | **Procedure** | **Medication** | **Relative risk** |
| Fujita *et al*[135] | 2018 | Japan | Prospective (non-HBT group) and retrospective (HBT group) | 84 | Size < 10mm (mean size 7.2-7.8 ± 2.2-3.2 mm | EMR | DOAC ± HBT (ceased morning of) | Incidence of PBB 2.3% (non-HBT). No incidence of PPB (HBT) |
| Ono *et al*[113] | 2019 | Japan | Retrospective | 825 | Size median size 8.5-9.5 ± 5 mm between groups | EMR | DOACs (ceased day of) | Incidence of PPB 6.5% |
| So *et al*[50] | 2019 | South Korea | Retrospective | 399 (1197) | Size mean lesion 34 mm | EMR and ESD | DOAC (ceased day of procedure or 0-4 d before or ceased 5-7 d before or ceased 8-14 d before procedure) | Incidence of PPB 16.7% (anticoagulant group) (study did not specify the risk comparing warfarin and DOAC individually) |
| Albéniz*et al*[114] | 2020 | Spain | Prospective | 977 | Size ≥ 20mm (mean size 30.5 mm) | EMR | DOAC (ceased 48-72 h before) | Expressed as OR (OR: 4.54, 95%CI: 2.14-9.63, *P* < 0.001) (anticoagulant use) (specific PPB rates between warfarin and DOACs not specified) |

EMR: Endoscopic mucosal resection; DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; OR: Odds ratio; PPB: Post-procedural bleeding.

**Table 54 Endoscopic submucosal dissection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Igarashi *et al*[56] | 2017 | Japan | Retrospective | 30  | ESD | DOAC (ceased 3-7 d before) | Incidence of PPB 10.0% (warfarin and DOAC combined) |
| Sato *et al*[57] | 2017 | Japan | Retrospective | 18 | ESD | DOAC (ceased 24-48 h before) | Incidence of PPB 5.6% |
| Yoshio *et al*[132] | 2017 | Japan | Retrospective | 24 | ESD | DOAC: (1) Rivaroxaban/Apixaban ceased 2 d before; (2) Dabigatran ceased 1-2 d before | Incidence of PPB on Rivaroxaban 45.5%. No incidence of PPB on dabigatran or apixaban |
| Kono et al[58] | 2018 | Japan | Retrospective | 872 | ESD | DOAC either: (1) Ceased 1-3 d before; (2) Ceased 2 d before with HBT | DOACs ceased 1-3 d before without HBT group: (1) Incidence of PPB 6.4%; (2) Warfarin and DOACs with HBT: Incidence of PPB 29% |
| Yamashita *et al*[60] | 2018 | Japan | Retrospective | 650 | ESD | DOAC (ceased morning of) | Incidence of PPB 22.2% |
| Harada *et al*[61] | 2020 | Japan | Retrospective | 25 | ESD | DOAC (ceased 1 d before ± HBT) | Incidence of PPB 16% |

DOAC: Direct oral anticoagulant; ESD: Endoscopic submucosal dissection; HBT: Heparin bridging therapy; OR: Odds ratio; PPB: Post-procedural bleeding.

**Table 55 Endoscopic retrograde cholangiopancreatography with sphincterotomy**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Yamamiya *et al*[122] | 2019 | Japan | Retrospective | 76 | Sphincterotomy | DOAC either: (1) Continued; (2) Switched to HBT before | No incidence of PPB in either continuous or HBT group |
| Muro *et al*[138] | 2020 | Japan | Retrospective | 62 (149) | Sphincterotomy | DOAC: (1) Continued; (2) With HBT | No incidence of PPB (continued DOAC). Incidence of PPB 6.5% (HBT) |

DOAC: Direct oral anticoagulant; HBT: Heparin bridging therapy; PPB: Post-procedural bleeding.

**Table 56 Percutaneous endoscopic gastrostomy/percutaneous endoscopic jejunostomy insertion**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Country** | **Study design** | ***n*** | **Procedure** | **Medication** | **Relative risk** |
| Lee *et al*[123] | 2013 | South Korea | Retrospective | 71 (1625) | PEG | DOAC (N/S whether continued or ceased before) | Study expressed risk of PPB as OR (OR: 7.26, 95%CI: 2.23-23.68, *P* = 0.001) (included both warfarin and DOAC) |

DOAC: Direct oral anticoagulant; OR: Odds ratio; PPB: Post-procedural bleeding; PEG: Percutaneous endoscopic gastrostomy.