

# Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures

A M Veitch,<sup>1</sup> T P Baglin,<sup>2</sup> A H Gershlick,<sup>3</sup> S M Harnden,<sup>1</sup> R Tighe,<sup>4</sup> S Cairns<sup>5</sup>

<sup>1</sup> Department of Gastroenterology, New Cross Hospital, Wolverhampton, UK; <sup>2</sup> Department of Haematology, Addenbrooke's Hospital, Cambridge, UK; <sup>3</sup> Department of Cardiology, University Hospitals of Leicester, Leicester, UK; <sup>4</sup> Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich, UK; <sup>5</sup> Department of Gastroenterology, Royal Sussex County Hospital, Brighton, UK

Correspondence to: Dr A M Veitch, New Cross Hospital, Wolverhampton, WV10 0QP, UK; andrew.veitch@rwh-tr.nhs.uk

The authors form a working party for the British Society of Gastroenterology, the British Committee for Standards in Haematology and the British Cardiovascular Intervention Society.

Revised 9 April 2008  
Accepted 16 April 2008  
Published Online First 9 May 2008

## 1.0 SUMMARY OF RECOMMENDATIONS

Please refer to fig 1 for an algorithmic representation of the recommendations, and tables 1–3 for a risk stratification of endoscopic procedures and medical conditions requiring anticoagulant or antiplatelet therapy. Aspirin therapy can be continued for all endoscopic procedures.

### 1.1 Acute gastro-intestinal haemorrhage

Acute gastro-intestinal haemorrhage in patients on anticoagulant or antiplatelet agents is a high-risk situation. The immediate risk to the patient from haemorrhage may outweigh the risk of thrombosis as a result of stopping anticoagulant or antiplatelet therapy. Patients need to be assessed on an individual basis, and it is not possible to give unequivocal guidance to cover all situations. For patients with high-risk conditions on warfarin, then this can be discontinued with or without substitution of heparin depending on the severity of haemorrhage and risk of discontinuing anticoagulant therapy. There is a high risk of acute myocardial infarction or death if clopidogrel is discontinued in patients with coronary stents, particularly early after implantation, but extending up to 1 year after this. Endoscopy should be attempted as soon as safely possible after urgent liaison between the patient's cardiologist and the consultant specialist undertaking endoscopy. Clopidogrel should not be discontinued without discussion with a cardiologist. If clopidogrel therapy needs to be discontinued in this context, then this should be limited to a maximum of 5 days as the risk of stent thrombosis increases after this interval. (Evidence grade III. Recommendation grade B.) Early therapeutic endoscopic intervention may achieve haemostasis with minimal or no cessation of anticoagulant or antiplatelet therapy, and should be the first aim. (Evidence grade IV. Recommendation grade C.)

### 1.2 Low-risk endoscopic procedures

Anticoagulation or antiplatelet therapy should be continued. (Evidence grade IV. Recommendation grade C.) If warfarin is continued then it should be ensured that the international normalised ratio (INR) does not exceed the therapeutic range: (Evidence grade IV. Recommendation grade C.)

- ▶ Tell the patient to continue warfarin and check the INR 1 week before the endoscopy.
- ▶ If the INR result is within the therapeutic range then continue with the usual daily dose.
- ▶ If the INR result is above the therapeutic range, but less than 5, then reduce the daily warfarin

dose until the INR returns to within the therapeutic range.

- ▶ If the INR is greater than 5 then telephone the endoscopy department to defer the appointment and contact the anticoagulation clinic, or a medical practitioner, for advice.

### 1.3 High-risk endoscopic procedure: low-risk condition

#### 1.3.1 Warfarin

Warfarin should be temporarily discontinued. (Evidence grade III. Recommendation grade B.)

- ▶ Stop warfarin 5 days before endoscopy.
- ▶ Check INR prior to procedure to ensure <1.5.
- ▶ On the day of the procedure restart warfarin with the usual daily dose that night.
- ▶ Check INR 1 week later to ensure adequate anticoagulation.

#### 1.3.2 Clopidogrel

Clopidogrel should be stopped 7 days prior to the procedure. (Evidence grade IIb. Recommendation grade B.) If the patient is on aspirin, this should be continued. If not, then consideration should be given to prescribing aspirin while clopidogrel is stopped. If clopidogrel is discontinued then all attempts should be made to undertake the endoscopy procedure at the end of the planned allotted discontinuation time period. If this has to be postponed beyond this time then consideration should be given to re-starting the clopidogrel and re-scheduling the endoscopy.

