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Gastrointestinal Endoscopy in Patients on Direct Oral Anticoagulants. A Consensus Paper of the Romanian Society of Gastroenterology and Hepatology

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ABSTRACT

Management of patients undergoing endoscopy and under treatment with the newer direct oral anticoagulants (DOACs) is a common and a complex clinical issue that gastroenterologists have to face more and more often these days. The increasing use of DOACs in patients requiring both short- and long-term anticoagulation is mostly due to the advantages these agents offer, among which the lack of monitoring requirements and the reduced need of dose adjustments are perhaps the most important ones. Managing these patients in the peri-endoscopic period implies balancing the risk for thrombosis that a certain patient carries and the bleeding risk associated with the endoscopic procedure itself. The Romanian Society of Gastroenterology and Hepatology decided to create a consensus paper to serve to practitioners and teachers. After reviewing the available published data and existing recommendations, a Delphi consensus process was carried out involving the leaders of opinion in this field. After reaching expert consensus, we provide herein guidance for a practical approach of DOACs therapy management in patients with endoscopic interventions.

Key words: direct oral anticoagulants – endoscopy – therapy management.

Abbreviations: APTT: activated partial thromboplastin time; ASA: acetylsalicylic acid; CrCl: creatinine clearance; DOACs: direct oral anticoagulants; EMA: European Medicines Agency; EMR/ESD: endoscopic mucosal resection/endoscopic submucosal dissection; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; FNA: fine-needle aspiration; GIB: gastrointestinal bleeding; H2RAs: histamine H2: receptor antagonists; NOACs: non-vitamin K oral anticoagulants; NSAIDs: non-steroidal anti-inflammatory drugs; PCC: prothrombin complex concentrates; PEG: percutaneous endoscopic gastrostomy; PEJ: percutaneous endoscopic jejunostomy; P-gp: P-glycoprotein; PPIs: proton pump inhibitors; PT: prothrombin time; RCTs: randomized clinical trials; VKAs: vitamin K antagonists.

INTRODUCTION

Direct oral anticoagulants (DOACs), also known as NOACs (non-vitamin K oral anticoagulants), have broadened the spectrum of anticoagulant therapy in the recent years, after almost seven decades when vitamin K antagonists (VKAs) were the only oral anticoagulant therapy available. Over the years various molecules have been developed and employed and a transition towards a new oral anticoagulant therapy has been established. Nowadays these drugs are being increasingly prescribed worldwide in patients requiring short and long term anticoagulation, accounting for more than 50% of oral anticoagulant prescriptions in countries such as UK and USA [1-3]. In Europe, the latest results on NOAC utilization, presented during the European Cardiology Society Congress in September 2017, indicated that 41% of patients were treated with NOACs among a cohort of 11,096 patients, from 27 countries, according to the data from the EORP-AF Long Term General Registry [4].

METHOD

In the intention to meet the needs in medical training and practice, our Society decided to develop a consensus paper to serve as a guide in the approach of gastroenterological

patients requiring endoscopy and on new oral anticoagulants. Therefore an initiative group was built. Intensive literature search was undertaken in all major databases: Pubmed, Scopus, Cochrane. After reviewing the available published data and existing recommendations, a consensus process was carried out involving all the leaders of opinion who wished to participate and representing the main university centers in this country. The resulting text with literature updates and recommendations was circulated and approved, after reaching expert consensus.

PHARMACOLOGICAL AGENTS

Ximelagatran was the first direct thrombin inhibitor to be approved on the market, an innovative prodrug produced by AstraZeneca [5], being shortly afterwards withdrawn from the market due to its serious immunologically mediated hepatotoxicity adverse profile [6]. *Dabigatran*, commercialized as *Pradaxa®* by Boehringer Ingelheim, a novel direct thrombin inhibitor designed as a prodrug, was the next DOAC to be approved for the prevention of thromboembolic disease following hip or knee replacement surgery and for non-valvular atrial fibrillation (AF), being available in the EU member states as of 2008. Inhibitors of activated factor X became commercially available later on, *rivaroxaban* (*Xarelto®*), a molecule from Bayer, being the one to enter the market in 2009. *Apixaban*, developed by Bristol-Myers Squibb, entered the European market as *Eliquis®* in 2012. The latest factor Xa inhibitor, *edoxaban*, produced by Daiichi Sankyo, and first marketed in 2011 in Japan, was authorized on the European market by the European Medicines Agency (EMA) as *Lixiana®* on April 2015.

