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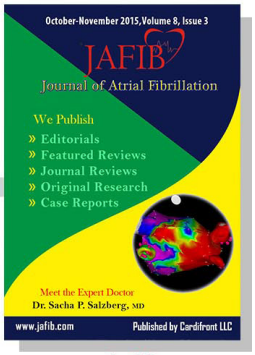

Patient Taking A Novel Oral Anticoagulant Presents With Major GI Bleeding

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Abstract

Novel Oral Anticoagulants (NOACs) such as Dabigatran, Rivaroxaban, Apixaban and Edoxaban are becoming increasingly popular choices for anticoagulation in place of oral Vitamin K Antagonists in various clinical settings. However, they are thought to be associated with an increased risk of gastrointestinal bleeding. Moreover, no specific antidote is available which can rapidly reverse the anti-coagulant action of NOACs raising concern that gastrointestinal bleeding with NOACs could carry a worse prognosis than that associated with conventional agents.

In this review, we describe a case of gastrointestinal bleeding in the setting of NOAC use, followed by a brief overview of the pivotal trials involving NOACs. Clinical issues such as pathophysiology, diagnosis and management of NOAC induced GI bleeding have been described. Future trials will help elucidate the true incidence, risk factors and preventive strategies for NOAC associated gastrointestinal bleeding.

Introduction

Vitamin K Antagonists (VKA) such as Warfarin have long been the agents of choice for oral anticoagulation in different clinical settings. However, warfarin poses problems of its own in terms of a narrow therapeutic range, need for regular INR monitoring and interactions with several drugs and food.[1] Risk of major bleeding is another limiting factor while using warfarin. Almost 50 years after the approval of warfarin, novel oral anticoagulants (NOACs) such as the direct thrombin inhibitor Dabigatran, and Factor Xa inhibitors - Rivaroxaban, Apixaban and Edoxaban have been developed. These NOACs have a more predictable pharmacokinetic profile than warfa¬rin, fewer dietary and drug interactions, and do not require routine monitoring.[2,3] NOACs are increasingly being considered to replace VKAs for indications such as thromboprophylaxis during orthopedic surgery, prevention of thromboembolic complications in patients with atrial fibrillation, treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT).[4]

Gastrointestinal Bleeding still remains one of the most dreaded complications of anticoagulation therapy and recent studies have suggested that NOACs carry an increased risk of GI bleeding compared to standard therapy.[5] Prothrombin Complex Concentrates (PCC) administered for rapid reversal of effects of warfarin has been introduced fairly recently. However,, no specific antidote is available which can rapidly reverse the anti-coagulant action of NOACs raising concern that gastrointestinal bleeding with NOACs could carry a worse prognosis than that associated with conventional agents such as VKAs.[6]

We present a case of GI Bleeding in the setting of using a NOAC , followed by a brief review of literature on the topic.

Key Words:
Novel Oral Anticoagulants, Dabigatran, Rivaroxaban, Apixaban, Edoxaban, Gastrointestinal Bleeding

Disclosures:
None.

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Case Report

A 72 year old female patient with a past medical history of diastolic heart failure with an ejection fraction (EF) of 60 % , recently diagnosed Atrial Fibrillation on renally dosed Rivaroxaban of 15 mg PO daily, Chronic Kidney Disease (CKD) with a baseline creatinine of 1.3 and Hypertension , was transferred to the Intensive Care Unit for worsening shortness of breath and a 12 hour history