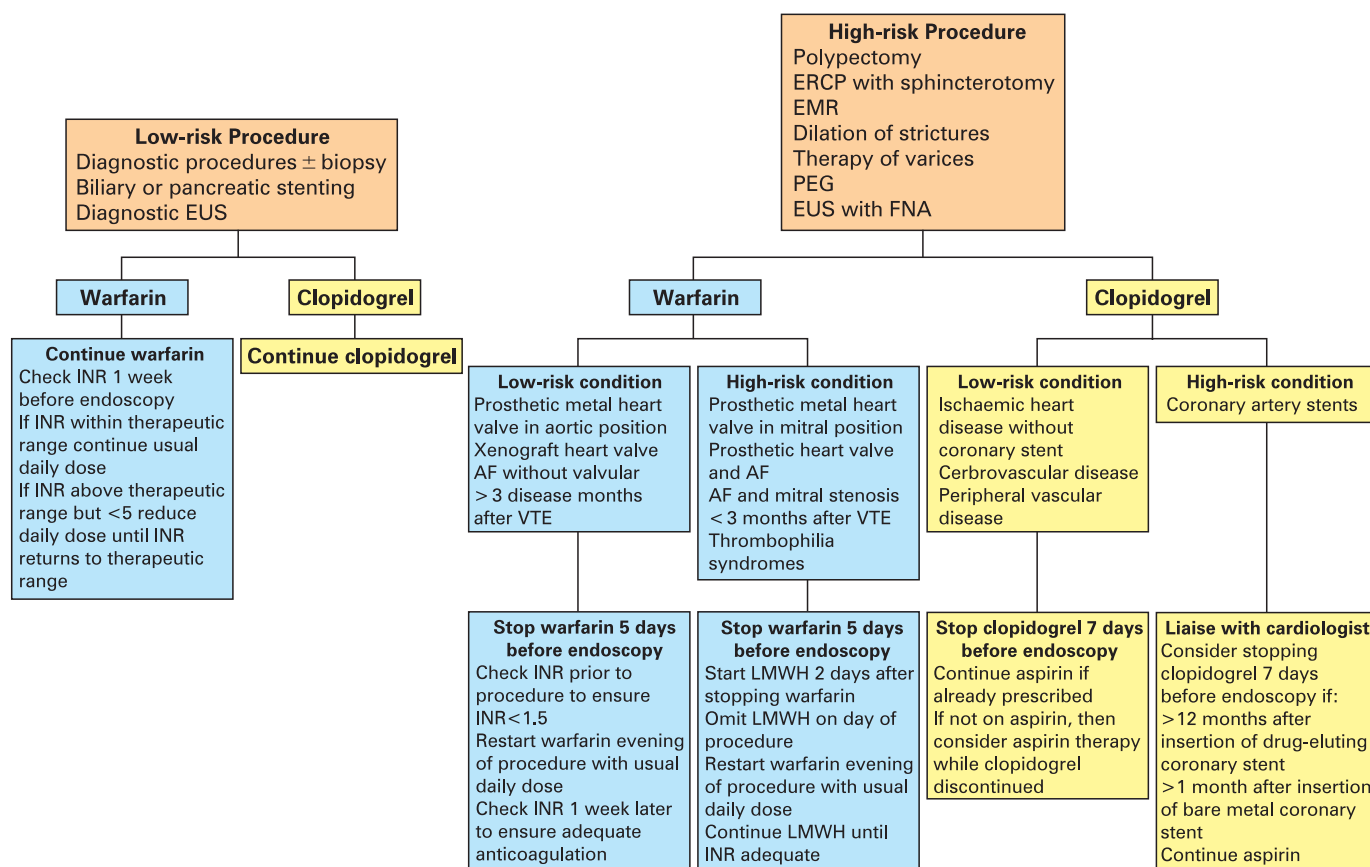
### 1.4 High-risk endoscopic procedure: high-risk condition

#### 1.4.1 Warfarin

Warfarin should be temporarily discontinued and substituted with low molecular weight heparin (LMWH). (Evidence grade III. Recommendation grade B.)

- ▶ Warfarin should be stopped 5 days before the procedure.
- ▶ Two days after stopping warfarin commence the daily therapeutic dose of LMWH.
- ▶ Omit LMWH on the day of the procedure.
- ▶ Warfarin can be recommenced on the day of the procedure with the usual dose that night.
- ▶ Recommence the daily therapeutic dose of LMWH on the day after the procedure.
- ▶ Continue LMWH until a satisfactory INR is achieved.

Patients should be advised that there is an increased risk of post-procedure bleeding compared



**Figure 1** Guidelines for the management of patients on warfarin or clopidogrel undergoing endoscopic procedures. AF, atrial fibrillation; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; INR, international normalised ratio; LMWH, low molecular weight heparin; PEG, percutaneous endoscopic gastroenterostomy; VTE, venous thromboembolism.

with non-anticoagulated patients. (Evidence grade III. Recommendation grade B.)

#### 1.4.2 Clopidogrel

Discontinuation of clopidogrel therapy should only be considered after discussion with the patient's cardiologist. A consultant gastro-intestinal physician or surgeon should be involved to confirm that the endoscopic procedure is essential.

- ▶ If bare metal coronary stents were placed more than 1 month ago then clopidogrel could be temporarily discontinued. (Evidence grade III. Recommendation grade B.)
- ▶ If drug-eluting coronary stents were placed more than 12 months ago then clopidogrel could be temporarily discontinued. (Evidence grade III. Recommendation grade B.)
- ▶ If drug-eluting coronary stents were placed more than 6 months ago, and the procedure is essential, then it may be safe to temporarily discontinue clopidogrel. (Evidence grade IV. Recommendation grade C.)
- ▶ Clopidogrel should be stopped 7 days prior to the procedure.
- ▶ Aspirin therapy should be continued.
- ▶ On the day following the procedure restart clopidogrel.

