Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies

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Over the past several years, dabigatran, rivaroxaban, and apixaban have been approved for stroke prevention in atrial fibrillation (AF). These new oral anticoagulants (NOACs) provide important clinical advantages over vitamin K antagonists such as warfarin, and are being used in place of warfarin in many patients in the United States, Europe, Canada, and other countries. NOACs are also indicated for prevention and treatment of venous thromboembolism (1, 2). In the pivotal AF trials, the NOACs proved to be either superior or non-inferior to warfarin for the prevention of stroke and systemic embolus (3–5). Unlike warfarin, the NOACs have predictable pharmacodynamics and therefore do not require routine monitoring, and are affected by relatively few food-drug or drug-drug interactions. Relative to warfarin, the NOACs afford rapid onset of action, and in patients with normal renal and hepatic function, rapid offset of action. This obviates the need for bridging with a rapidly acting parenteral anticoagulant. In comparison to warfarin, all three NOACs are associated with a decreased risk of intracranial haemorrhage, and apixaban and

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dabigatran (110 mg twice daily) are associated with a decreased risk of major bleeding into any site (3–5).

The "Achilles heel" of the NOACs for major bleeding appears to be the gastrointestinal (GI) tract. In pivotal stroke prevention in AF trials, the NOACs have been associated with an increased risk of major GI bleeding compared with warfarin. In this Clinical Focus, we review the relationship of the NOACs to GI bleeding and suggest management strategies.

NOAC pharmacology

Unlike warfarin, which inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX, and X, the NOACs inhibit coagulation by directly and specifically binding to the active site of either thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban). Dabigatran is administered as a prodrug, dabigatran etexilate, to facilitate absorption, whereas rivaroxaban and apixaban are administered as active drugs. After absorption, dabigatran etexilate is cleaved by serum and hepatic esterases, yielding the biologically active drug. Non-absorbed dabigatran etexilate is cleaved in the intestinal lumen by unknown mechanisms, yielding active intra-luminal drug. The balance between absorbed and non-absorbed NOAC is also influenced by the p-glycoprotein efflux receptor. Concomitant use of inducers of this receptor, such as rifampin, decreases blood levels of the three NOACs, while use of p-glycoprotein inhibitors, such as amiodarone, increases levels (6). The NOACs achieve therapeutic anticoagulation within 2-4 hours (h) of oral administration, and their half-life ranges from 5-15 h. Dabigatran is eliminated primarily by the kidney, and therefore its half-life is prolonged with renal insufficiency,

requiring careful use and dosing of the drug in this setting. Rivaroxaban and apixaban are eliminated by both renal excretion and hepatic metabolism. With all three drugs, non-absorbed, active NOAC traverses the luminal GI tract and is excreted into the faeces (7–9).

Major GI bleeding in the anticoagulated patient – lessons from the warfarin era

In general, candidates for anticoagulation for AF are elderly, have co-morbid medical conditions, and take concurrent medications. Therefore, compared with the general population, AF patients have an increased risk of GI bleeding; this risk is estimated to be 0.3-0.5% per year (10). In meta-analyses of the early AF stroke prevention trials, warfarin was associated with a rate of major GI bleeding approximately three-fold higher than placebo/control (odds ratio [OR]= 3.21, 95% confidence interval [CI] 1.32-7.82). Co-administering an anti-platelet agent such as aspirin with warfarin was associated with a risk of major GI bleeding approximately twice that seen with warfarin alone (OR=2.66, CI 1.05-6.74) (10) (►Table 1). Gastrointestinal bleeding in the anticoagulated patient may occur at any level along the GI tract, reflecting the common bleeding pathologies represented in the population (11) (►Figure 1). The most common sources of upper GI bleeding (proximal to the Ligament of Treitz) are peptic ulcer and gastritis, while the most common sources of lower GI bleeding are colonic diverticulosis and neoplasia. The small intestine is recognised as another important site of bleeding now that modalities for visualising the small intestine have improved with the advent of video capsule endoscopy and

single- and double-balloon enteroscopy (12, 13). Important causes of acute and chronic small intestinal bleeding in the general population include angioectasia and ulceration induced by non-steroidal anti-inflammatory drugs (NSAIDs) (14).

NOACs and major GI bleeding

Because the three pivotal NOAC trials contain a common comparator (i.e. adjusted-dose warfarin), indirect comparison of the relative impact of the NOACs on GI bleeding can be made. However, differences in the pivotal trials among the study populations (e.g. the patients in ROCKET-AF were older and more infirm), definitions (e.g. of major bleeding events), and the study protocols, and the absence of head-to-head trials limit the conclusiveness of such comparisons.

In RE-LY and ARISTOTLE the primary safety endpoint was major bleeding, which

Table 1: The relative risk of major GI bleeding in the non-valvular atrial fibrillation population: take home points.