DOACs were approved having several benefits over VKAs, such as ease of use, favorable pharmacokinetics allowing for fixed dosing, lack of anticoagulation monitoring requirements and decreased drug-drug and drug-food interactions. DOACs have proved comparable efficacy with conventional VKAs therapy for the prevention of stroke in AF and for secondary prevention of venous thromboembolism, in both randomized clinical trials and `real world` data from post-marketing studies. Phase III clinical trials conducted in patients with non-valvular AF were all randomized, parallel group, active-control studies, designed to prove non-inferiority to warfarin. The RE-LY trial compared dabigatran [110 mg twice daily (bid) or 150 mg bid] with dose-adjusted warfarin [7]. The ROCKET AF trial compared 20 mg once daily (od) rivaroxaban, respectively 15 mg od in patients with renal impairment (CrCl 30–49 mL/min) with dose adjusted warfarin [8]. The ARISTOTLE trial compared apixaban (5 mg bid, or 2.5 mg bid in selected patients) or dose-adjusted warfarin [9]. A second trial on apixaban (AVERROES) was designed as a double blind superiority study that compared 5 mg bid apixaban (or 2.5 mg bid in selected patients) with ASA (81–324 mg at the investigator's discretion) in patients who were unsuitable for warfarin or in whom warfarin therapy was unsuccessful [10]. In all these trials, DOACs non-inferiority for the primary endpoint of stroke or systemic embolism risk reduction was demonstrated. As a result DOACs are now recommended as a first-line anticoagulant treatment for stroke prevention in AF by the European Society of Cardiology [11] and the American College of Chest Physicians [12]. For edoxaban the two key phase III studies to introduce it into clinical practice were the ENGAGE F-TIMI 48 and Hokusai-VTE trials, that randomized patients to receive 30 or 60 mg edoxaban od, compared to standardized warfarin therapy, which also proved non-inferiority to warfarin [13, 14].

Pharmacokinetic properties

The individual DOACs have pharmacokinetic properties that differ. As the knowledge of these differences will allow for appropriate decisions in clinical practice regarding interrupting and reinitiating DOAC therapy before and after the endoscopic procedure, the pharmacokinetic profile of the DOACs available will be briefly presented here. In the pre- and post-endoscopic period there are three important pharmacokinetic considerations when holding and restarting a DOAC: time to maximum effect, half-life, and drug excretion, half-life being influenced by renal function when the drug undergoes renal excretion. Table I provides an overview of the pharmacokinetic properties of the different DOACs.

Table I. Pharmacokinetic properties summary of DOACs [15-19]

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Time to maximum activity	0.5-2 h	2-5 h	3-4 h	1-2 h
Half-life (normal renal function)	12-14 h	5-9 h	8-15 h	10-14h
Renal excretion	80%	66%	25%	50%

Dabigatran is a prodrug which achieves its anticoagulant effects through direct thrombin (factor IIa) inhibition, being prescribed as a 110 mg or 150 mg dose twice daily. It is absorbed in the proximal small bowel and its maximum activity is achieved 0.5-2 hours after administration. The mean half-life of dabigatran is 12 to 14 hours, according to age and renal function. Up to 80% is eliminated through renal excretion [3]. Therefore, the dose must be reduced in renal impairment, and it should be avoided altogether if the creatinine clearance (CrCl) is <30mL/min [15].

Rivaroxaban is a direct factor Xa inhibitor, acting by attenuating thrombin formation. It is administered in a single daily dose: 20 mg daily for stroke and systemic embolism prevention in patients with AF or 15 mg twice daily for 3 weeks, followed by 20 mg once daily thereafter for the venous thromboembolism (VTE) treatment. It is absorbed rapidly (t_{max} 2-5 hours) [16] in the proximal small intestine without interacting with food. Its half-life is 5 to 9 hours in younger patients and 11 to 13 hours in the elderly [16, 17]. It is partially eliminated through renal excretion (66%) and partially metabolized by the liver (CYP3A4 and CYP2J2 dependent), being contraindicated in patients with advanced liver disease (Child Pugh B and C) and severe renal insufficiency (CrCl<15mL/min). A dose reduction from 20mg once daily to 15mg once daily has been recommended for patients with a CrCl between 15 and 30mL/min.

Apixaban is also a direct factor Xa inhibitor administered twice daily in a 2.5 mg dose. It is absorbed in the small

bowel, with a maximum plasma concentration 3 to 4 hours after administration [18]. It goes through a greater liver metabolism than rivaroxaban. It has a half-life of 8 to 15 hours [18]. Thirty-five percent of the drug is excreted through feces without previous absorption, and only about 25% is excreted by the kidneys. It should be avoided in patients with CrCl<15mL/min and used with caution in those with hepatic impairment.

Edoxaban, the newest inhibitor of factor Xa, has a dosing regimen of 60 mg once daily (the twice daily regimen was also trialed, but was associated with greater bleeding risk). Its peak effects are seen within 1–2 hours, with a half-life of 10 to 14 hours. Edoxaban is predominantly eliminated in feces and urine, and renal elimination ranges from 35% to 50% [19]. In patients with renal impairment, a 50% dose reduction should be considered if CrCl is 15–29 mL/min, being contraindicated if CrCl <15 mL/min [20]. The drug is also contraindicated in patients with severe hepatic impairment or with hepatic disease associated with coagulopathy and hemorrhagic risk.

DOACs ASSOCIATED BLEEDING RISK

Anticoagulant therapy has long been disputed due to its associated risks, such as bleeding in patients undergoing anticoagulation therapy, and DOACs are not spared from these adverse effects.

In phase III clinical trials, compared to warfarin, rates of major bleeding were significantly lower for 110 mg bid dabigatran (p = 0.003) [7] and 5 mg bid apixaban (p < 0001), [9] and similar for 150 mg bid dabigatran (p = 0.31) [7] and 20 mg od rivaroxaban (p = 0.58) [8]. However, gastrointestinal bleeding (GIB) was significantly more frequent with a high dose (150 mg bid) dabigatran (p < 0.001) [7] and 20 mg od rivaroxaban (p < 0.001) [8], but similar for 110 mg bid dabigatran (p = 0.43) [7] and 5 mg bid apixaban (p = 0.37) [9]. Rates of life threatening bleeding with 110 mg bid and 150 mg bid dabigatran (p < 0.001 and p= 0.04, respectively) [7] and rates of fatal bleeding with 20 mg od rivaroxaban (p = 0.003) [8] and 5 mg bid apixaban (no p-value reported) [9] were lower when compared to warfarin. Rates of major bleeding were similar between the apixaban and ASA groups (p = 0.57) in the AVERROES trial [10]. ENGAGE-AF TIMI 48 edoxaban trial also reported lower bleeding rates (p=0.001) for both low-dose (30 mg) and high-dose (60 mg) edoxaban when compared to warfarin [13].