## 2.0 ORIGIN AND PURPOSE OF THESE GUIDELINES

These guidelines were commissioned by the British Society of Gastroenterology, and essential expertise was provided by collaboration with the British Committee for Standards in

Haematology and the British Cardiovascular Intervention Society. Prescription of anticoagulants is very common, and in addition there has been increasing prescription of antiplatelet agents for ischaemic heart disease, and in the context of coronary artery stenting. There is a risk of haemorrhage associated with many endoscopic procedures and this may be exacerbated in patients receiving these agents. Excellent guidelines have been produced by the American Society for Gastrointestinal Endoscopy,<sup>1,2</sup> but these provide limited guidance on the management of cardiac patients on antiplatelet agents. Our guidance does not conflict with the American guidance, but expands upon it. A recent survey of UK endoscopists found a wide variation in practice regarding the management of anticoagulants in patients undergoing endoscopy.<sup>3</sup> There is a need for clear up-to-date guidance on the management of patients undergoing endoscopic procedures who are receiving these drugs, and who may be at risk from the procedure itself or from discontinuing their medication.

## 3.0 PREPARATION OF THE GUIDELINES

These guidelines were drafted by a working party of representative members of the Endoscopy Committee of the British Society of Gastroenterology, the British Committee for Standards in Haematology, and the British Cardiovascular Intervention Society. Authors were nominated as representatives of their respective societies. A literature research was conducted using PubMed, and further sources were obtained from the reference lists of those papers identified. Additional

references were identified by members of the respective committees involved. This guidance has been supported unanimously by the authors, and the Endoscopy Committee of the British Society of Gastroenterology.

### 3.1 Grading of evidence

- ▶ *Grade Ia*: Meta-analysis of randomised controlled trials (RCTs)
- ▶ *Grade Ib*: At least one RCT
- ▶ *Grade IIa*: At least one well-designed controlled study without randomisation
- ▶ *Grade IIb*: At least one other type of well-designed quasi-experimental study
- ▶ *Grade III*: Well-designed non-experimental descriptive studies (for example, comparative, correlation or case studies)
- ▶ *Grade IV*: Expert committee reports or opinions and/or clinical experiences of respected authorities

### 3.2 Grading of recommendations

- ▶ *Grade A*: At least one RCT (Ia, Ib)
- ▶ *Grade B*: Well-conducted clinical studies (IIa, IIb, III)
- ▶ *Grade C*: Respected opinions but the absence of directly applicable good quality clinical studies (IV)

## 4.0 ANTICOAGULANTS

The most commonly used oral anticoagulant is warfarin. Heparin is the most commonly used parenteral anticoagulant and is available in unfractionated and low molecular weight forms. Other oral and parenteral anticoagulants are available but seldom indicated. Recommendations for the management of patients on warfarin or heparin, respectively, can be applied in these instances.

### 4.1 Pharmacology and mechanism of action

#### 4.1.1 Warfarin

Warfarin is a coumarin derivative that inhibits vitamin K epoxide reductase, which leads to intrahepatic depletion of the reduced form of vitamin K which is a necessary co-factor for the post-translational modification of vitamin K-dependent proteins. Warfarin is the most widely used oral vitamin K antagonist because it has excellent bioavailability, with maximum blood concentrations in healthy volunteers within 90 min and it rapidly accumulates in the liver. It has a half-life in excess of 40 h, with a prolonged dose-dependent terminal phase of elimination with detectable warfarin levels 120 h after a single dose. The average dose required to achieve an INR of 2.5 is between 3 and 5 mg, although some patients require as little as 1 mg and some as much as 30 mg, or more.

The major complication of treatment with warfarin is haemorrhage. As well as a risk of excessive bleeding after trauma or surgery there is also a risk of spontaneous bleeding. The risk of bleeding is related to the INR, not the dose of warfarin. The higher the INR, the greater the risk of bleeding. The risk of developing a high INR is related to the target INR and is increased during intercurrent illness especially when additional drugs are prescribed. The risk of over-anticoagulation and bleeding is also more likely in patients whose anticoagulant control is unstable. The INR is derived from the prothrombin time ratio and is a standardised method of reporting which permits comparability between laboratories.<sup>4</sup>

**Table 1** Risk stratification of endoscopic procedures based on risk of haemorrhage

High risk	Low risk
Colonoscopic polypectomy	Diagnostic procedures, with or without biopsy
ERCP with sphincterotomy	Biliary or pancreatic stenting
Endoscopic mucosal resection or endoscopic submucosal dissection	Diagnostic endoscopic ultrasound
Endoscopic dilatation of strictures in the upper or lower GI tract	
Endoscopic therapy of varices	
Percutaneous gastrostomy	
Endoscopic ultrasound with fine needle aspiration	

This table is adapted from the American Society for Gastrointestinal Endoscopy (ASGE) guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures.<sup>1</sup>

ERCP, endoscopic retrograde cholangiopancreatography; GI, gastro-intestinal.

#### 4.1.2 Heparin

Heparins are naturally occurring glycosaminoglycans. All the products currently used in the UK are of porcine origin. The anticoagulant action of heparin is due to a combination of indirect antithrombin and anti-Xa activity. LMWHs are less protein bound than unfractionated heparin (UFH) and have a predictable dose-response profile. They also have a longer half-life than standard heparin preparations. Bleeding is the main complication of heparin therapy. It is uncommon, but patients with impaired hepatic or renal function, with carcinoma, and those over 60 years appear to be most at risk. An activated partial thromboplastin time (APTT) ratio >3 is associated with an increased risk of bleeding in patients receiving UFH.