of 2 episodes of passing bright red blood per rectum. She had recently returned home from a rehabilitation facility where she had spent 2 weeks following a successful right knee replacement surgery. On presentation, her vitals were as follows: T- 36 C, BP- 86/54, Pulse- 120 bpm , RR- 24, O2 saturation- 94 % on Room Air. Her H/H was 7.4/22 (her baseline H/H is 10/30, probably secondary to CKD). Platelet count was 180,000/ul and coagulation profile was unremarkable with a PT of 14 s, PTT of 32 s and INR of 1.1 . Serum creatinine was 1.42, which was close to her baseline and estimated creatinine clearance was 35 ml/min. On examination, lungs were clear to auscultation and there was no jugular venous distention (JVD) or pedal edema. Cardiovascular examination was unremarkable apart from tachycardia with a normal rhythm. Her abdomen appeared soft and non tender with normoactive bowel sounds and no organomegaly. Rectal examination was positive for bright red blood with no evidence of hemorrhoids. Chest X Ray was unremarkable and EKG revealed sinus tachycardia. She was kept NPO and started on aggressive IV fluid replacement. Group and Cross Match was taken and patient was transfused 3 units of Packed Red Blood Cells (PRBC). She was monitored closely and she responded well to therapy. Her blood pressure improved to 122/76 and she was saturating at 98 % on room air with symptomatic improvement of her dyspnea.

Once she was stable for imaging, a CT scan of her abdomen was performed which did not reveal any overt pathology. Of note, her last upper GI endoscopy was done 2 months ago and was normal with no evidence of ulceration or gastritis. She was kept under close observation and there were no further episodes of bleeding per rectum. Post transfusion H/H was 10.3/30.8, indicating an appropriate response. The following morning, she was taken for colonoscopy which turned out to be completely normal with no areas of active bleeding. Repeat upper GI endoscopy was again unremarkable. As the patient was no longer actively bleeding, it was decided not to proceed with further imaging studies such as video capsule endoscopy to evaluate the small bowel. With the exclusion of any obvious gastrointestinal pathology, it was concluded that her GI bleed was likely an adverse effect of her daily rivaroxaban therapy and this was subsequently discontinued. She was eventually stable for discharge and went home. On follow up a week later, she denied any further episodes of bleeding and her H/H appeared stable at 10.1/30. She was later started on warfarin therapy with serial INR checks and dose adjustments. She was followed closely as an outpatient and no further events of major GI bleeding were observed.

Discussion

Gastrointestinal bleeding is one of the most serious adverse effects and a major limitation in the use of new oral anticoagulants. However, the exact risk of gastrointestinal bleeding with NOACs is still unknown and precise risk related to individual NOACs remains inconclusive. A brief overview of the NOAC's used in clinical practice, as well as a review of results from the major trials exploring their efficacy and safety are described below.

Dabigatran

Dabigatran is a direct thrombin inhibitor that is FDA approved for prevention of stroke in non valvular atrial fibrillation as well as for treatment and reduction in risk of recurrence of DVT/PE.

The RE-COVER trial showed that dabigatran 150 mg twice daily was as effective as dose adjusted warfarin for the treatment of acute venous thromboembolism. Major bleeding episodes occurred in 1.6 % patients assigned to dabigatran and 1.9 % patients assigned to warfarin (HR 0.82; 95% CI, 0.45 to 1.48) while episodes of any bleeding were observed in 16.1 % patients assigned to dabigatran and 21.9 % patients assigned to warfarin (HR 0.71; 95% CI, 0.59 to 0.85). Gastrointestinal bleeding occurred in 53/1274 subjects in the dabigatran group and 35/1265 subjects in the warfarin group (OR 1.52; 95 % CI, 0.99 to 2.32).[7]

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial compared the efficacy and safety of dabigatran 110 mg or 150 mg twice a day with dose adjusted warfarin for prevention of stroke in atrial fibrillation. Dabigatran 150 mg twice daily was superior to warfarin (P=0.001) for reduction of the risk of stroke or systemic embolism, while dabigatran 110 mg twice daily dosage was non inferior to warfarin in reducing the risk of stroke or systemic embolism (P=0.001). However, dabigatran 110 mg twice a day was associated with a lower risk of major bleeding compared to Warfarin (2.87 % versus 3.57 % ; P= 0.002), whereas dabigatran 150 mg twice a day was associated with a similar risk of major bleeding (3.31 % versus 3.57 %; P = 0.32). Bleeding rates were higher among patients who received treatment with dual antiplatelet agents than those who did not. The risk of bleeding was progressively higher with increasing age, possibly due to higher drug concentrations from age related decline in renal function and drug clearance. The risk of gastrointestinal bleeding was higher with dabigatran 150 mg twice daily than with warfarin (1.85% vs 1.25 %; P<0.001), but was similar in the dabigatran 110 mg twice daily and warfarin groups (1.36 % vs 1.25 % ;P=0.43).[8]