GASTROINTESTINAL BLEEDING AND ASSOCIATED RISK FACTORS IN PATIENTS RECEIVING DOACs

The target DOACs treatment population is represented by the elderly, with significant comorbidities and polypharmacy, most often including aspirin and/or thienopyridines, and NSAIDs, and therefore at increased risk for GIB, even in the absence of anticoagulation. Several meta-analyses that included randomized clinical trials (RCTs) or post-marketing data from real life settings already summarized the risk of GIB and discussed the associated risk factors. The Holster et al. meta-analysis, including 17 RCTs, proved that there was an increased risk of GIB among DOACs users compared with standard of care, with an overall OR of 1.45 (95% confidence interval [CI], 1.07-1.97) [21]; however there was substantial heterogeneity among analyzed studies. Compared with VKAs, other meta-analyses of RCTs available in patients with non-valvular AF have suggested that treatment with DOACs could increase the risk of GIB by 25% [22, 23].

Among the different DOACs studied, the highest risk of GIB was associated with dabigatran [OR 1.58 (95% CI, 1.29-1.93)], and rivaroxaban [OR 1.48 (95% CI, 1.21-1.82)] [21]. Head to head comparison in patients with AF showed that GIB was similarly manifested between dabigatran and rivaroxaban (OR: 0.98, 95% CI: 0.43-2.25; p = 0.97); this was the case for all bleeding events (OR: 1.28, 95% CI: 0.95-1.72; p = 0.11) [24]. Among various indications of DOACs, the highest risk was seen for patients with acute coronary syndrome [OR 5.21 (95% CI, 2.58-10.53)], in whom antiplatelet agents were co-prescribed [21]. Concomitant antiplatelet use is known to be associated with 30% up to 50% higher risk of GIB among dabigatran users [25]. Moreover, patients with AF and with acute coronary syndrome receive anticoagulant therapy for a long period of time, suggesting a therapy duration effect for dabigatran and rivaroxaban [26]. Furthermore, it has also been demonstrated that higher doses of dabigatran (150 mg bid) [25] or edoxaban (60 mg daily) [27] were associated with an increased risk of GIB when compared to warfarin and low dose edoxaban (30 mg daily) respectively, indicating a dose-related effect.

Observational data existing to date are, in general, consistent with the findings from RCTs. Eight cohort studies evaluating exposure to DOACs, and reporting GIB, were discussed in a systematic review with a meta-analysis. The summary risk ratio (RR) was 1.21 (95% CI 1.05 - 1.39) for dabigatran compared with warfarin, and 1.09 (95% CI 0.92 - 1.30) for rivaroxaban, suggesting a slightly higher risk of GIB with dabigatran only, with a significantly increased risk of major GIB (RR = 1.30, 95% CI 1.17 - 1.46) [28]. Higher dose of dabigatran was also associated with a higher risk for GIB, compared to the lower dose, in real life setting. Use of proton pump inhibitors (PPIs)/histamine H2-receptor antagonists (H2RAs) influenced the observed association in dabigatran users, having a modest effect in rivaroxaban users [26]. The risk of GIB was reported to increase over the age of 65 in dabigatran or rivaroxaban users, particularly concerning people aged over 75 years [29, 30].

Decreased renal function leading to drug accumulation, especially for dabigatran which has the greatest dependence on renal elimination, is another factor that might lead to higher bleeding risk. Pre-existing history of peptic ulcer, including infection with *Helicobacter pylori* or previous GIB, and other lower gastrointestinal tract lesions such as colonic diverticula or angiodysplasia in the elderly are also reported among risk factors for GIB in DOAC users [24, 31]. Patients with a high risk of bleeding can be also identified by a HAS-BLED score of ≥3 [32]. However, balancing all these risk factors contributing to a patient's bleeding risk should not preclude the use of DOACs, but indicate an appropriate caution and regular patient monitoring. Table II summarizes the risk factors for GIB in patients with DOAC therapy.

Table II. Risk factors for gastrointestinal bleeding [25-27, 29-32]

Risk factor	Specifics
Age ≥ 65 years	Risk particularly concerning for ≥75 years
High dose administered	Particular for: Dabigatran 150 mg bid Edoxaban 60 mg once daily
Renal impairment (dose reduction recommended according to European Product Specification)	CrCl 30–49 mL/min for Dabigatran CrCl 15-49 mL/min for Rivaroxaban CrCl 15-29 mL/min for Apixaban CrCl 15-50 mL/min for Edoxanban
History of GIB or stomach/peptic ulcer with or without *Helicobacter pylori* infection	
Lower GI tract lesions	Colonic diverticular bleeding/ Angiodysplasia
Concomitant use of ulcerogenic drugs	Antiplatelets/ NSAIDs/ Aspirin/ Steroids
Concomitant use of P-gp and/or CYP3A4 inhibitors	May lead to increased dabigatran plasma concentrations

P-gp: P-glycoprotein; GIB: gastrointestinal bleeding; NSAIDs: non-steroidal anti-inflammatory drugs

MANAGEMENT OF GIB IN PATIENTS RECEIVING DOACs

The management options of bleeding complications of DOACs can be divided into supportive measures and more specific anticoagulation reversal strategies, mostly depending on the severity of bleeding [33, 34]. Existing guidelines indicate that the decision to reverse anticoagulation should be made on a case-by-case basis, weighting the potential risk for thrombosis with the risk of continued bleeding [34].