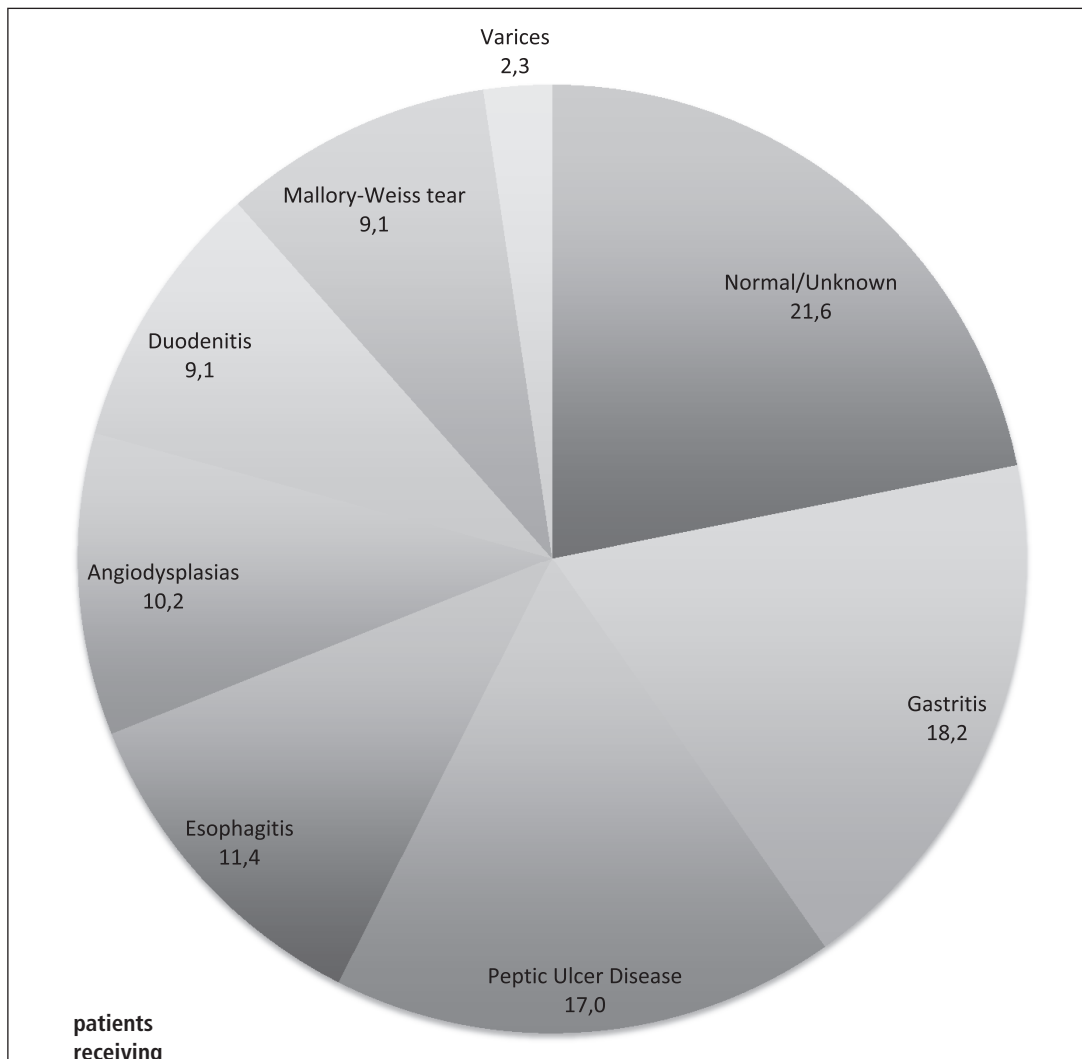| |
|---|
| 1. Adjusted-dose warfarin increases the risk of major GI bleeding approximately three-fold compared with placebo. |
| 2. The addition of aspirin or other anti-platelet agents to warfarin increases the risk of major GI bleeding approximately two-fold (compared with warfarin alone). |
| 3. Compared with warfarin, rivaroxaban and dabigatran (at the 150 mg twice daily dose) increase the risk of major GI bleeding approximately 1.5 fold. |
| 4. Compared with warfarin, apixaban does not significantly alter the risk of major GI bleeding. |
| 5. Compared with warfarin, dabigatran 110 mg twice daily does not significantly alter the risk of major GI bleeding. |
| 6. Concurrent use of anti-platelet agents increases the risk of major GI bleeding associated with rivaroxaban and of major extra-cranial bleeding (presumably including major GI bleeding) associated with dabigatran. Data related to impact of anti-platelet agents on apixaban-related major GI bleeding are not yet available. |

Varices 2,3
Mallory-Weiss tear 9,1
Duodenitis 9,1
Angiodysplasias 10,2
Esophagitis 11,4
Peptic Ulcer Disease 17,0
Normal/Unknown 21,6
Gastritis 18,2

patients receiving

Figure 1A: Endoscopic findings for suspected upper GI bleeding in patients receiving sys-

was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria (15) (▶Table 2). In ROCKET-AF, the primary safety endpoint was a composite of major bleeding plus "non-major clinically relevant bleeding events." In all three trials, event rates of when major bleeding came from the GI tract were supplied. The study protocols contain minor differences in the definition of major GI bleeding, but the impact of these varying definitions on bleeding event adjudication is not clear. Life-threatening bleeding and fatal bleeding were also recorded.

Compared with warfarin, dabigatran 150 mg twice daily was associated with an increased risk of major GI bleeding (1.85 vs 1.36%/year, p=0.002; relative risk [RR] 1.49 [1.21-1.84]) (▶Table 3) (16). For dabi-

gatran 110 mg twice daily, the major GI bleeding risk was comparable to that with warfarin. The major GI bleeding rate with dabigatran 75 mg twice daily, the lower dose available in the United States, has not been reported. In ROCKET-AF, as compared with warfarin, rivaroxaban 20 mg once daily was associated with an increased rate of major GI bleeding (2.00 vs 1.24%/y, HR 1.61 [CI 1.30-1.99]) (17). In ARIS-TOTLE, no significant difference in the rate of major GI bleeding was noted between the apixaban (5 mg twice daily) and warfarin groups (5). Limited data exist regarding the safety of the NOACs in clinical practice, and the information that is available reflects the limitations of post market studies, such as reporting bias. Nonetheless, these safety reports suggest that the major bleeding rates in patients receiving

NOACs in clinical practice do not exceed the rates reported in the pivotal trials (18–20).