In the dabigatran group, 53% had bleeding from the upper gastrointestinal tract, and 47% had bleeding from the lower gastrointestinal tract. In the warfarin group, 75% had bleeding from the upper gastrointestinal tract, and 25% had bleeding from the lower gastrointestinal tract. Metabolism of the pro-drug dabigatran etexilate by esterases in the gut flora may lead to progressively higher concentrations of the active drug during transit through the gastrointestinal tract. In contrast, warfarin has a high bioavailability and first requires hepatic biotransformation to exert its anticoagulant effect, which is why unabsorbed warfarin the lower gut would not be expected to cause significantly higher localized bleeding. With advancing age, there is also an increase in gastrointestinal tract pathology such as diverticulosis and angiodysplasia.[9] The risk of bleeding from affected areas may increase due to direct exposure to dabigatran. Thus, local effects of dabigatran on diseased mucosa could account for the relative increase in lower gastrointestinal bleeding seen with dabigatran compared with warfarin patients in the RE-LY trial.[8]

Rivaroxaban

Rivaroxaban is an oxazolidinone derivative capable of inhibiting both free Factor Xa and Factor Xa bound in the prothrombinase complex.[10] This highly selective direct Factor Xa inhibitor has high oral bioavailability , a rapid onset of action and a predictable pharmacokinetic profile across a wide spectrum of patients with respect to age, gender, weight and race.[11]

Rivaroxaban is FDA approved for both DVT/PE Prophylaxis in adults undergoing hip/ knee replacement surgery and for prevention of stroke in patients with non valvular atrial fibrillation.

The 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) Trial showed that rivaroxaban 20 mg daily was non inferior to dose adjusted warfarin for

prevention of stroke or systemic embolism in patients with non valvular atrial fibrillation (HR 0.79; 95 % CI 0.66 to 0.96; P<0.001 for non inferiority). However, superiority was not shown in the intention to treat analysis (HR 0.88; 95% CI, 0.74 - 1.03; P = 0.12 for superiority).[12]

The rate of major and clinically relevant non major bleeding was 14.9% per year in the rivaroxaban group and 14.5% per year in the warfarin group. (HR, 1.03; 95% CI, 0.96 - 1.11; P = 0.44). The composite principal safety endpoint for GI bleeding events (upper, lower, rectal) occurred more frequently in patients receiving rivaroxaban than warfarin (HR 1.39; 95% CI 1.19-1.61). Despite the increased rate of major GI bleeding with rivaroxaban, the incidence of life-threatening GI bleeding (i.e. requiring transfusion of >3 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 than warfarin (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 use of H2 receptor antagonist or proton pump inhibitors ; prior vitamin K antagonist use; decreased creatinine clearance; transient ischemic attack or systemic embolism ;cigarette smoking; male gender; prior stroke,; chronic obstructive pulmonary disease, and prior upper and lower GI bleeding. The majority of major GI bleeding in the setting of rivaroxaban (like dabigatran) was from the lower GI tract.[13]

The EINSTEIN study showed that Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) was non inferior to standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for treatment of acute DVT and for prevention of recurrence. (HR 0.68; 95% CI 0.44 -1.04; P<0.001). First major or clinically relevant non major bleeding rates were similar in both groups (HR 0.97; 95% CI 0.74-1.22; P = 0.77) . Rivaroxaban was associated with a lower risk of major bleeding (HR 0.65 ; 95 % CI 0.33–1.30;P=0.21) in the acute DVT study. However, 4 patients in the rivaroxaban group had gastrointestinal bleeding in the Continued Treatment Study, compared to none in the comparator group.[14]

Apixaban

Apixaban is a direct and competitive inhibitor of factor Xa. which has about 50% bioavailability, and is approximately 25% excreted by the kidney.[15]

