
Periendoscopic Use of Anticoagulants and Antiplatelet Agents

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Abstract

Anticoagulants and antiplatelet agents are very commonly prescribed. They have clear benefits in cardiovascular disease but confer a risk of haemorrhage, particularly in the context of therapeutic procedures. Therapeutic endoscopic procedures also have clear benefits but confer a risk of haemorrhage, which is increased by anticoagulants and antiplatelet therapy. Discontinuation of anticoagulants or antiplatelet agents may result in thrombosis. In the context of clopidogrel therapy for coronary artery stents, discontinuation of therapy could lead to acute myocardial infarction or death. There is therefore a risk:benefit scenario in the case of patients undergoing endoscopy while taking these medications. Here a practical evidenced-based approach is discussed to resolve these issues and offer clinical guidance

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Anticoagulants and antiplatelet agents are very widely prescribed. It is estimated that there are more than 1 million individuals in the United Kingdom, and more than 2 million in the United States taking warfarin. Clopidogrel has been prescribed to millions of individuals worldwide. These drugs are of proven benefit in reducing risks associated with cardiovascular disease, but confer an increased risk of bleeding; spontaneously or after therapeutic interventional procedures. When planning endoscopic procedures in patients taking these drugs it is important to consider the potential increased risks of the procedure in relation to the risks of discontinuing drug therapy. However, evidence for the risks associated with continuing or discontinuing these drugs in the periendoscopic period is limited. Following published guidance from the American Society for Gastrointestinal Endoscopy (ASGE) [1, 2] there has been wide variation in practice noted in surveys in the United Kingdom and the Far East [3, 4]. Guidance produced by the ASGE and the British Society of Gastroenterology (BSG) [1, 2, 5] forms the basis of the advice in this chapter. Discussion will be limited to the most widely prescribed anticoagulants, warfarin and heparin, and to the most widely prescribed antiplatelet agents, aspirin and clopidogrel.

Benefits and Risks of Therapy

Anticoagulants

Warfarin is widely prescribed to patients at risk of cardiovascular and cerebrovascular disease. The risk of stroke associated with atrial fibrillation (AF) varies from 1.9 to

18.2%/annum depending on comorbidity. Hypertension, heart failure and diabetes mellitus increase this risk, which can be estimated using the CHADS2 score [6]. A retrospective study of anticoagulated AF patients, whose anticoagulation was adjusted pre-endoscopy, examined the subsequent risk of stroke [7]. This ranged from 0.13% in those with uncomplicated AF to 2.93% in complex patients of advanced age. Mitral stenosis increases the risk of stroke associated with AF by 3–7 times [8, 9]. In a meta-analysis involving greater than 9,000 patients, warfarin reduced the risk of stroke associated with AF by 62% [10]. Venous thromboembolism is a major source of morbidity and mortality, resulting in approximately 25,000 deaths/year in the UK and 200,000 in the US. Warfarin is the mainstay of treatment, initially co-prescribed with heparin until satisfactory anticoagulation levels are achieved with warfarin.

Metal prosthetic heart valves confer a risk of thromboembolism, and anticoagulation is indicated. Biological valve prostheses generally require only aspirin therapy in the absence of other indications for anticoagulation. Metal prostheses in the aortic position are at lower risk of thromboembolism than those in the mitral position [11]. The relative risk of thromboembolism associated with metal prosthetic heart valves is high, but the absolute risk low: a meta-analysis of studies covering more than 50,000 patient years estimated the risk of thromboembolism when not on warfarin to be only 4 events/100 patient years. This is reduced to 2.2 events/100 patient years on aspirin and 1 on warfarin [12]. Over a 7-day period of discontinuation of anticoagulation the risk of thromboembolism would be approximately 0.2%. This has not been tested prospectively in the context of endoscopy.

In the elderly, warfarin confers an annual risk of severe haemorrhage of 1.5%, including cerebral haemorrhage of 0.3% [13]. Response to warfarin therapy is measured by the international normalised ratio (INR). This is used to monitor treatment, and the level required depends on the indication. A high INR confers a higher risk of spontaneous haemorrhage but is a poor predictor of haemorrhage in response to interventional medical procedures [14].