In an effort to elucidate the GI bleeding patterns identified in RE-LY and ROCKET-AF, limited post-hoc analyses have been reported. In the dabigatran 110 and 150 mg twice daily arms in RE-LY, 53% of major GI bleeding occurred in the "lower" GI tract and 47% occurred in the "upper" GI tract" (vs 25% and 75%, respectively, in the warfarin arm) (16). The relatively high rate of lower GI bleeding in the dabigatran arms contrasts with the warfarin group, and also with aspirin- and NSAID-related GI bleeding, which is likewise primarily "upper" gastrointestinal (21), due to deleterious effects of cyclo-oxygenase inhibition on prostaglandin-mediated mucosal protection at the level of
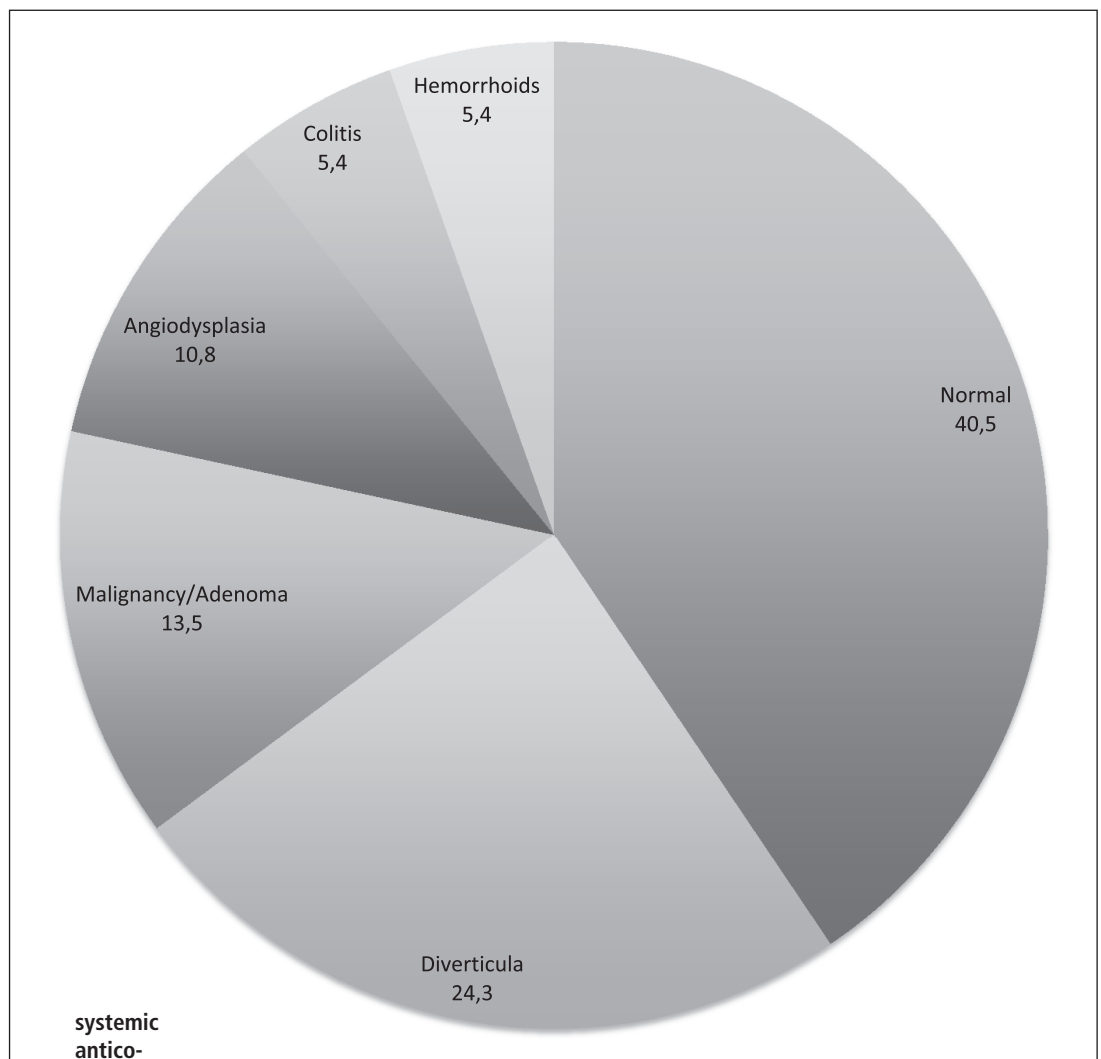
temic anticoagulation with adjusted-dose warfarin (11).