The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K) trial showed that Apixaban 5mg twice daily lowered the risk of stroke or systemic embolism when compared to 81mg-324 mg Aspirin in patients with prior stroke /TIA (HR 0.29 ; 95% CI 0.15–0.60) as well as in patients with no prior stroke/ TIA (HR 0.29; 95% CI 0.15–0.60).[16] Major bleeding was more frequent in patients with history of stroke or TIA than in patients without this history (HR 2.88; 95% CI 1.77–4.55) but risk of this event did not differ between treatment groups. The rate of gastrointestinal bleeding with apixaban was similar to that of aspirin (HR 0.86; 95% CI 0.4-1.86, P=0.71). Overall, apixaban was well tolerated and showed a profile of adverse events similar to that of aspirin.[17]

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trial showed that Apixaban 5 mg twice daily was superior to dose adjusted Warfarin for prevention of stroke or systemic embolism in patients with atrial fibrillation. (HR 0.79; 95% CI 0.66 -0.95; P = 0.01 for superiority).[18]

The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR 0.69; 95% CI, 0.60 - 0.80; P<0.001). In a modified intention-to-treat sensitivity analysis over the entire treatment period, there was a 27% relative reduction in rate of major bleeding in the apixaban group, as compared with the warfarin group (P<0.001). The risk of gastrointestinal bleeding was similar between both apixaban and warfarin groups (OR 0.88, 95 % CI 0.67-1.14). Apixaban had an acceptable side-effect profile with no unexpected events, and the rate of discontinuation of the study drug was lower in the apixaban group than in the warfarin group.[18]

Edoxaban

Edoxaban is a direct oral Factor Xa inhibitor that was approved by the FDA as recently as January 2015, for the prevention of stroke and non–central-nervous-system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation. Pharmacokinetically, edoxaban has a 62 % bioavailability,[19] achieves maximum concentrations within 1-2 hours and is 50% renally excreted.[20]

Most of the data on edoxaban comes from the ENGAGE AF-TIMI 48 trial which showed that edoxaban (60 mg and 30 mg once daily) was non inferior to dose adjusted warfarin for reduction in the risk of stroke or systemic embolism (modified intent-to-treat population, P=0.001 and P=0.005 for noninferiority, respectively; intent-to-treat population, P=0.08 and P=0.10 for superiority, respectively). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high dose edoxaban (HR, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (HR, 0.47; 95% CI, 0.41 to 0.55; P<0.001). Compared with Warfarin, there were lower rates of major bleeding with both high dose edoxaban (3.43 % vs 2.75 %; P<0.001) and low dose edoxaban.(3.43 % vs 1.61 %; P<0.001). However, the risk of gastrointestinal bleeding was higher with high dose edoxaban compared to warfarin (1.51% vs 1.23 %; P=0.03) but lower with low dose edoxaban compared to warfarin (0.82% vs 1.23%;P<0.01). Bleeding was more common from the Upper GI tract than the Lower GI tract in all 3 subgroups.[21]

Thus we see that the risk of GI Bleeding varied in different trials and with different NOAC's, but overall NOAC's were associated with a higher risk of GI Bleeding.

Comparison Of Different Agents For GI Bleeding Risk

A number of meta-analyses have been performed comparing the risk of GI Bleeding with NOACs used for various indications, to that of standard therapy. A meta-analysis of 19 Randomized Control Trials (RCT) showed that the overall Odds Ratio for Gastrointestinal Bleeding among patients taking NOAC was 1.45 (95% CI 1.07- 1.97). Subgroup analyses showed that the OR for atrial fibrillation was 1.21 (95% CI 0.91- 1.61), for thromboprophylaxis after orthopedic surgery the OR was 0.78 (95% CI 0.31- 1.96), for treatment of venous thrombosis the OR was 1.59 (95% CI 1.03 - 2.44), and for acute coronary syndrome the OR was 5.21 (95% CI 2.58 - 10.53). Among the drugs studied, the OR for apixaban was 1.23 (95% CI 0.56- 2.73), the OR for dabigatran was 1.58 (95% CI, 1.29- 1.93), the OR for edoxaban was 0.31 (95% CI 0.01-7.69), and the OR for rivaroxaban was 1.48 (95% CI 1.21- 1.82).[5]