Heparin is available in unfractionated (UFH) and low molecular weight (LMWH) forms. UFH has to be administered by continuous intravenous injection, compared to subcutaneously once daily for LMWH. In addition, UFH therapy has to be monitored by measurement of the activated partial thromboplastin time, and this is unnecessary for LMWH. LMWH has therefore superseded UFH for most indications. LMWH is widely used for the prevention and treatment of deep vein thrombosis and pulmonary embolism, and in the treatment of unstable coronary syndromes. Traditionally UFH has been used as bridging therapy for patients with metal prosthetic heart valves who need temporary discontinuation of warfarin for a therapeutic procedure. One study of greater than 1,000 patients in this situation found no thromboembolic events during short-term bridging with LMWH [15]. Substitution of LMWH rather than UFH in this context is widely practiced, but there have been no randomised controlled trials.

LMWH can be administered as a temporary substitute for warfarin in patients who require continued anticoagulation prior to an endoscopic procedure with a high risk of haemorrhage. It can be administered where necessary on an outpatient basis with appropriate nursing input, or by the patient themselves. The short half-life of LMWH (5 h) compared to warfarin (2.5 days) allows this to be administered safely until the day before the procedure, omitting the dose on the morning of the procedure. Warfarin can be recommenced that evening and LMWH recommenced the following day until the INR is within the therapeutic range.

Antiplatelet Agents

The most commonly prescribed antiplatelet agents are aspirin and clopidogrel. Aspirin is effective in the treatment and prevention of cardiovascular and cerebrovascular disease, and is very widely prescribed. Fortunately, aspirin therapy is safe in the context of both diagnostic and therapeutic endoscopic procedures. This has been demonstrated in large series involving endoscopic polypectomies or sphincterotomies [16–19].

Clopidogrel inhibits platelet aggregation. Its effects last for the life of the platelets, and platelet function has been demonstrated to return to normal 7 days after discontinuation of therapy. Clopidogrel is indicated in the treatment and prevention of acute coronary syndromes, and in the prevention of occlusion of coronary artery stents. Coronary stents are at risk of occlusion, but this is diminished in the case of drug-eluting stents, with a reduction in the need for repeat intervention from 20 to 5% in randomised controlled trials [20, 21]. The risk of stent thrombosis is present until the stent has undergone re-endothelialisation; this takes approximately 1 month for bare metal stents and at least 6 months for drug-eluting stents. Dual therapy with aspirin and clopidogrel must be prescribed until this process has occurred; discontinuation of therapy is associated with a 50% risk of myocardial infarction or death [22]. Case reports of late stent thrombosis have prompted the Food and Drug Administration in the United States and the British Cardiovascular Intervention Society to recommend continuation of aspirin and clopidogrel for 1 year. The risk of stent thrombosis on discontinuation of clopidogrel is greatest after 5 days. In the event of cessation of therapy for an emergency endoscopic procedure, the endoscopy should be carried out as soon as possible within that time period.

Antiplatelet agents confer an increased risk of bleeding, but the risk of spontaneous gastrointestinal haemorrhage is less for clopidogrel than with aspirin [23]. Clopidogrel is widely held to increase the risk of haemorrhage during operative procedures but there are limited data, and none for gastrointestinal endoscopy. Data from studies of cardiac surgery demonstrate an increase in perioperative haemorrhage in those patients who remained on clopidogrel [24, 25]. For any interventional procedure with a risk of haemorrhage, the benefit of the procedure must be balanced against the risk of discontinuing clopidogrel, and this will be dependent on the indication for clopidogrel therapy.