Figure 1B: Endoscopic findings for suspected-lower GI bleeding in

systemic antico-

Pie chart:
- Normal 40,5
- Diverticula 24,3
- Malignancy/Adenoma 13,5
- Angiodysplasia 10,8
- Colitis 5,4
- Hemorrhoids 5,4

the gastro-duodenum. In RE-LY, approximately 50% of major GI bleeds with dabigatran 150 mg twice daily met the criteria for life-threatening bleeding (►Table 2) (22). The concomitant use of single or dual antiplatelet therapy increases the rate of extra-cranial bleeding associated with dabigatran 150 mg twice daily (23). IN RE-LY, 55 patients (0.9%) in the dabigatran 150 mg BID arm and 39 patients in the 110 mg BID arm permanently discontinued study drug after gastrointestinal haemorrhage, compared with 39 (0.7%) in the warfarin arm. In a post-hoc analysis of data from ROCKET-AF, it was noted that despite the increased rate of major GI bleeding with rivaroxaban, the incidence of life-threatening GI bleeding (i.e. requiring transfusion of ≥ 4 units of red blood cells) was similar with rivaroxaban and warfarin (n= 52 and 47, respectively) and there were fewer fatal GI bleeding events with rivaroxaban (n= 1 and 5, respectively). The following clinical characteristics were associated with an increased risk for major GI bleeding in patients receiving rivaroxaban: concurrent aspirin or NSAID use; concomitant histamine-2 receptor antagonist or proton pump inhibitor use; prior vitamin K antagonist use; decreased creatinine clearance; sleep apnea; cigarette smoking; male gender; prior stroke, transient ischaemic attack or systemic embolisation; chronic obstructive pulmonary disease, and prior upper and lower GI bleeding. Most of these characteristics were also associated with an increased risk of major GI bleeding in patients treated with warfarin. The majority (342/394 = 87%) of rivaroxaban-associated major GI bleeds in ROCKET-AF did not meet criteria for life-threatening GI bleeding. In ROCKET-AF, 20.81% of subjects in the rivaroxaban arm permanently discontinued the study drug following an episode of major GI bleeding (vs 17.24% in the warfarin arm, CI= -0.02-0.09). The majority of major GI bleeding in the setting of rivaroxaban (like dabigatran) was from the lower GI tract. Data related to major GI bleeding in ARISTOTLE have not been reported, nor have data related to the specific lesions responsible for major GI bleeding in the pivotal NOAC trials.

Pathophysiology of major GI bleeding

The gastrointestinal tract possesses a rich intra- and sub-mucosal blood supply, and even in health, the integrity of the GI mucosa is regularly disrupted. For example, gastric erosions are noted in 5-10% and small bowel erosions are noted in 10-15% of healthy volunteers (24, 25). This mucosal vulnerability, which reflects the impact of acid and digestive enzymes, such as pepsin, trypsin and amylase, as well as exogenous intra-luminal factors, such as bacteria, renders the highly vascular lining of the GI tract uniquely prone to sub-clinical and clinical bleeding. Orally-administered antithrombotic drugs may abet the tendency of the GI tract to bleed via at least four mechanisms: 1) systemic anticoagulant effect; 2) topical anticoagulant effect; 3) topical direct caustic action; 4) topical biological action of the drug unrelated to coagulation (e.g. inhibition of mucosal healing). These mechanisms may occur in combination: for example, aspirin may promote gastro-duodenal ulcer bleeding via topical injury and systemic anti-platelet effects.

It is uncertain why dabigatran 150 mg twice daily and rivaroxaban are associated with a higher rate of major *gastrointestinal* bleeding than warfarin, but simultaneously lower rates of *intracranial* haemorrhage and similar rates of *all-site* major bleeding. One hypothesis relates to the incomplete absorption of the NOACs across the GI mucosa and thus the potential for topical drug activity. Warfarin is over 95% absorbed, and non-absorbed warfarin within the gut lumen has no anticoagulant activity. Thus, the increase in major GI bleeding observed in patients taking warfarin likely reflects the *systemic* anticoagulant action of the drug, and not a topical effect on the gastrointestinal mucosa. In contrast, the absorption of the NOACs is variable. The prodrug dabigatran etexilate has only 6% oral bioavailability; the remainder traverses the GI tract and is excreted in the faeces. During this passage, at least two-thirds of the prodrug is converted to active dabigatran by gut esterases. The bioavailability of rivaroxaban (60-80%) and apixaban (50%) is higher than that of dabigatran; however, even with these agents a significant amount of active drug is recovered in the faeces. Therefore, with all three NOACs, active anticoagulant is present within the lumen of the GI tract after oral ingestion, and in theory could (in combination with systemic drug) potentiate bleeding from vulnerable lesions. Furthermore, this could explain the relative increase of lower GI bleeding observed in pa-

Table 2: Definitions of bleeding used in pivotal NOAC trials.

Major bleeding	Life-threatening bleeding
• Decrease in haemoglobin of ≥ 2 g/dl, or • Transfusion of ≥ 2 units of packed RBCs, or • Bleeding into a critical site (intracranial, intra-spinal, intraocular, pericardial, intra-articular, intra-muscular with compartment syndrome, retroperitoneal)	• Fatal bleeding, or • Symptomatic intra-cranial bleeding, or • Bleeding with decrease of haemoglobin of ≥ 5 g/dl, or • Bleeding requiring inotropic support, or • Bleeding requiring surgery, or • Transfusion of ≥ 4 units of packed RBCs

Table 3: The rates of major GI bleeding in the non-valvular atrial fibrillation population from the three pivotal trials.

	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg daily	Apixaban 5 mg twice daily
Total patients (n)	6076	7131	9088
Major GI bleeding (n)	223	224	105
Major GI bleeding (%/year)	1.85	2.00	0.76
Hazard ratio for major GI bleeding (vs. warfarin)	1.49 [CI 1.21–1.84]	1.61 [CI 1.30–1.99]	0.89 [CI 0.70–1.15]

tients receiving dabigatran compared to those receiving warfarin.