When bleeding is not severe, initial bleeding management consists of supportive measures, while discontinuing the therapy in patients with normal renal function might also be sufficient due to the relatively short half-life of DOACs. If the anticoagulant is stopped, the coagulation will be restored rapidly in most cases (12-24 hours and 5 drug half-lives for near complete recovery) [33]. In parallel, the time of the last DOAC intake should be determined and laboratory evaluations for measuring the anticoagulant effect should be required for supplemental information. Activated partial thromboplastin time (APTT) has a linear response to dabigatran concentration, up to the therapeutic range, so a normal value should exclude dabigatran as being the cause for bleeding. In a similar way, prothrombin time (PT) indicates if rivaroxaban is in the therapeutic range. Apixaban has no significant effect on PT [31, 35]. However, there are sources suggesting that these tests are unspecific and unreliable indicators for the anticoagulant activity and the results cannot be used to determine the plasma concentration of the drug [36, 37].

Among further supportive measures, whenever needed, oral activated charcoal has been suggested to prevent drug absorption, if drug intake was within the past two hours or in the case of overdose/intoxication. There is no solid evidence for the use of tranexamic acid in bleeding complications of the new anticoagulants, but its long proven efficacy in reducing blood loss and safety should sustain its use in GIB [37, 38]. Fluid replacement and correction of anemia with transfusion of red cells or other blood products should be initiated, if appropriate. Endoscopic haemostasis could be also performed for stopping severe bleeding [34]. In patients with life-threatening bleeding, hemodialysis can remove dabigatran, especially in patients with renal impairment, as it has a relatively low plasma protein binding (35%), but not rivaroxaban or apixaban due to their high protein binding (~90%) [33, 35, 39]. Administration of prothrombin complex concentrates (PCC) in up to a 40-50 IU/kg dose has been suggested in life-threatening bleeding, mostly based on animal studies, but there is little clinical evidence to date that this will reduce bleeding [34, 35]. In all severe and challenging cases, advice should be sought from a hematologist.

Specific antidotes for reversing DOACs effects were recently approved or are under development. *Idarucizumab* (*Praxbind®*), a specific antidote for dabigatran is licensed for patients with severe life-threatening dabigatran induced bleeding. It is a monoclonal antibody fragment binding both free and thrombin-binded dabigatran, with 350 times the affinity of thrombin, thus reversing its anticoagulant effect in minutes [40]. Antidotes for factor Xa inhibitors are not yet licensed, but in development, including the new agent *andexanet alfa* [36].

Reinitiating DOAC therapy after GIB

Once hemostasis is secured and the bleeding location has been stabilized, it should be safe to reinitiate anticoagulant therapy. While making this decision one should take into account the severity of bleeding and the risk of recurrent GIB versus the risk of stroke. Restarting DOAC at 7 days post-hemorrhage was suggested based on the experience with warfarin [36]. Re-introduction of DOAC will result in rapid anticoagulation. The DOAC could be re-started at the same or at a lower dose, longterm PPIs could also be associated, which may lower the risk of bleeding, or the patient might be switched to VKA if the risk of GIB is high [33, 36].

ENDOSCOPIC PROCEDURES IN PATIENTS RECEIVING DOACs

In patients undergoing endoscopic procedures, haemorrhage can be usually controlled endoscopically. However, thrombosis could result in myocardial infarction or stroke, potentially leading to permanent disability or even death.

For these reasons, management of patients on anticoagulant therapy undergoing endoscopy implies balancing the risks between bleeding due to the procedure, and thrombosis due to discontinuation of the therapy. Thrombotic and bleeding risks may vary depending on individual circumstances.

There is a lack of outcome data to guide the gastroenterologist in anticoagulation management in a patient undergoing endoscopic procedures. As clinical studies are still required in order to establish which practices provide the greatest clinical benefit, to date, most recommendations primarily reflect expert opinion. The European Society of Gastrointestinal Endoscopy (ESGE) in collaboration with the British Society of Gastroenterology (BSG) [34, 41] and the American Society of Gastrointestinal Endoscopy (ASGE) [42] guidelines were recently updated, and may assist the physician in the decision-making process. Management of DOAC for endoscopy is a balance between the bleeding risk of the procedure itself, and the risk of thrombosis, on a case-by-case assessment of the patient specifics. For therapeutic procedures with a risk of bleeding and for which a direct hemostatic action is possible, prevention modalities are very important and should always be available and used (clips, endoloop, etc). The risk of bleeding for endoscopic procedures according to BSG-ESGE [34] and ASGE [42] is presented in Table III.