Heparin-induced thrombocytopenia with or without thrombosis (HITT) is due to an autoantibody against heparin in association with platelet factor 4, causing platelet activation.<sup>5</sup> HIT should be suspected in any patient in whom the platelet count falls by 50% or more after starting heparin. It usually occurs after 5 or more days of heparin exposure (or sooner if the patient has previously been exposed to heparin). Thrombosis occurs in less than 1% of patients treated with LMWH but is associated with a mortality and limb amputation rate in excess of 30%. Patients with a diagnosis of HITT should have all heparin (UFH and LMWH) stopped and an alternative thrombin inhibitor, such as danaparoid or lepirudin should be given. Warfarin should not be started until adequate anticoagulation has been achieved with one of these agents and the platelet count has returned to normal.

### 4.2 Clinical indications for use

#### 4.2.1 Warfarin

Long-term oral anticoagulation with warfarin is particularly effective for the prevention and treatment of venous thromboembolism and prevention of embolisation in association with atrial fibrillation or prosthetic heart valves. The British Society for Haematology has recently reviewed guidelines for intensity and duration of anticoagulation for specific indications.<sup>6</sup> The benefits of anticoagulation need to be balanced against the risks. For elderly patients on warfarin there is an annual risk of 1.5% of major haemorrhage and of 0.3% of intracerebral haemorrhage.<sup>7</sup>

#### 4.2.2 Heparin

Heparin remains the most widely used parenteral antithrombotic.<sup>6</sup> Although unfractionated heparin (UFH) is still used, for many indications there has been a trend towards the use of

fractionated or low molecular weight heparins (LMWHs). Heparin is used when it is necessary to achieve immediate anticoagulation. Unfractionated heparin was the type of heparin used for the prevention and treatment of deep vein thrombosis and pulmonary embolus for many years. It is given either as a continuous intravenous infusion or by subcutaneous injection. Treatment is monitored by determining the APTT ratio. A typical regimen would be to give sufficient heparin to prolong the APTT to 2.0 times normal (range, 1.5–2.5). A normal starting dose would be 15–20 U/kg/day. The APTT should be measured within 6–12 h of starting treatment and the dose of heparin adjusted accordingly. Thereafter, the APTT should be measured preferably on a daily basis and the dose of heparin adjusted each day. Nowadays, the heparin of choice for prevention and treatment of deep vein thrombosis and pulmonary embolus and unstable coronary disease is a low molecular weight heparin (LMWH). LMWHs have the advantage that they can be given as a once daily subcutaneous injection without the need for monitoring or dose adjustment. Some trials of LMWH heparin as an alternative to warfarin during therapeutic procedures in patients with prosthetic heart valves have used a higher twice daily dosage,<sup>8</sup> but there is no evidence that this is superior to the standard daily dosage, and it is likely to carry an increased risk of haemorrhage.

Compared to unfractionated heparin, LMWH has a superior benefit:risk profile with an appreciably lower risk of heparin-induced thrombocytopenia with thrombosis (HITT syndrome).<sup>9</sup> Unfractionated heparin is still used in some circumstances as the short duration of action can be advantageous when it is necessary to vary the intensity of anticoagulation over a short time period, for example in a patient undergoing surgery.

## 5.0 ANTIPLATELET AGENTS

Aspirin, clopidogrel and dipyridamole are the most commonly prescribed antiplatelet agents. Ticlopidine was associated with severe side effects and has been superseded by clopidogrel. Glycoprotein IIb/IIIa inhibitors, abciximab, eptifibatid and tirofiban, may be indicated in the context of acute coronary syndromes. They are administered parenterally and are for short-term use. Endoscopic intervention in this group of patients would be high risk and reserved for life-threatening gastro-intestinal haemorrhage. In this context cardiac therapy may need to be discontinued after discussion with a cardiologist. These guidelines are primarily concerned with elective endoscopic procedures, and glycoprotein IIb/IIIa inhibitors will not be discussed further. There are no studies of the risks of endoscopic procedures on dipyridamole. The risk of spontaneous gastro-intestinal bleeding is less with dipyridamole than with aspirin.<sup>10</sup> As discussed below, aspirin can be safely continued during endoscopic procedures and the same policy can therefore be applied to dipyridamole. Further discussion will be limited to aspirin and clopidogrel therapy.

**Table 2** Risk stratification for discontinuation of anticoagulant therapy

High risk	Low risk
Prosthetic metal heart valve in mitral position	Prosthetic metal heart valve in aortic position
Prosthetic heart valve and atrial fibrillation	Xenograft heart valve
Atrial fibrillation and mitral stenosis	Atrial fibrillation without valvular disease
<3 months after venous thromboembolism	>3 months after venous thromboembolism
Thrombophilia syndromes	

## 5.1 Pharmacology and mechanism of action

Platelets are activated by multiple agonists through numerous intracellular second-messenger pathways and complex networks. The activation pathways converge on activation of the fibrinogen receptor such that an induced conformational change results in fibrinogen/fibrin binding. In addition to adhesion and aggregation at sites of vascular injury a major role of platelets in coagulation is the provision of an anionic phospholipid surface for assembly of the macromolecular coagulation factor complexes required for thrombin generation and clot formation. Receptors on the platelet membrane known to result in platelet activation through intracellular second-messengers include receptors for thrombin, adenosine diphosphate (ADP), collagen, thromboxane and adrenaline (epinephrine).

### 5.1.1 Aspirin

Thromboxane is synthesised by platelets in response to agonists, and receptors for thromboxane are present on the platelet membrane. Thromboxane synthesis is dependent on cyclooxygenase (COX). Aspirin (acetylsalicylic acid) inactivates COX by acetylation. Acetylation of COX is irreversible and whilst the pharmacokinetic half-life of aspirin is only 20 min the pharmacodynamic effect persists for the duration of the platelet lifespan of 7–10 days as the platelet is unable to effectively synthesise new COX enzymes.