Dabigatran etexilate is formulated with tartaric acid in order to increase absorption. Although it has been hypothesised that the tartaric acid may promote GI bleeding through caustic injury, this is unlikely to be the case because the anti-platelet medication Aggrenox® (aspirin and dipyridamole, Boehringer Ingelheim, Ingelheim, Germany), which is formulated with similar amounts of tartaric acid, is not associated with increased GI bleeding. Furthermore, bleeding related to a caustic injury would be more likely to occur in the upper GI tract, where drug concentrations are higher. Therefore, it is unlikely that direct caustic injury contributes to dabigatran-associated GI bleeding.

It is also unclear why the risk of GI bleeding associated with rivaroxaban and apixaban compared with warfarin should be different. Both are factor Xa inhibitors, are administered as active drug, and are incompletely absorbed. If not due to study-related differences such as differences in the definitions of bleeding or in patient inclusion criteria, this difference may reflect the impact of twice daily (apixaban) versus once daily (rivaroxaban) dosing; that is, once-daily dosing may create higher peak anticoagulant effect systemically and/or intra-luminally.

Major GI bleeding: prevention and management

It is likely that preventive strategies can significantly reduce the incidence rate of NOAC-related major GI bleeding (►Table 4). Utilisation of the NOAC drugs outside of appropriate indications or at inappropriate doses can induce supra-therapeutic anticoagulation, and this may be associated with an increased risk of severe or even fatal GI bleeding (26–28). Therefore, adherence to appropriate indications and drug dosing is recommended. Likewise, identification of modifiable and non-modifiable bleeding risk factors will help ascertain and manage the risk of major GI bleeding. The HAS-BLED score, a tool for assessing bleeding risk during anticoagulation, may be useful for this purpose (29).

Modifiable risk factors may include patient behaviours (e.g. alcohol ingestion) and the use of concurrent medications such as anti-platelet agents. Established risk factors (e.g. a history of prior gastro-duodenal ulcer bleeding) may lead to diagnostic tests (e.g. upper endoscopy with biopsy) and therapeutic interventions (e.g. eradication of *Helicobacter pylori* and/or co-administration of a proton pump inhibitor) that can mitigate NOAC-related upper GI-bleeding risk. Age-appropriate colon cancer screening is advisable before initiation of NOAC. In the patient receiving dabigatran, careful attention must be directed to renal protective strategies, and the patient must be alerted to risks that concurrent medications (e.g. NSAIDs) or clinical co-morbidity (e.g. dehydration) carry that may cause an acute deterioration in renal function and hence increase and prolong dabigatran's anticoagulant effect.

In general, the management of acute GI bleeding in the patient receiving NOAC therapy parallels the management of GI bleeding in the patient who is not anticoagulated or who is anticoagulated with warfarin. However, the novel pharmacology of the NOACs creates several important management differences, primarily related to strategies for restoring normal coagulation and to the timing of diagnostic and therapeutic interventions such as gastrointestinal endoscopy.

If the patient receiving NOAC treatment develops occult GI bleeding (i.e. as suggested by iron deficiency anaemia and/or positive fecal occult blood testing), semi-elective endoscopic evaluation (i.e. within 1-2 weeks) is generally indicated. To mitigate stroke risk, the NOAC may be continued during the evaluation period. The diagnostic evaluation strategy is typically guided by symptoms: e.g. in the patient with epigastric pain, upper endoscopy is performed first. In the absence of symptoms, the evaluation generally begins with colonoscopy and proceeds to upper endoscopy and/or small bowel enteroscopy as dictated by the findings.

The patient taking NOACs who develops clinically overt or major GI bleeding is best managed in the hospital, unless the bleeding is of small volume and anorectal in origin. In the emergency department, standard resuscitation measures and clini-

Table 4: NOACs and GI bleeding: prevention strategies.

1. Confirm that NOAC indication is appropriate and that there are no absolute contra-indications to NOAC administration.
2. Confirm that NOAC dosage is appropriate (e.g. dose dabigatran as indicated by creatinine clearance).
3. Screen all patients for presence of on-going GI bleeding by history (history of recent melena or rectal bleeding) and physical exam (digital rectal exam). Consider screening with laboratory testing (faecal occult blood testing, haemoglobin evaluation and evaluation of iron stores). If GI bleeding is suggested, consider GI investigation prior to initiating NOAC treatment.
4. Assess for history of previous GI bleeding and consider diagnostic interventions (e.g. endoscopy) or therapeutic interventions (e.g. concomitant administration of a PPI) where indicated.
5. Assess for co-administration of drugs such as anti-platelet agents or NSAIDs which increase the risk of NOAC related GIB.
6. If patient is concurrently taking anti-platelet medication, weigh the risks, benefits, and alternatives of continuing NOAC plus anti-platelet agent.
7. If patient is taking chronic NSAIDs, consider alternative therapies and/or co-administration of a gastro-protective agent such as a PPI.
8. Consider non-medication risk factors such as alcohol intake, and encourage risk factor modification.
9. Assess creatinine clearance and institute renal protective measures as indicated (especially in patients receiving dabigatran).
10. Counsel the patient regarding the potential for increased risk of GI bleeding in the setting of dehydration, concomitant illness, or concomitant medication use, and the recommended measures in these settings (e.g. seeking prompt medical attention, maintaining hydration, performing laboratory assessments of renal function).

cal and laboratory monitoring measures should be initiated, and the NOAC should generally be withheld. If the patient is also taking an anti-platelet agent, it may be reasonable to interrupt this therapy as well, although the risks of discontinuation (e.g. thrombosis in a recently implanted coronary stent) must be considered. Multi-disciplinary consultation including haematology, gastroenterology, and cardiology is optimal. In patients receiving dabigatran or rivaroxaban, laboratory studies of coagulation function will provide useful qualitative information related to the extent of anticoagulation, and therefore the PT, aPTT, and (where available) thrombin time should be obtained (30); apixaban has little or no effect on these tests.