Another meta-analysis evaluating 6 trials also suggested higher GI bleeding with NOACs. (RR, 1.30; 95 % CI 0.97 - 1.73).[22]

We performed a meta analysis of 17 RCTs including 91,933 patients to evaluate the risk of gastrointestinal bleeding with NOACs

compared with conventional anticoagulants.[23] We found that NOACs were associated with a significantly higher GI bleeding compared with conventional anticoagulants [Peto's odds ratio (POR) 1.23, 95% CI 1.10 to 1.36; number needed to harm (NNH)=295 patients]. Trial sequential analysis (TSA) showed a 20% relative risk increase of any GI bleeding with NOACs versus conventional agents.. Compared with controls, the risk of GI bleeding was significantly higher with dabigatran (POR 1.31, 1.10 to 1.57; NNH=205) and rivaroxaban (POR 1.35, 1.16 to 1.57; NNH=139) but not with apixaban (POR 0.85, 0.67 to 1.08). TSA showed a relative risk increase of 20% for dabigatran and rivaroxaban but showed insufficient data for apixaban. NOACs caused significantly higher risk of any GI bleeding compared with warfarin (NNH=212) and LMWH followed by warfarin (NNH=134), but not against low molecular weight heparin alone.[23] Thus we saw heterogeneity in risk - while there was a statistically significant excess risk of GI bleeding with dabigatran and rivaroxaban, the risk of GI bleeding remained inconclusive for apixaban, when compared with controls. Although this suggests that apixaban may be safer than other NOACs, further trials are needed to exclude true bleeding risks associated with apixaban .

Pathophysiology

Gastrointestinal bleeding in the anticoagulated patient may occur at any level along the GI tract . The mucosa of the GI tract has a rich blood supply that can be sensitive to bleeding by various endogenous or exogenous insults. Orally administered anticoagulants may cause bleeding by different mechanisms such as (a) systemic anticoagulant effect; (b) topical anticoagulant effect; (c) topical direct caustic action; (d) topical biological action of the drug unrelated to coagulation (e.g. inhibition of mucosal healing). These mechanisms may occur alone or in combination.[24] As Warfarin requires systemic absorption and activation prior to exerting its anticoagulant effect, the increase in GI Bleeding with warfarin is not a topical effect and is likely a manifestation of its systemic anticoagulation action. In contrast, NOACs have variable absorption and active anticoagulant is present within the lumen of the GI Tract which could, in theory, cause topical anticoagulation effects in addition to systemic action.

Diagnosis

Warfarin has a narrow therapeutic window and monitoring of its anticoagulant activity by measuring the INR range is necessary to reduce the risk of bleeding. However, INR is not an useful test to gauge the anticoagulant effect of NOACs because INR is calibrated for use with vitamin K antagonists only.[25] Although NOAC use may be associated with an increase in INR, this increase does not relate to the effectiveness of therapy or provide a linear correlation of concentration and effect that is seen when measuring warfarin levels.[26] As dabigatran directly inhibits Thrombin, measurement of Prothrombin Time [PT] lacks the sensitivity to detect therapeutic levels and often a sub-therapeutic level is noted, regardless of the concentration of dabigatran.[27] Other appropriate tests include partial thromboplastin time (aPTT), and diluted thrombin time (dTT). aPTT however, is not very sensitive for low doses of dabigatran. A very sensitive test for measurement of dabigatran activity is the Ecarin Clotting Time (ECT) as a close linear relationship has been shown between pro¬longation of ecarin clotting time and plasma concentrations of dabigatran.[28] However, ECT assay is not widely used in the United States.