### 5.1.2 Clopidogrel

Clopidogrel is an inhibitor of ADP-induced platelet aggregation.<sup>11</sup> It is a thienopyridine derivative whose metabolites block the interaction of ADP with an ADP receptor on the platelet membrane. It is activated in the liver via the cytochrome P450 system and therefore there is a 3–5 day delay in the onset of significant antiplatelet activity. Like aspirin the antiplatelet action is irreversible, but platelet function has been demonstrated to return to normal 7 days after withdrawal of clopidogrel.

## 5.2 Clinical indications for use

### 5.2.1 Aspirin

Aspirin reduces the mortality associated with acute myocardial infarction by 25% if started within 24 h of infarction. It also reduces the risk of fatal and non-fatal infarction in patients with unstable coronary syndromes. Doses of 75 and 162.5 mg are used. Aspirin at a dose of 160 or 300 mg daily reduces mortality and recurrent stroke in patients with acute cerebrovascular ischaemia. When given as long-term secondary prevention aspirin reduces vascular events by approximately one-third and vascular deaths by about one-sixth. Whilst the beneficial cardiovascular effect of aspirin is attributed to its antithrombotic action it is possible that some benefit of aspirin therapy relates to other aspects such as atherogenesis.

### 5.2.2 Clopidogrel

Clopidogrel may be a more potent antiplatelet agent than aspirin. Clopidogrel is used for prevention of arterial

**Table 3** Risk stratification for discontinuation of clopidogrel

High risk	Low risk
Drug eluting coronary artery stents within 12 months of placement	Ischaemic heart disease without coronary stents
Bare metal coronary artery stents within 1 month of placement	Cerebrovascular disease
	Peripheral vascular disease

thromboembolism in patients with atherosclerosis, for example those with peripheral vascular disease, myocardial infarction and acute coronary syndromes or thromboembolic stroke. It may be slightly more effective than aspirin alone and produces a synergistic effect when added to aspirin therapy, although combination therapy increases the bleeding risk. Clopidogrel has a specific and critical role in the prevention of occlusion of coronary artery stents which will be discussed below.

## 6.0 ENDOSCOPIC PROCEDURES: RISK OF HAEMORRHAGE

There is an intrinsic risk of haemorrhage with endoscopic procedures. Minor haemorrhage is not uncommon during therapeutic endoscopic procedures, but we shall consider it to be clinically significant when necessitating blood transfusion or an unplanned admission to hospital. Haemorrhage may be immediately apparent at the time of endoscopy, or delayed up to 2 weeks or more following the procedure. The latter situation presents a particular risk for patients who have received anticoagulants following the procedure. Diagnostic procedures, including biopsies, have a minimal risk of haemorrhage.<sup>12</sup> It is important to understand baseline risks of haemorrhage associated with common therapeutic endoscopic procedures as these will be exacerbated by agents that inhibit coagulation or platelet action.

Therapeutic dilatation of the oesophagus by bouginage or pneumatic dilatation carries a small risk of haemorrhage. Elective banding of oesophageal varices may provoke haemorrhage, although this can usually be effectively treated at the time of endoscopy. In a comparative study of oesophageal stents for palliation of malignant oesophageal strictures, fatal haemorrhage occurred in 7.3% of cases.<sup>13</sup> In another series, mortality due to stent-related haemorrhage was similar at 8%.<sup>14</sup> Haemorrhage was delayed in these studies, however, often by several weeks. Percutaneous endoscopic gastrostomy carries a risk of haemorrhage of up to 2% but this is often delayed to due to ulceration around the flange or coincident peptic ulceration, rather than by direct puncture of a vessel at the time of endoscopy.<sup>15</sup> There have been case reports of splenic trauma and resultant haemorrhage during colonoscopy, which may be associated with unsuspected splenic adhesions.<sup>16–19</sup> This appears to be a very rare complication, and no cases were reported in the large British and American series reported below which included a total of more than 20 000 cases. It is possible that subclinical splenic trauma may occur on occasions, but there are no data to support this. Haemorrhage due to colonoscopic polypectomy has been reported in 0.07–1.7% of cases.<sup>20–24</sup> In a prospective study of colonoscopic practice in the UK, encompassing 9223 colonoscopies, the proportion of episodes of post-polypectomy haemorrhage requiring admission to hospital was 1.7%.<sup>20</sup> An American prospective study of 13 580 colonoscopies found a post-polypectomy haemorrhage rate of 0.07%, although only 0.01% required transfusion.<sup>24</sup> Endoscopic technique may influence the risk of haemorrhage following therapeutic procedure. One study has examined the role of adrenaline injection in preventing haemorrhage in upper and lower gastro-intestinal polyps.<sup>25</sup> Patients were randomised to receive adrenaline injection or no injection into the base or stalk of polyps prior to polypectomy, and there was a reduction in immediate haemorrhage from 9.2% to 2.7% in the adrenaline groups. The overall rate of bleeding was 11% for gastric polypectomies and 2.2% for colonoscopic polypectomies; 6/9 of the patients who experienced haemorrhage had gastric polypectomies. Use of the techniques of endoscopic mucosal resection or endoscopic submucosal dissection in experienced

hands results in low rates of significant procedural haemorrhage. In a large series from Japan only 1/655 patients experienced haemorrhage requiring transfusion.<sup>26</sup> Use of coagulation current during diathermy is held by many to result in a lower risk of haemorrhage during polypectomy or sphincterotomy, but there are no randomised trials to support this. Sphincterotomy at endoscopic retrograde cholangiopancreatography (ERCP) carries a risk of haemorrhage of 1.13–5.3%.<sup>27–31</sup> The risk of haemorrhage during biliary or pancreatic stenting is minimal. Diagnostic endoscopic ultrasound (EUS) is not associated with haemorrhage but this has been reported as a consequence of fine needle aspiration during the procedure.<sup>32–35</sup>