Endoscopic Procedures

The benefits of endoscopy in the diagnosis and therapy of diseases within the gastrointestinal tract are well recognised, and the boundaries are continually expanded by new and improved technologies. This also applies to non-endoscopic diagnostic techniques, particularly radiology, where effective alternatives to diagnostic endoscopy exist, and continue to be developed. Alternative diagnostic modalities are important to consider in patients at high risk of thrombosis if discontinuing anticoagulants or antiplatelet agents, although they may ultimately require a therapeutic intervention if pathology is found. Data on the risks of haemorrhage associated with endoscopic procedures are generally good for commonly performed interventions such as colonoscopic polypectomy or endoscopic sphincterotomy. For newer and less frequently performed procedures, however, data are limited and tend to be less universally applicable due to the influence of local expertise or case mix in the published series. Minor haemorrhage during endoscopic procedures is not uncommon, but for the purposes of this discussion, haemorrhage which requires an unplanned admission to hospital, or transfusion, will be considered. Haemorrhage may occur at the time of the procedure, or be delayed by up to 2 weeks or more.

Table 1. Risk of haemorrhage associated with therapeutic endoscopic procedures

Procedure	Risk of haemorrhage %	References
Colonoscopic polypectomy	0.07–1.7	26, 27
Endoscopic mucosal resection	5.3	32
Endoscopic submucosal dissection	0.15–6	29, 30, 31
ERCP + sphincterotomy	1.13–5.3	17, 33–36
Oesophageal dilatation	2.2	39
Oesophageal stent	7.3–8	40, 41
Percutaneous endoscopic gastrostomy	≤2	42
Endoscopic ultrasound with FNA	6	37, 38

ERCP = Endoscopic retrograde cholangiopancreatography; FNA = fine needle aspiration.

Before considering the risks of endoscopy on anticoagulation or antiplatelet therapy it is helpful to consider the risks associated with therapeutic procedures undertaken in patients not taking these medications (table 1). Haemorrhage following colonoscopic polypectomy has been reported in large prospective series. A British study of 9,223 colonoscopies reported an incidence of 1.7% [26], and an American series of 13,580 reported 0.07% [27]. A number of factors will influence the risk of haemorrhage, including endoscopic technique and the size of polyp. Experience suggests that diathermy using ‘coagulation’ current results in a lower risk of haemorrhage than ‘blend’ or ‘cut’ current, but there are no prospective data to support this. Injection of adrenaline into the base or stalks of large polyps has been demonstrated to reduce the incidence of haemorrhage in one small randomised study [28]. Endoscopic submucosal dissection (ESD) is a relatively new technique associated with a high incidence of intra-procedural haemorrhage, although this is usually controlled by coagulation diathermy during the procedure. Delayed haemorrhage can, however, be problematic. The greatest experience to date comes from Japan. In a series of gastric ESDs only 1/655 (0.15%) experienced haemorrhage requiring transfusion [29]. In a series of colonic ESDs 4/200 (2%) had delayed bleeding after 1–3 days which required endoscopic haemostasis; none required transfusion [30]. The incidence of delayed haemorrhage has been reported to be as high as 6% after ESD [31] and 5.3% after endoscopic mucosal resection [32].

Several large series have examined post-sphincterotomy haemorrhage at endoscopic retrograde cholangiopancreatography: range 1.13–5.3% [17, 33–36]. Biliary or pancreatic stenting has not been demonstrated to be associated with significant haemorrhage. Diagnostic endoscopic ultrasound is not associated with haemorrhage, but this has been reported in association with fine needle aspiration performed at the time of the procedure [37, 38]. Emergency banding of oesophageal varices occurs in the context of acute haemorrhage. Elective therapy of oesophageal varices can provoke immediate haemorrhage but there are no data available regarding the incidence of this, and it is usually resolved by the procedure. Oesophageal dilatation carries a small risk of haemorrhage but recent data on incidence are lacking. A study of balloon dilatation of oesophageal strictures published in 1986 demonstrated post-procedural haemorrhage in 2.2% [39]. Oesophageal stenting has been reported as being associated with a risk of fatal haemorrhage of 7.3–8% [40, 41], but in many of these cases haemorrhage occurred weeks after stent insertion. Haemorrhage due to percutaneous endoscopic gastroenterostomy insertion has been reported at 2% [42], but again many of these instances occurred at a delayed interval, and due to pathology such as local ulceration rather than the endoscopic intervention itself. Diagnostic procedures,

including endoscopic pinch biopsies, are generally not associated with significant haemorrhage [43]. There have been isolated case reports of splenic haemorrhage due to trauma during colonoscopy [44–46], but this complication has not been reported in very large case series [26, 27].