As rivaroxaban, apixaban and edoxaban are direct inhibitors of Factor Xa , the anti factor Xa assay is the most sensitive method of monitoring their anticoagulant activity.[29]

Management

The incidence of NOAC associated GI bleeding can be significantly reduced by successful preventive strategies. Adherence to appropriate indications for NOAC use and proper drug dosing is imperative as usage of NOACs beyond their approved indications or at different doses can induce supra-therapeutic anticoagulation, and this may be associated with an increased risk of severe or even fatal GI bleeding.[30] Identification of modifiable and non-modifiable bleeding risk factors will help stratify patients at risk and also ascertain the degree of risk. Tools such as the HAS-BLED score can be used for this purpose.[31]

Management of GI Bleeding from use of NOACs is similar to the standard management of GI bleeding and resuscitation takes precedence before anything else in the hemodynamically compromised patient. Measurement and monitoring of the degree of anticoagulation using the different tests described above should be initiated and administration of the NOAC should be stopped immediately. If the patient is also receiving anti platelet agents, these should be withheld as well. Unlike VKAs, there is no drug specific antidote to reverse the effect of NOACs. Administration of Prothrombin Complex Concentrates have been suggested as a potential agent to reverse NOAC anticoagulation , but data regarding their absolute efficacy is lacking.[32,33]

Recently however, Idarucizumab - a monoclonal antibody fragment that binds free and thrombin-bound dabigatran thereby neutralizing its activity, was developed to reverse the anticoagulant effects of dabigatran. The Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) Study was a prospective cohort study undertaken to examine the efficacy and safety of idarucizumab for the reversal of anticoagulant effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention. Results of this study were recently published and showed that 5g intravenous idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran in 88 to 98% of the patients who had had elevated clotting times at baseline.[34]

In current clinical practice however , reduction of NOAC exposure mostly depends on the short half lives of these novel agents (5-17 h), causing rapid reductions in anticoagulant levels with time in patients without renal or hepatic dysfunction. In contrast, it takes a much longer time to reverse the effects of warfarin as it causes a biologic reduction of active clotting factors. This temporal advantage over warfarin is important in the setting of bleeding into the GI tract lumen because intra-luminal bleeding over time can occur without creating high local pressure and its sequelae, unlike bleeding into a closed space such as the skull which can quickly develop catastrophic consequences. Therefore, if after resuscitation, the patient is hemodynamically stable, it is reasonable to postpone endoscopic evaluation , while providing supportive care and close observation.[24] If the patient experiences rapid GI bleeding and remains hemodynamically unstable despite resuscitation efforts, urgent intervention is necessary in the form of emergency upper GI endoscopy and colonoscopy, followed as required by other studies such as small bowel enteroscopy, computed tomography- or catheter-based angiography and nuclear scintigraphy. These interventions entail numerous strategies for control of GI bleeding, including thermal modalities, mechanical tamponade, and embolization.[24] If these interventions are unsuccessful, surgery remains the final option.

Conclusion

The convenience of no routine monitoring and a wide therapeutic window make the NOACs desirable first-line options for anticoagulation. In addition, all NOACs have been associated with lower risk of intracranial hemorrhage compared to standard antithrombotic therapy.[35] However, NOAC use may be related to higher rates of GI bleeding and this notion has been supported by many meta-analyses which have compared NOACs to conventional VKAs. Analysis from our group showed that GI bleeding risk is definitely higher with dabigatran and rivaroxaban, but we lacked sufficient evidence for apixaban.[23] Further trials are needed to test whether the risks of GI bleeding associated with dabigatran and rivaroxaban is dose dependent and can be overcome by using low dose dabigatran or rivaroxaban, provided that such doses show superiority or equivalence to conventional anticoagulants regarding thromboembolic complications.

There is a paucity of recommendations on how to transition patients from one NOAC to another in the setting of adverse effects such as GI bleeding and care should be taken to ensure continuous anticoagula¬tion when stopping, interrupting, or switching between NOACs to avoid an increased risk of stroke. Thus, increased risk of GI bleeding should be kept in mind prior to starting therapy with NOACs. It is fortunate that the majority of the GI bleeds associated with NOAC use is not life threatening. Future trials will help elucidate the true incidence, risk factors and appropriate preventive strategies for NOAC associated gastrointestinal bleeding.

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