## 7.0 ANTICOAGULANTS AND ANTIPLATELET AGENTS: RISK OF HAEMORRHAGE DURING ENDOSCOPIC PROCEDURES

### 7.1 Warfarin

Warfarin increases the risk of haemorrhage. There are few studies involving therapeutic procedures on warfarin as endoscopists have generally avoided this situation by stopping warfarin, or using heparin as an alternative. A retrospective study including 1657 patients undergoing colonoscopic polypectomy demonstrated an increased risk of post-polypectomy haemorrhage on warfarin with an odds ratio of 13.37.<sup>34</sup> In one small uncontrolled retrospective study colonoscopic polypectomies <1 cm in size were safely performed on therapeutic doses of warfarin with the aid of endoscopic clipping of the polypectomy site.<sup>35</sup> Diagnostic procedures can be conducted under anticoagulation, but this limits the scope of the procedure should pathology be detected. Expert opinion suggests that endoscopic pinch biopsies can be safely performed on warfarin,<sup>1,36</sup> but there are no trial data to support this. There have been anecdotal reports of rare instances of significant haemorrhage following pinch biopsies on warfarin within the therapeutic range. Heparin has some advantages over warfarin in the context of therapeutic endoscopic procedures. It has a shorter duration of action, and can also be reversed with protamine in the event of haemorrhage.

Anticoagulation is measured with the INR, and safe therapeutic ranges are quoted according to the indication. There are varying views as to what constitutes a safe level of INR in order to perform therapeutic endoscopic procedures, but a level below 1.5–1.3 is most commonly accepted. INR is, however, an unreliable indicator of the safety of performing therapeutic procedures. Extensive review of various invasive procedures performed with abnormal coagulation results has found no randomised controlled trials and very few quality studies.<sup>37–38</sup> None were of gastro-intestinal endoscopic procedures, but two studies of bronchoscopy with transbronchial biopsy found no association between mild to moderately abnormal coagulation results and the incidence of post-procedure bleeding. Similar conclusions were obtained for procedures such as liver biopsy, renal biopsy and femoral angiography, but confidence intervals were wide for all studies.

A systematic review of the safety and efficacy of management strategies for patients on oral anticoagulants requiring surgical procedures did not identify any randomised trials.<sup>39</sup> From an overview of descriptive studies 29 thromboembolic events were identified in 1868 patients (1.6%; 95% confidence interval (CI), 1.0 to 2.1%), including seven strokes (0.4%; 95% CI, 0 to 0.7%). Major bleeding was rare despite continuation of oral anticoagulation for the following procedures; dental (4/2014), joint and soft tissue aspirations and injections (0/32), cataract surgery (0/203) and upper endoscopy or colonoscopy with or without biopsy (0/111). Limited data in relation to prosthetic

mechanical valves, and not knowing the indications for anticoagulation in each of the management strategies, limits the usefulness of this review. When oral anticoagulation is stopped completely consideration should be given to low molecular weight heparin for patients at high risk of thromboembolic events.

### 7.2 Aspirin

Therapeutic endoscopic procedures can be safely performed on aspirin. In a case-control study involving 20 636 colonoscopies with polypectomy, there was no increased risk of haemorrhage associated with aspirin therapy.<sup>40</sup> This has been corroborated by other studies of polypectomy or sphincterotomy.<sup>30 34 41</sup>

### 7.3 Clopidogrel

There are no data on the risks of haemorrhage during gastrointestinal endoscopic procedures on clopidogrel, but anecdotal experience, and experience from other invasive procedures, suggests an increased risk for therapeutic procedures. Clopidogrel has been found to increase the risk of haemorrhage from transbronchial biopsies at bronchoscopy.<sup>42</sup> Moderate or severe haemorrhage occurred in 61% of clopidogrel patients compared to 1.8% in controls. Gastrointestinal endoscopic biopsies are safe on warfarin, and anecdotal experience suggests biopsies are safe on clopidogrel.