In the absence of renal or hepatic failure, the offset of the anticoagulation effect of NOACs occurs gradually over 12-24 h (6, 9, 31). This advantage of the NOAC class of drugs relative to warfarin is particularly important in the setting of bleeding into the GI tract lumen (as opposed to bleeding into a "closed space", such as the skull). Because the gastrointestinal tract is an "open space," intra-luminal bleeding over 12-24 h can occur without creating high local pressure and its sequelae. Therefore, if after resuscitation, the patient is haemodynamically stable, it is reasonable to defer the endoscopic evaluation for 24 h, while providing supportive care and close observation. During this period the coagulation system will "auto-correct" (►Table 5). Deferring endoscopy provides other theoretical advantages, including providing time for thorough colonic lavage prior to colonoscopy, providing an opportunity for consultation among subspecialists, and avoiding the inevitable inefficiencies and risks of emergency intervention. Knowledge of the time of the patient's most recent NOAC dose helps predict the duration of the anticoagulant effect. If the most recent dose of NOAC was taken within approximately 2 h, administration of activated charcoal in an effort to reduce absorption of residual drug in the upper GI tract may be of benefit, though it may de-tract from subsequent endoscopic visualisation (32).

If the bleeding is rapid and the patient is persistently or intermittently unstable, emergent intervention is appropriate, because such features often reflect arterial bleeding (e.g. from the base of a gastroduodenal ulcer or a colonoscopic polypectomy site) or venous bleeding from unsuspected esophageal or gastric varices. Evaluation typically includes emergency upper endoscopy and colonoscopy (i.e. performed within 12 h of presentation), followed as required by small bowel enteroscopy, computed tomography- or catheter-based angiography, or nuclear scintigraphy. If possible, emergent whole-gut lavage should be performed prior to colonoscopy to permit mucosal visualisation (33). Endoscopy and angiography offer numerous strategies for control of GI bleeding, including thermal modalities, mechanical tamponade, and embolisation (►Table 6). The topical application of thrombin, fibrin sealants, or pro-coagulant powders such as Haemospray® (Cook Medical, Bloomington, IN, USA) to the bleeding site is an additional endoscopic strategy for control of GI haemorrhage, and warrants study in NOAC-related bleeding (34, 35). Although anti-fibrinolytic drugs, such as tranexamic acid, attenuate mucosal bleeding in patients with haemophilia or von Willebrand disease, their utility in the management of NOAC-associated GI bleeding is uncertain. Nonetheless, topical or systemic administration of these agents could be considered in patients with ongoing NOAC-associated GI bleeding.

Surgical management of the bleeding lesion is the final therapeutic alternative. The diagnostic and therapeutic yield and the optimal timing of gastrointestinal endoscopy or other interventions in the management of NOAC-related major GI bleeding have not been studied. If the patient is experiencing life-threatening on-going GI bleeding, administration of pro-coagulants such as prothrombin complex concentrate or recombinant activated factor VII may be considered (36–38), though their value must be weighed against the risk of thrombotic complications. In patients receiving dabigatran and presenting with renal failure, haemodialysis and haemo-perfusion

Table 5: Relative advantages of emergent versus urgent endoscopy in evaluation of major GI bleeding in patient receiving NOACs.

Emergent endoscopy (< 12 hours of presentation)	Urgent endoscopy (<48 hours of presentation)
• Potential for immediate diagnosis and endoscopic intervention to control bleeding • Site more likely to be actively bleeding and thus may be easier to pinpoint	• More convenient for providers and more likely to align with standard hospital protocols • Provides time for the drug's anticoagulant effect to wear off, thus increasing chance that bleeding will stop spontaneously or that endoscopic therapy will be effective • Facilitates consultation among different sub-specialty services • Facilitates initial resuscitation and stabilisation of the patient

Table 6: Acute major GI bleeding: therapeutic modalities.

Oral/pharmacologic	IV Proton-pump inhibitor
Endoscopic/thermal	Bipolar cautery, heater probe, argon plasma coagulation
Endoscopic/mechanical	Metallic clips Banding
Endoscopic/injection	Saline Epinephrine
Arteriographic	Particle or coil embolisation Vasoconstrictor infusion (vasopressin)
Surgical	Resection of bleeding site/affected bowel

may also be considered (39); these strategies are ineffective for eliminating apixaban and rivaroxaban, because they are > 90% protein-bound. There is currently no specific reversal agent routinely available for emergency use for the NOACs, though antidotes are under investigation (40).