For elective procedures, there is adequate time to plan best management of antithrombotic therapy. The endoscopic procedure should be performed when the DOAC level is at its lowest, so the anticoagulant effect. In general, because of their short half-life, DOACs can be continued until shortly before the procedure, and because of their rapid onset of action, the anticoagulation effect is achieved within a few hours after re-initiating the treatment [43]. These DOACs properties proved that bridging therapy with parenteral unfractionated or low molecular weight heparin is unnecessary, obviating the inconveniences of heparin therapy and of laboratory testing of coagulation parameters [44, 45]. This approach was also proven beneficial in the prospective, non-interventional DRESDEN registry on DOAC patients, when heparin bridging therapy was used in only 25.3% of the endoscopic procedures, predominantly in cases of DOAC therapy interruption for longer than 72 hours [46].

For low-risk elective endoscopic procedures the general recommendation is to omit the morning DOAC dose in the day of the procedure, to allow for a 2 to 3 half-life interval before the procedure (very low quality evidence, weak recommendation) [33, 34, 36].

Table III. Bleeding risk according to endoscopic procedure [34, 42]

	BSG-ESGE Guideline	ASGE Guidelines
High risk procedures	• Endoscopic polypectomy	• Polypectomy
	• ERCP with sphincterotomy	• Biliary or pancreatic sphincterotomy
	• Sphincterotomy + large balloon papillary dilatation	• Therapeutic balloon-assisted enteroscopy
	• Ampullectomy	• PEG placement
	• Device-assisted enteroscopy without polypectomy	• Treatment of varices
	• EMR/ESD	• Endoscopic hemostasis
	• Endoscopic dilatation of strictures in the upper or lower GI tract	• PEJ
	• Endoscopic therapy of varices	• ESD
	• Percutaneous endoscopic gastrostomy	• Pneumatic or bougie dilation • EMR
	• Endoscopic ultrasound with fine needle aspiration	• Ampullary resection • Tumor ablation • EUS with FNA
	• Oesophageal, enteral or colonic stenting	• Cystgastrostomy
Low risk procedures	• Diagnostic procedures ± biopsy	• Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy
	• Biliary or pancreatic stenting	• ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
	• Device-assisted enteroscopy without polypectomy	• Push enteroscopy and diagnostic balloon-assisted enteroscopy
		• Capsule endoscopy
		• Enteral stent deployment (controversial)
		• EUS without FNA
		• Argon plasma coagulation
		• Barrett's ablation

EMR/ESD: endoscopic mucosal resection/endoscopic submucosal dissection; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; FNA: fine-needle aspiration; PEG: percutaneous endoscopic gastrostomy; PEJ: percutaneous endoscopic jejunostomy.

For high-risk elective endoscopic procedures the general recommendation is to take the last DOAC dose at least 48 hours before the procedure (4 to 5 half-lives). For patients with a CrCl 30-50 mL/min on dabigatran the last dose should be taken at least 72 hours before the procedure (very low quality evidence, weak recommendation) [33, 34, 36, 43].

However, the above general recommendations should be individualized, taking into account the patient renal function and the DOAC used (Tables IV and V) [34, 42, 44, 47]. This is due to the fact that the different DOACs available have different half-lives, and are eliminated to a lesser or to a greater extent via the kidneys, thus renal impairment may lead to drug accumulation [48, 49]. Therefore, in patients with impaired renal function the DOAC should be discontinued for a longer period of time before endoscopy. The renal function should be checked before the procedure, especially if the patient on DOAC is clinically deteriorating, and a hematologist advice should be asked for, in this situation [34].

Table IV. Pre-endoscopic management of dabigatran [34, 42, 44, 47]

Creatinine Clearance (mL/min)	Time to discontinue drug before procedure	
	Standard Bleeding Risk	High Bleeding Risk
>80	24 hours	48-72 hours
50-80	24-48 hours	48-72 hours
30-49	48 hours	72-96 hours
≤29*	48-72 hours	96-144 hours

*Dabigatran should be avoided if CrCl<30 mL/min

Table V. Pre-endoscopic management of factor Xa inhibitors [34, 42, 47]

Creatinine Clearance (mL/min)	Time to discontinue drug before high risk procedures		
	Rivaroxaban	Apixaban	Edoxaban
>90	24-48 hours	-	-
>60	48 hours	24-48 hours	At least 24 hours
30-59	72 hours	72 hours	At least 24 hours
15-29	96 hours	96 hours	At least 24 hours

In case of urgent surgery, a 12 hours delay of the procedure is recommended, if clinically acceptable, following the last DOAC dose. Due to the short half-lives of these drugs this delay should be sufficient along with further supportive care, and haemostatic control. In case of severe bleeding or in patients that require an emergency surgery due to trauma or other emergencies, appropriate reversal strategies (e.g. idarucizumab for dabigatran or adexanet alfa as it will be available for factors Xa inhibitors) should be considered [50, 51].

Bleeding risk associated with endoscopic procedures per se

It is well known that endoscopic procedures are associated with an increased risk of acute GIB. Most studies suggest that this occurs both during endoscopy and up to two weeks afterwards.

Gastrointestinal endoscopy and the acquisition of tissue samples are essential for the diagnosis and treatment of various diseases of the digestive system. One of the main advantages of these techniques is providing tissue for histopathological examination. Endoscopic mucosal resection is a safe technique that has a minimal risk of bleeding, with no severe hemorrhage reported in previous studies, including patients on anticoagulant therapy [52].