## 8.0 ANTICOAGULANTS AND ANTIPLATELET AGENTS: RISKS ASSOCIATED WITH DISCONTINUATION OF THERAPY

### 8.1 Atrial fibrillation

Anticoagulants are the most effective treatment for prevention of thromboembolic complications in chronic atrial fibrillation. The risk of stroke or thromboembolism in patients with atrial fibrillation in the absence of cardiac valvular disease is increased by five times compared to those in sinus rhythm.<sup>43</sup> The annual risk of stroke in this category of patients has been estimated according to the degree of co-morbidity at 1.9–18.2% per year.<sup>44</sup> Warfarin reduced the risk of stroke by 62% in a meta-analysis of 16 trials including 9874 participants.<sup>45</sup> With mitral stenosis, development of atrial fibrillation increases the risk of thromboembolic disease, particularly cerebrovascular events, by 3 to 7.<sup>46 47</sup> These events affect 9–20% of such patients.<sup>47 48</sup> Warfarin is, however, associated with an increased risk of major haemorrhage.<sup>7</sup> Co-existing heart failure, hypertension or diabetes mellitus can increase the risk of stroke in atrial fibrillation. A scoring system called CHADS2 has been devised to quantify this.<sup>44</sup> Guidance is also available from the National Institute for Health and Clinical Excellence.<sup>49</sup> A retrospective study of anticoagulant patients with atrial fibrillation undergoing endoscopy examined the subsequent risk of stroke.<sup>50</sup> The overall risk of stroke in those patients whose anticoagulation was adjusted for the procedure was low, but was significantly higher in those patients with added cardiovascular risk factors as outlined above. The risk ranged from 0.31% for patients with uncomplicated atrial fibrillation to 2.93% for complex patients with advanced age and severe illness.

### 8.2 Venous thromboembolism

Venous thromboembolism (VTE) results in 25 000 deaths per year in England and in excess of 200 000 deaths per year in the United States. Treatment with warfarin remains the treatment for choice for the majority of patients with VTE. Treatment is initiated with heparin, and LMWH is as effective as unfractionated heparin.<sup>51</sup> Heparin is continued until a therapeutic INR

(2.0–3.0) is achieved on warfarin. Treatment duration depends on the presence of risk factors and previous episodes.<sup>52 53</sup> Data from a British Thoracic Society multicentre study suggests that for patients with postoperative VTE 4 weeks of anticoagulant is adequate,<sup>52</sup> although the American College of Chest Physicians recommends a more conservative 3 months.<sup>53</sup> A first event with a recognised time-limited risk factor would be treated for 3 months. After 3 months of oral anticoagulant therapy the risk of recurrent venous thromboembolism is low. In the majority of patients on long-term oral anticoagulant therapy for prevention of recurrent venous thromboembolism the risk of thrombosis is low when treatment is temporarily stopped for a few days. Those with thrombophilia or recurrent VTE may be at higher risk, particularly in the context of endoscopic procedures associated with more prolonged immobility such as ERCP, or in the context of dehydration associated with bowel preparation. There are no published data to support this, however.

### 8.3 Cardiac valvular disease and prosthetic valves

The risk of thromboembolism associated with prosthetic heart valves has been well established.<sup>54</sup> However, the type of prophylactic anticoagulation and its duration will depend on the type of valve, its deployment position (aortic versus mitral), and the underlying inherent patient risk of thromboembolism. Valves in the aortic position carry a lower risk of thromboembolism than those in the mitral position. Patients regarded as being at higher risk are those with previous thromboembolism, on-going sustained atrial fibrillation, >1 valve prosthesis, older age or left ventricular dysfunction.

In general, aspirin will be the sole antithrombotic in patients with biological valves (aortic or mitral) when the patient is in sinus rhythm (although some advocate warfarin for 3 months for mitral biological valves). Warfarin will be used whenever a mechanical valve is used (whether the patient is in sinus rhythm or atrial fibrillation). Warfarin plus aspirin may be used when the patient is known to have coronary artery disease (treated with coronary artery surgery or not) together with valve replacement or may be used in those with mechanical valves and who are at higher risk of thromboembolism. Where warfarin is required, the level of anticoagulation will vary according to valve type and position.

A meta-analysis of studies covering a period of 53 647 patient-years indicated that the risk of all thromboembolic events when not on oral anticoagulant therapy was only 8 per 100 patient-years. This equates to a risk of less than 0.2% over a 7 day period.<sup>55</sup> However, this study did not specifically address the perioperative period when the risk may be higher due to the prothrombotic state associated with surgery. In a retrospective analysis of 180 non-cardiac operations in 159 patients with valve prostheses (170 Starr-Edwards, 59 mitral and 108 aortic), 153 operations were performed more than 12 months after valve replacement. In 62% of patients anticoagulation was discontinued 1–3 days before surgery and in 23% more than 3 days before. Anticoagulation was resumed 1–3 days later in 60% and after 4 days in 24%. Total perioperative cessation averaged 6.6 days. No postoperative thromboembolic events occurred in relation to the surgical procedure.<sup>56</sup> In another study in which patients with metal prostheses underwent non-cardiac surgery with cessation of oral anticoagulation two of 10 procedures in patients with mitral prostheses were complicated by perioperative thromboembolism compared with 0 of 25 procedures in patients with aortic prostheses.<sup>57</sup>

#### 8.4 Ischaemic heart disease and coronary artery stents

Patients with ischaemic heart disease are generally treated with antiplatelet therapy rather than anticoagulant therapy. Those who have not undergone revascularisation therapy will tend to be taking aspirin alone although if they have had an episode of unstable angina with a troponin release they may require clopidogrel in addition. Clopidogrel in combination with aspirin improves outcomes in acute coronary syndromes without ST elevation, but with an increased risk of haemorrhage.<sup>58</sup> If patients develop dyspepsia on low-dose aspirin, or in any patient at risk from gastro-intestinal bleeding co-prescription of a proton pump inhibitor (PPI) should be considered initially. Failing that, and after discussion with the cardiologist, the patient taking aspirin alone could be given clopidogrel instead.