After an episode of GI bleeding, it will be appropriate to resume the NOAC in most AF patients due to the on-going risk of stroke. The decision regarding when to re-initiate the NOAC requires balancing the risks of thrombosis and bleeding. The interventionalist can often estimate the relative risk of future bleeding after treatment of a bleeding lesion. In some instances, a relatively modest intervention (e.g. fulguration of a bleeding angioectasia) definitively treats the acute bleeding, and anticoagulation can safely be re-instituted within 24 to 48 h. In other instances (e.g. resection of a segment of bowel, or colonoscopic resection of a large adenoma), a longer period of anticoagulant interruption (e.g. 5-7 days) may be desirable. If the bleeding site is identified but cannot be treated (as may be the case for the patient with innumerable small bowel angioectasias), or cannot be identified despite a comprehensive gastrointestinal evaluation, then decision-making is particularly challenging. In these settings, it is reasonable to consider strategies such as: modifying bleeding risk factors (e.g. discontinuing concurrent anti-platelet medication); reducing the NOAC dose (e.g. from dabigatran 150 mg twice daily to 110 mg twice daily); or eliminating the need for anticoagulation (e.g. amputating or occluding the left atrial appendage). It is also reasonable in this setting to consider switching the oral anti-coagulant. If a patient has a GI bleed on warfarin, dabigatran (150 mg dose) or rivaroxaban, consideration should be given to switching to apixaban once the patient is stable. If a patient has a GI bleed on apixaban at the usual 5 mg twice daily dose, consideration can be given to lowering the dose to 2.5 mg twice daily. If a patient experiences GI bleeding while receiving a NOAC, consideration may also be given to switching to a vitamin K antagonist; however this switch will confer an increased risk of intra-cerebral haemorrhage

Peri-endoscopic management of the NOACs

Therapeutic endoscopy is associated with a risk of GI bleeding. There is little data available to guide peri-endoscopic management of anticoagulants, and therefore recommendations primarily reflect expert opinion, and patients must be managed on a case-by-case basis. Endoscopic interventions may be stratified into low-risk for bleeding (e.g. diagnostic endoscopy or endoscopy with forceps biopsy) and higher-risk for bleeding (e.g. snare resection of large colon polyps or endoscopic sphincterotomy) (41). Bleeding can also be divided into early bleeding (i.e. presenting within 6 h of the endoscopic intervention), which reflects inadequate primary haemostasis, and delayed bleeding, which reflects sloughing of tissue that was devitalised at the time of the endoscopic intervention.

For low-risk procedures, the NOAC can generally be continued through the endoscopic period. It may be beneficial to schedule the procedure toward the end of the NOAC dosing interval (e.g. 10 h after the last apixaban dose) so that anticoagulant effect is at its trough. For higher-risk endoscopic procedures, it is appropriate to interrupt the anticoagulation (41). Because of the favourable pharmacokinetics of the NOACs, bridging therapy is not necessary. It is recommended that in the absence of renal insufficiency or other mitigating factors, the NOAC should be held for 2-3 half-lives (approximately one day) prior to the surgical procedure (42). In the case of impaired NOAC clearance, the duration of time that the drug is withheld prior to the procedure is appropriately increased (42).

After the elective endoscopic procedure, the NOAC is generally resumed either immediately (e.g. if there has been no therapeutic intervention) or within 2-3 days (e.g. after endoscopic biliary sphincterotomy), after primary haemostasis is achieved. The precise timing will reflect the relative risks of thrombosis and haemorrhage; consultation among hematologist, cardiologist, and gastroenterologist may be useful. In contrast to warfarin, therapeutic anticoagulation occurs within hours of the first NOAC dose. The results of a post-hoc analysis of all patients in RE-LY who

underwent at least one surgical procedure (N=4,591), suggests that if appropriate guidelines are followed the rate of post-procedural bleeding with NOACs is comparable to that observed with warfarin (43).

Conclusion

The use of adjusted dose-warfarin for stroke prevention in non-valvular AF increases the risk of major GI bleeding approximately three-fold. Based on the NOAC pivotal trials, it appears that the rate of major GI bleeding in patients treated with apixaban is comparable to that seen in patients treated with adjusted dose-warfarin, whereas the major GI bleeding rate patients treated with rivaroxaban or dabigatran 150 mg twice daily is approximately 1.5 times higher. Fortunately, the majority of major GI bleeding events in patients receiving NOACs are not life-threatening. The short half-life of the NOACs in the absence of renal or hepatic failure is an important advantage to the clinician confronted with major GI bleeding. Future studies will elucidate the common sources of major GI bleeding in the patient receiving NOACs, predictors of major GI bleeding, strategies for major GI bleeding prevention, and the roles for specific endoscopic and haematologic interventions.

Abbreviations

ARISTOTLE, Apixaban for Reduction in Stroke and Thromboembolic Events in Atrial Fibrillation; AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; FFP, fresh frozen plasma; GI, gastrointestinal; NOAC, new oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PPI, proton-pump inhibitor; RBC, red blood cells; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk.