Polypectomy procedure represents the endoscopic removal of polyps in order to prevent them from becoming malignant. The most common complications of polypectomy are bleeding and perforation. The risk of bleeding depends especially on the polyp size. It was estimated that each 1 mm increase in polyps' diameter increases the risk of bleeding by 9% [53]. The use of pure cutting current also represents an independent predictive factor for bleeding compared with blended or coagulation current [54]. Prophylactic measures, such as mechanical techniques – detachable loop, endoclip or submucosal injection of diluted adrenaline have an important role in preventing bleeding [55].

Endoscopic retrograde cholangiopancreatography associates clinically significant hemorrhage in 0.1%-2% of sphincterotomies. As risk factors related to this procedure the literature mentions coagulopathy, initiation of anticoagulant therapy within three days after the procedure, active cholangitis, low experience of the endoscopist [56]. To reduce the risk of bleeding sphincterotomy blended current is recommended in detriment of pure-cutting current. As well, to decrease the risk of bleeding, endoscopic papillary balloon dilatation represents an alternative to sphincterotomy for biliary stone extraction [34].

Endoscopic ultrasound-guided fine needle core biopsy (EUS-FNA) is a minimally invasive method with a complication rate of approximately 1%–2%. Complications include pancreatitis, infection, bleeding, and abdominal pain requiring analgesics [57]. Also the size of the needle and the number of passes made may also influence the overall risk of complications. It is believed also that guided brushing has a higher risk of bleeding especially in pancreatic cysts [58].

Esophageal dilatation is performed in certain esophageal stricture pathologies or motility disorders. Related to this procedure, no significant hemorrhage has been reported [59].

Endoscopic stent insertion is proved to be a major therapeutic advance because it can be used in various sites of the gastrointestinal tract. It has an important role either as a definitive treatment, as a bridge to surgery, or for palliation of obstructive syndromes. In this procedure immediate hemorrhage rates are low, although consideration should be given to delayed severe bleeding [60].

Percutaneous endoscopic gastrostomy is the preferred route of nutritional support in patients requiring long-term enteral nutrition. It is usually considered a safe procedure; however, complications may occur. Among them we mention bleeding, aspiration pneumonia, internal organ injury, necrotizing fasciitis. Severe bleeding is rare, minor bleeding around the wound site being more frequently encountered [61].

Endoscopic therapy for varices aims to reduce variceal wall tension by obliteration of the varix. In this case the risk

of bleeding is associated especially with delayed hemorrhage due to band- induced ulcers [62].

Post-endoscopic management of DOACs

Re-initiating DOAC after endoscopy, provided that the haemostasis has been achieved, depends on the nature of endoscopic intervention, upon the risk of bleeding post procedure and upon the thrombotic risk [33, 34]. It is important for the clinician to be aware of the fact that, unlike the reintroduction of vitamin K antagonists, which results in delayed anticoagulation for several days, the anticoagulant effect of therapeutic DOAC doses will be achieved much faster, in 2 to 4 hours [34, 42]. Hence, for low-risk procedures, the DOAC can be reintroduced in therapy in the first 24 hours, and even earlier, at 6-8 hours after the procedure, if there has been no significant bleeding [39]. For high-risk procedures the re-initiation of DOAC should be postponed for 48 hours after endoscopy [33, 34]. A longer period of discontinuation could be taken into consideration for procedures associated with a high risk of delayed hemorrhage, such as EMR and ESD, if patients are in a low thrombotic risk category [34]. In patients at a higher risk of thrombotic complications, a prophylactic dose of low molecular weight heparin should be considered until the DOAC can be safely restarted [39]. The DOACs should be restarted at the same dose the patient was receiving before the procedure.

On the other hand, special care should be given to cardiovascular patients under DOAC at risk of developing GIB [63]. This emphasizes the importance of the management of subjects on DOACs. Therefore, collaboration with cardiologists should be considered [63].

CONCLUSION

In recent years there has been an increase in the prescription of new oral anticoagulant agents, with a higher expansion of their use foreseeable in the years to come. DOACs offer some advantages, such as a lower risk of major and intracranial bleeding, besides the absence of the need for routine monitoring and fewer drug-drug and drug-food interactions. However, they are associated with the same or even a higher incidence of GIB events as compared to VKAs, being thus in the loop of gastroenterologists. Their anticoagulant effects are difficult to reverse in an emergency situation for the moment, as specific antidotes are not largely available or still under development. In the peri-endoscopic period they might pose particular challenges for the gastroenterologist when it comes to making the appropriate decisions for holding and restarting a DOAC, while keeping at a minimum the risk for thrombosis, along with the potential bleeding risk that an endoscopic procedure carries. While limited or no data exists from well-designed clinical trials on the perioperative management of DOACs, the present opinion paper's objective was to be an educational tool providing valuable information and recommendations to guide clinical decisions of endoscopists.

Key recommendations:

- For low-risk endoscopic procedures, DOAC dose should be omitted in the day of procedure.
- For high-risk endoscopic procedures, the last DOAC dose should be taken at least 48 hours before the procedure.
- The last dose of dabigatran should be taken at least 72 hours before a high-risk endoscopic procedure, when it concerns patients with a CrCl of 30-50 mL/min.
- For more individualized management of DOAC therapy, the pharmacokinetic properties should be considered when holding and restarting a DOAC, along with the patient renal function and procedure bleeding risk.
- DOACs should be restarted in general in 24-48 hours after the procedure, upon achieving haemostasis, and depending on the bleeding and thrombotic perceived risks of each individual patient.
- For procedures with a significant risk of delayed hemorrhage, a longer period of DOAC discontinuation may be considered, taking into account the thrombotic risk and the option for bridge therapy (heparin) to provide thromboprophylaxis.