Anticoagulants or antiplatelet agents are likely to increase the risks of haemorrhage described above. Diagnostic biopsies are considered safe while on anticoagulant or antiplatelet therapy [1, 47, 48] but there are no prospective data. There are very few studies on the risks of haemorrhage due to therapeutic endoscopic procedures while on warfarin as this is usually discontinued, or substituted with heparin. In a retrospective study of 1,657 patients undergoing colonoscopic polypectomy, the risk of post-polypectomy haemorrhage while on warfarin was increased by a factor of 13.37 [16]. One small study, however, demonstrated safe removal of small polyps while on warfarin after endoscopic clipping of the polypectomy site [48]. However, it should be considered generally that therapy with warfarin or clopidogrel will increase the risks of haemorrhage associated with the above procedures.

Risk:Benefit Analysis

Emergency Procedures

In the context of acute severe gastrointestinal haemorrhage in a patient on anticoagulants or antiplatelet therapy, the immediate risk to the patient is from bleeding rather than thrombosis. For those patients on therapy for conditions with a relatively low risk of thrombosis, then temporary discontinuation of anticoagulation or antiplatelet therapy is clearly indicated. Indeed for patients on warfarin it may be necessary to administer fresh frozen plasma if the haemorrhage is life-threatening. As discussed above, even in the instance of anticoagulation for metal prosthetic heart valves, temporary discontinuation confers a small absolute risk of thrombosis [12]. Adequate resuscitation of the patient is of course paramount, as is early endoscopic intervention to achieve haemostasis.

In the event of acute gastrointestinal haemorrhage in a patient on clopidogrel for coronary artery stents, then discontinuation of therapy might result in a life-threatening occlusion of a coronary stent. It is recommended that a senior cardiologist is involved in the patient's management at an early stage. If clopidogrel needs to be discontinued then endoscopy should be performed as soon as possible. Clopidogrel therapy should be discontinued for as short an interval as possible, and not beyond 5 days, as the risk of stent thrombosis increases markedly after this period. It may be that, with early effective endoscopic haemostasis, clopidogrel can be continued in many cases.

Elective Procedures

The decision whether to continue or discontinue anticoagulant or antiplatelet therapy in a patient due to undergo endoscopy depends on the relative risk of thrombosis on stopping therapy vs. the risk of haemorrhage due to the procedure. Figure 1 summarises these risk categories and advises on management in each instance. In applying this guidance the individual clinical situation should be taken into consideration, as should the limited data upon which this guidance is based. In the context of clopidogrel for coronary artery stents, it is advisable to liaise with the patient's cardiologist as there may be additional risk factors pertinent to that patient. In the American and British guidelines [1, 2, 5], AF without valvular disease is considered a low risk condition, but additional comorbidity such as heart failure and diabetes increase the risk of thrombosis. If