Conflicts of interest

References

1. Kwong LM. Rivaroxaban, an oral, direct factor Xa inhibitor: a new option for thromboprophylaxis. Orthopedics 2012; 35: e932–938.
2. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010; 375: 807–815.
3. Connolly S, Ezekowitz M, B C, Salim Y, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. New Engl J Med 2009; 361: 1139–1151.
4. Patel M, Mahaffey K, Garg J, et al. Rivaroxaban versus Warfarin in Nonvavular Atrial Fibrillation. New Engl J Med 2011; 365: 883–891.
5. Granger C, Alexander J, McMurray J, et al. Apixaban versus Warfarin in Patients with Atrial Fribrillation. New Engl J Med 2011; 365: 981–992.
6. Ganetsky M, Babu KM, Salhanick SD, et al. Dabigatran: review of pharmacology and management of bleeding complications of this novel oral anticoagulant. J Med Toxicol 2011; 7: 281–287.
7. Raghavan N, Frost CE, Yu Z, et al. Apixaban Metabolism and Pharmacokinetics after Oral Administration to Humans. Drug Metab Dispos 2009; 37: 74–81.
8. Blech S, Ebner T, Ludwig-Schwellinger E, et al. The Metabolism and Disposition of the Oral Direct Thrombin Inhibitor, Dabigatran, in Humans. Drug Metabol Disp 2008; 36: 386–399.
9. Weinz C, Schwarz T, Kubitza D, et al. Metabolism and Excretion of Rivaroxaban, an Oral, Direct Factor Xa Inhibitor, in Rats, Dogs, and Humans. Drug Metab Dispos 2009;37 (5):1056–64.
10. Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. Int J Clin Pract 2012; 66: 53–63.
11. Rubin T, Murdoch M, Nelson DB. Acute GI bleeding in the setting of supratherapeutic international normalized ratio in patients taking warfarin: endoscopic diagnosis, clinical management, and outcomes. Gastrointest Endoscopy 2003; 58: 369–373.
12. Di Caro S, May A, Heine DGN, et al. The European experience with double-balloon enteroscopy: indications, methodology, safety, and clinical impact. Gastrointest Endoscopy 2005; 62: 545–550.
13. Gay G, Delvaux M, Rey JF. The role of video capsule endoscopy in the diagnosis of digestive diseases: a review of current possibilities. Endoscopy 2004; 36: 913–920.
14. Zuckerman GR, Prakash C, Askin MP, et al. AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2000; 118: 201–221.

15. Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihaemostatic medicinal products in surgical patients. J Thromb Haemost 2010; 8: 202–204.
16. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011; 123: 2363–2372.
17. Nessel C, Mahaffey K, Piccini JP, et al. Incidence and Outcomes of Gastrointestinal Haemorrhage in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin: Results From the ROCKET AF Trial (abstract). Chest 2012; 142: 84A.
18. Southworth MR, Reichman ME, Unger EF. Dabigatran and Postmarketing Reports of Bleeding. New Engl J Med 2013; Epub ahead of print.
19. European Medicines Agency - Human medicines - European Medicines Agency updates patient and prescriber information for Pradaxa [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/05/human_pha_detail_000061.jsp&mid=WC0b01ac058001d126.
20. Drug Safety and Availability - FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) [Internet]. Center for Drug Evaluation and Research; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm.
21. Lim YJ, Yang C-H. Non-steroidal anti-inflammatory drug-induced enteropathy. Clin Endoscopy 2012; 45: 138–144.
22. FDA Advisory Committee Briefing Document. Boehringer Ingelheim. Dabigatran etexilate. 2010; pp. 1–168.
23. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial. Circulation 2013; 127: 634–640.
24. Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Therapeut 2007; 25: 1211–1222.
25. Laine L, Maller ES, Yu C, et al. Ulcer formation with low-dose enteric-coated aspirin and the effect of COX-2 selective inhibition: a double-blind trial. Gastroenterology 2004; 127: 395–402.
26. Kernan L, Ito S, Shirazi F, et al. Fatal gastrointestinal haemorrhage after a single dose of dabigatran. Clin Toxicol 2012; 50: 571–573.
27. Fellows SE, Rosini JM, Curtis JA, et al. Haemorrhagic Gastritis with Dabigatran in a Patient with Renal Insufficiency. J Emerg Med 2012; 44: e221–e225.
28. Wychowski MK, Kouides P a. Dabigatran-induced gastrointestinal bleeding in an elderly patient with moderate renal impairment. Ann Pharmacotherapy 2012; 46: e10.
29. Pisters R, Lane D, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093–1100.

30. Garcia D, Barrett YC, Ramacciotti E, et al. Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. J Thromb Haemost 2013; 11: 245–252.
31. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol 2013; 75: 476–487.
32. Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010; 103: 1116–1127.
33. Davila RE, Rajan E, Adler DG, et al. ASGE Guideline: the role of endoscopy in the patient with lower-GI bleeding. Gastrointest Endoscopy 2005; 62: 656–660.
34. Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. Drugs 1999; 58: 863–886.
35. Leung Ki E-L, Lau JYW. New endoscopic haemostasis methods. Clin Endoscopy 2012; 45: 224–229.
36. Pragst I, Zeitler SH, Doerr B, et al. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost 2012; 10: 1841–1848.
37. Dumkow LE, Voss JR, Peters M, et al. Reversal of dabigatran-induced bleeding with a prothrombin complex concentrate and fresh frozen plasma. American journal of health-system pharmacy : J Am Soc Health System Pharmacists 2012; 69: 1646–1650.
38. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. Anesthesiology 2012; 116: 94–102.
39. Stangier J, Rathgen K, Stähle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010; 49: 259–268.
40. Van Ryn J, Litzenburger T, Schurer J. Reversal of Anticoagulant Activity of Dabigatran and Dabigatran-induced Bleeding in Rats by a Specific Antidote (Antibody Fragment) (abstract). Circulation 2012; Available from: http://circ.ahajournals.org/cgi/content/meeting_abstract/126/21_MeetingAbstracts/A9928.
41. Kwok A, Faigel DO. Management of anticoagulation before and after gastrointestinal endoscopy. Am J Gastroenterol 2009; 104: 3085–3097; quiz 3098.
42. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural Management and Approach to Bleeding in Patients Taking Dabigatran. Circulation 2012; 126: 2428–2432.
43. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012; 126: 343–348.