Coronary artery stenting has increasingly become the dominant therapy for treating patients with coronary artery disease. Coronary stents may invoke a scar tissue response in 15–20% of patients necessitating a repeat interventional procedure in about 70% of these (~12%). Some patients are at particular risk of within-stent scarring (such as those with long coronary lesions >15 mm, small vessel diameters <3 mm because there is greater impact of the scarring on the lumen of the stented vessel, or in diabetics). In such patients drug-eluting stents may be used. These agents, which are loaded onto the stent, are released locally and may reduce the need for a repeat procedure from 20% to 5% in randomised controlled trials.<sup>59–60</sup> All stents require a minimum of 1 month combination of dual antiplatelet therapy (aspirin and clopidogrel 75 mg once daily of each). With bare metal stents the risk of stent thrombosis is present until the stent has undergone re-endothelialisation (after 1 month) Until that time the risk of interruption of antiplatelet therapy is highly associated with stent thrombosis and a 50% risk of acute myocardial infarction or death. With drug eluting stents re-endothelialisation takes up to 6 months, and following reported cases of late stent thrombosis in patients with drug-eluting stents, the Food and Drug Administration in the United States<sup>61</sup> and the British Cardiovascular Intervention Society now recommend dual antiplatelet therapy for 1 year. Should the patient spontaneously bleed or requires a non-cardiac operative procedure within this time period, the risks associated with stopping antiplatelet therapy are great. In one study which examined factors associated with stent thrombosis, discontinuation of therapy was associated with a hazard ratio of 161.<sup>62</sup> Of those reported with a stent thrombosis, 27% had discontinued dual antiplatelet therapy. The risk of stent thrombosis increases after 5 days without antiplatelet therapy. If clopidogrel needs to be temporarily stopped in the context of an acute gastro-intestinal haemorrhage then discontinuation of therapy should be limited to this interval.

Patients on clopidogrel requiring coronary artery bypass surgery have an increased risk of haemorrhage if clopidogrel is discontinued for fewer than 5 days.<sup>58–63</sup> Issues related to the need to consider discontinuation of dual antiplatelet therapy for non-cardiac surgical procedures are discussed in a recent editorial in the *British Medical Journal*.<sup>64</sup> The key messages are:

- ▶ All patients should carry a warning card.
- ▶ Discuss the case with the interventional cardiologist who performed the procedure so that the risks of stent thrombosis (with its 50% risk of AMI/death) can be weighed against the bleeding risk associated with the non-cardiac surgical procedure.
- ▶ If possible, procedures should be undertaken without complete lack of antiplatelet cover, such that if clopidogrel

does need to be stopped because of excess bleeding risk, then aspirin should be continued if possible.

- ▶ For patients with known high risk of needing a future non-cardiac surgical procedure (eg, planned future surgery for cancer) bare metal stenting will be undertaken since dual antiplatelet therapy will only be required for 1 month.

#### 9.0 HEPARIN AS AN ALTERNATIVE TO ORAL ANTICOAGULANTS

In a meta-analysis short-term LMWH compared favourably to unfractionated heparin (0% thromboembolism) but patients requiring long-term treatment because of intolerance to oral anticoagulants did less well suffering a 20% incidence of thromboembolism.<sup>65</sup> In a review of outcomes after short-term bridging with LMWH (~10 days) one study reviewed 1082 patients started on enoxaparin 1 mg/kg/12 h or dalteparin 100 anti-factor Xa U/kg, subcutaneously, twice daily.<sup>8</sup> Minor bleeding was seen in 7.6%, major bleeding in 0.3% but no thromboembolic episodes during the bridging period. While such a practice has been endorsed in this and other publications, there is a need for randomised controlled trials.

#### 10.0 ENDOSCOPY ON ANTICOAGULANTS AND ANTIPLATELET AGENTS: RISK STRATIFICATION

It is apparent that certain endoscopic procedures carry a higher risk of haemorrhage, and certain clinical situations will result in a high risk of thromboembolic complications should anticoagulants or antiplatelet agents be withdrawn. The American Society for Gastrointestinal Endoscopy has produced guidelines on the management of anticoagulants during endoscopy,<sup>1, 2</sup> and we have adapted their risk stratification model for endoscopic procedures in table 1. Procedures have been characterised as high risk or low risk for haemorrhage on anticoagulant or clopidogrel therapy based on data for baseline risks of haemorrhage, and the limited data available regarding endoscopy during therapy with these agents. Tables 2 and 3 stratify risk for discontinuation of anticoagulant or antiplatelet therapy according to clinical scenario and the risks of thromboembolic sequelae on discontinuation of therapy.

Diagnostic endoscopic procedures, with or without biopsy, are classified as low risk. This applies to diagnostic colonoscopy, but polyps are likely to be encountered in 22.5–34.2% in large studies.<sup>20–24</sup> Endoscopists may therefore choose to manage all colonoscopies as if they were high-risk procedures with respect to anticoagulants and antiplatelet agents. Similar considerations apply to ERCP if there is uncertainty as to the pathology from previous imaging.

#### 11.0 ACKNOWLEDGEMENTS

Dr Andrew Veitch of the Endoscopy Committee of the British Society of Gastroenterology convened the working party for the guideline. Haematological advice was provided by Dr Trevor Baglin from the British Committee for Standards in Haematology, and cardiologist advice from Dr Tony Gershlick of the British Cardiovascular Intervention Society. Miss Sarah Harnden, Dr Richard Tighe and Dr Stuart Cairns were contributing authors from the British Society of Gastroenterology.

**Competing interests:** None.

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