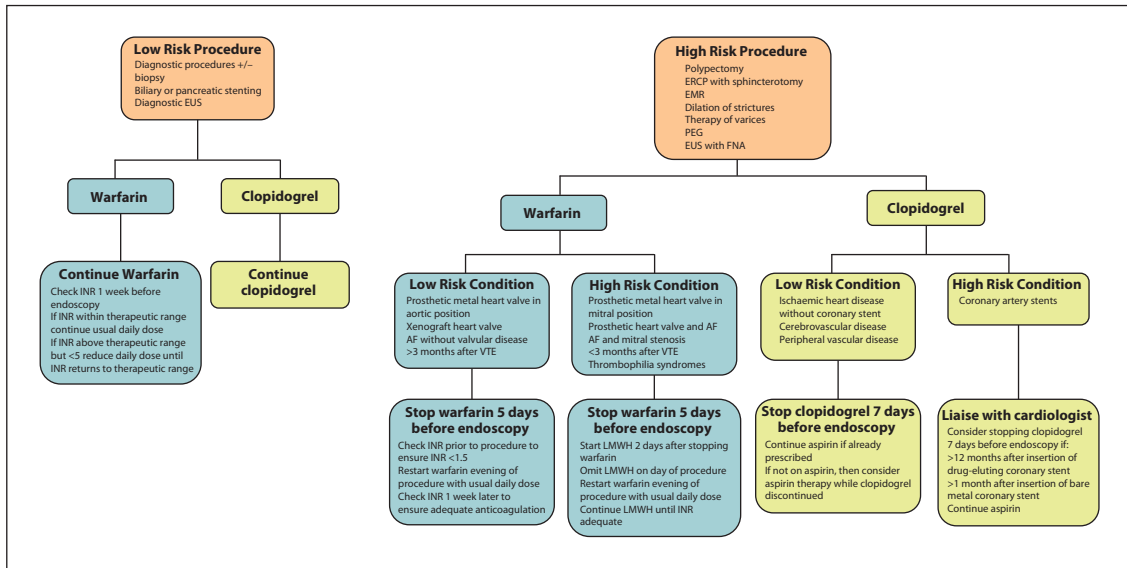


Fig. 1. Periendoscopic use of anticoagulants and antiplatelet agents. EUS = Endoscopic ultrasound; ERCP = endoscopic retrograde cholangiopancreatography; EMR = endoscopic mucosal resection; PEG = percutaneous endoscopic gastroenterostomy; FNA = fine needle aspiration; INR = international normalised ratio; AF = atrial fibrillation; VTE = venous thromboembolism; LMWH = low molecular weight heparin. Reproduced from Veitch et al. [5] with permission from BMJ publishing.

desired, further categorisation according to CHADS2 score could be undertaken to quantify this risk [6]. In patients with coronary artery stents receiving clopidogrel, an alternative radiological investigation could be considered in the first instance. Removal of a small colonic polyp may be delayed until clopidogrel is no longer required. If malignant disease is found then the risks of surgery will need to be considered. Diagnostic colonoscopy is considered low risk, but polyps are likely to be present in 22.5–34.2% [26, 27]. One could pragmatically categorise colonoscopy as high risk on this basis, but on an individual level, a young patient with undiagnosed diarrhoea or known inflammatory bowel disease is likely to just need diagnostic biopsies. For endoscopic retrograde cholangiopancreatography in a patient with a known malignant stricture, then stenting is required which is low risk. If stones are suspected, or the diagnosis uncertain, then a sphincterotomy may be required, which is high risk.

In patients in whom warfarin is temporarily discontinued, it is advised to restart anticoagulation on the night of the procedure. In one study 41/4,592 (0.9%) colonoscopic polypectomies developed severe post-polypectomy haemorrhage [49]. Case-control analysis identified that 34% of patients who bled had resumed anticoagulation within 1 week of the procedure compared to 9% of controls (OR 5.2). It would be prudent to advise all patients resuming anticoagulant therapy after endoscopic therapy that they have an increased risk of delayed haemorrhage.

The time intervals advised for discontinuation or substitution of drug therapy (fig. 1) are based on the pharmacology of the drugs involved. A safe level of INR of <math>< 1.5</math> for therapeutic procedures is arbitrary, and based on anecdotal experience. This has not been prospectively tested, but moderately elevated INR levels have been found to be a poor predictor of subsequent haemorrhage in a variety of non-endoscopic invasive procedures [14].

Conclusion

The periendoscopic management of patients on anticoagulant or antiplatelet agents depends on a balance of risk factors. There is a risk of thrombosis on discontinuation of these drugs, and a risk of haemorrhage associated with the endoscopic procedure. The clinical context, including comorbidity and the likelihood of detecting pathology in individual patients, should also be considered. The guidance in this chapter is based on that published by the ASGE [1, 2] and the BSG [5]. None of the guidance has been rigorously prospectively tested, but neither have there been case reports to refute it.

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