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REFERENCES

1. Hanemaaijer S, Sodihardjo F, Horikx A, et al. Trends in antithrombotic drug use and adherence to non-vitamin K oral anticoagulants in the Netherlands. Int J Clin Pharm 2015;37:1128-1135. doi:10.1007/s11096-015-0174-4
2. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol 2017;83:2096-2106. doi:10.1111/bcp.13299
3. Huisman MV, Rothman KJ, Paquette M, et al. Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II. Am J Med 2015;128:1306-1313. doi:10.1016/j.amjmed.2015.07.013
4. Boriani G. EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long Term General Registry: Analysis of Treatment with Oral Anticoagulants in More than 11,000 Patients. Presented at the European Cardiology Society Congress on 27 August 2017, Barcelona, Spain. Abstract no 1061.
5. Hrebickova L, Nawarskas JJ, Anderson JR. Ximelagatran: a new oral anticoagulant. Heart Dis 2003;5:397–408. doi:10.1097/01.hdx.0000099777.39577.e8
6. Agnelli G, Eriksson BI, Cohen AT, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. Thromb Res 2009;123:488–497. doi:10.1016/j.thromres.2008.02.017
7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–1151. doi:10.1056/NEJMoa0905561
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365: 883–891.

9. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–992. doi:10.1056/NEJMoa1107039
10. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364:806–817. doi:10.1056/NEJMoa1007432
11. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609-1678. doi:10.1093/europace/euw295
12. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S–e575S. doi:10.1378/chest.11-2304
13. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015;385:2288–2295. doi:10.1016/S0140-6736(14)61943-7
14. Said K. Hokusai-VTE: Edoxaban for the treatment of venous thromboembolism. Glob Cardiol Sci Pract 2013;2013:416–420.
15. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007;64:292-303. doi:10.1111/j.1365-2125.2007.02899.x
16. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939—an oral, direct Factor Xa inhibitor—after multiple dosing in healthy male subjects. Eur J Clin Pharmacol 2005;61:873-880. doi:10.1007/s00228-005-0043-5
17. Baron TH, Kamath PS, McBane RD. New anticoagulant and antiplatelet agents: a primer for the gastroenterologist. Clin Gastroenterol Hepatol 2014;12:187-195. doi:10.1016/j.cgh.2013.05.020
18. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos 2009;37:74-81. doi:10.1124/dmd.108.023143
19. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol 2010;50:743–753. doi:10.1177/0091270009351883
20. Bathala MS, Masumoto H, Oguma T, He L, Lowrie C, Mendell J. Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans. Drug Metab Dispos 2012;40:2250–2255. doi:10.1124/dmd.112.046888
21. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013;145:105-112.e15. doi:10.1053/j.gastro.2013.02.041
22. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-962. doi:10.1016/S0140-6736(13)62343-0
23. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 2012;110:453-460. doi:10.1016/j.amjcard.2012.03.049
24. Bundhun PK, Soogund MZ, Teeluck AR, Pursun M, Bhurtu A, Huang WQ. Bleeding outcomes associated with rivaroxaban and dabigatran in patients treated for atrial fibrillation: a systematic review and meta-analysis. BMC Cardiovasc Disord 2017;17:15. doi:10.1186/s12872-016-0449-2
25. 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. doi:10.1161/CIRCULATIONAHA.110.004747
26. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World J Gastroenterol 2017;23:1954-1963. doi:10.3748/wjg.v23.i11.1954
27. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-2104. doi:10.1056/NEJMoa1310907
28. He Y, Wong IC, Li X, et al. The association between non-vitamin K antagonist oral anticoagulants and gastrointestinal bleeding: a meta-analysis of observational studies. Br J Clin Pharmacol 2016;82:285-300. doi:10.1111/bcp.12911
29. Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. BMJ 2015;350:h1857. doi:10.1136/bmj.h1857
30. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology 2017;152:1014-1022.e1. doi:10.1053/j.gastro.2016.12.018
31. Lanas-Gimeno A, Lanas A. Risk of gastrointestinal bleeding during anticoagulant treatment. Expert Opin Drug Saf 2017;16:673-685. doi:10.1080/14740338.2017.1325870
32. Habert JS. Minimizing bleeding risk in patients receiving direct oral anticoagulants for stroke prevention. Int J Gen Med 2016;9:337–347. doi:10.2147/IJGM.S109104
33. Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. Gastrointest Endosc 2013;78:227-239. doi:10.1016/j.gie.2013.04.179
34. Veitch AM, Vanbiervliet G, Gershlick AH, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. Endoscopy 2016;48:385-402. doi:10.1055/s-0042-102652
35. Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. Best Pract Res Clin Haematol 2013;26:191-202. doi:10.1016/j.beha.2013.07.001
36. Veitch AM. Endoscopy in Patients on Antiplatelet Agents and Anticoagulants. Curr Treat Options Gastroenterol 2017;15:256-267. doi:10.1007/s11938-017-0137-z
37. Leitch J, van Vlymen J. Managing the perioperative patient on direct oral anticoagulants. Can J Anaesth 2017;64:656-672. doi:10.1007/s12630-017-0868-2
38. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23–32. doi:10.1016/S0140-6736(10)60835-5
39. Woodhouse C, Evans G, Muller AF. The new oral anticoagulants: practical management for patients attending for endoscopic procedures. Frontline Gastroenterol 2013;4:213-218. doi:10.1136/flgastro-2013-100325

40. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med 2015;373:511–520. doi:10.1056/NEJMoa1502000
41. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:a1-a46. doi:10.1055/s-0034-1393172
42. ASGE Standards of Practice Committee, Acosta RD, Abraham NS, et al. The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83:3-16. doi:10.1016/j.gie.2015.09.035
43. Zullo A, Hassan C, Radaelli F. Gastrointestinal endoscopy in patients on anticoagulant therapy and antiplatelet agents. Ann Gastroenterol 2017;30:7-14. doi:10.20524/aog.2016.0096
44. Schulman S, Carrier M, Lee AY, et al. Perioperative management of dabigatran: a prospective cohort study. Circulation 2015;132:167–173. doi:10.1161/CIRCULATIONAHA.115.015688
45. Lange CM, Fichtlscherer S, Miesbach W, Zeuzem S, Albert J. The Periprocedural Management of Anticoagulation and Platelet Aggregation Inhibitors in Endoscopic Interventions. Dtsch Arztebl Int 2016;113:129-135. doi:10.3238/arztebl.2016.0129
46. Heublein V, Pannach S, Daschkow K, Tittl L, Beyer-Westendorf J. Gastrointestinal endoscopy in patients receiving novel direct oral anticoagulants: results from the prospective Dresden NOAC registry. J Gastroenterol 2018;53:236-246. doi:10.1007/s00535-017-1346-x
47. Sunkara T, Ofori E, Zarubin V, Caughey ME, Gaduputi V, Reddy M. Perioperative Management of Direct Oral Anticoagulants (DOACs): A Systemic Review. Health Serv Insights 2016;9(Suppl 1):25-36. doi:10.4137/HSI.S40701
48. Wanat MA. Novel oral anticoagulants: a review of new agents. Postgrad Med 2013;125:103-114. doi:10.3810/pgm.2013.07.2683
49. Cheng JW, Barillari G. Non-vitamin K antagonist oral anticoagulants in cardiovascular disease management: evidence and unanswered questions. J Clin Pharm Ther 2014;39:118-135. doi:10.1111/jcpt.12122
50. Lai A, Davidson N, Galloway SW, Thachil J. Perioperative management of patients on new oral anticoagulants. Br J Surg 2014;101:742-749. doi:10.1002/bjs.9485
51. Levy JH. Discontinuation and management of direct-acting anticoagulants for emergency procedures. Am J Emerg Med 2016;34:14-18. doi:10.1016/j.ajem.2016.09.048
52. Capell MS, Abdullah M. Management of gastrointestinal bleeding induced by gastrointestinal endoscopy. Gastroenterol Clin North Am 2000;29:125-167. doi:10.1016/S0889-8553(05)70110-2
53. Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008;40:115-119. doi:10.1055/s-2007-966959
54. Kim HS, Kim TI, Kim WH, et al. Risk factors for immediate postpolypectomy bleeding of the colon: a multicenter study. Am J Gastroenterol 2006;101:1333-1341. doi:10.1111/j.1572-0241.2006.00638.x
55. Li LY, Liu QS, Li L, et al. A meta-analysis and systematic review of prophylactic endoscopic treatments for postpolypectomy bleeding. Int J Colorectal Dis 2011;26:709-719. doi:10.1007/s00384-011-1141-8
56. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909-918. doi:10.1056/NEJM199609263351301
57. Adler DG, Jacobson BC, Davila RE, et al. ASGE guideline: complications of EUS. Gastrointest Endosc 2005;61:8–12. doi:10.1016/S0016-5107(04)02393-4
58. Al-Haddad M, Gill KR, Raimondo M, et al. Safety and efficacy of cytology brushings versus standard fine-needle aspiration in evaluating cystic pancreatic lesions: a controlled study. Endoscopy 2010:42:127-132. doi:10.1055/s-0029-1215351
59. Raymondi R, Pereira-Lima JC, Valves A, et al. Endoscopic dilation of benign esophageal stricures without fluoroscopy: experience of 2750 procedures. Hepatogastroenterology 2008;55:1342-1348.
60. Conio M, Repici A, Battaglia G, et al. A randomized prospective comparison of self- expandable plastic stents and partially covered self- expandable metal stents in the palliation of malignant esophageal dysphagia. Am J Gastroenterol 2007;102:2667-2677. doi:10.1111/j.1572-0241.2007.01565.x
61. Schurink CA, Tuynman H. Scholten P, et al. Percutaneous endoscopic gastrostomy: complications and suggestions to avoid them. Eur J Gastroenterol Hepatol 2001;13:819-823.
62. Vanbiervliet G, Giudicelli-Bornard S, Piche T, et al. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case –control study. Aliment Pharmacol Ther 2010;32:225-232. doi:10.1111/j.1365-2036.2010.04331.x
63. Negovan A, Mester A, Dumitrașcu D. Gastroenterological perspectives on acute cardiac care - the management of patients with implanted coronary stents following an acute coronary syndrome. Journal of Cardiovascular Emergencies 2018;4:8-16. doi:10.2478/jce-2018-0006