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Direct oral anticoagulants and digestive bleeding: therapeutic management and preventive measures

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***Abstract*:** The use of direct oral anticoagulants (DOACs) was an important step forward in the management of atrial fibrillation and venous thromboembolism (VTE). The DOACs, anti-IIa for dabigatran and anti-Xa for rivaroxaban, apixaban and edoxaban, all have a rapid onset of action and a short half life. There is no need for routine hemostasis testing for treatment monitoring of a DOAC. Compared with vitamin K antagonists (VKAs), DOACs may increase the risk of gastrointestinal bleeding (relative risk 1.25). Withholding the DOAC treatment, evaluating the time of the last intake and estimating the patient's renal function are the first steps in the management of gastrointestinal bleeding. For patients without impaired renal function, achieving low coagulation takes around 24 h after the last intake of a DOAC. The use of DOAC antagonists will be helpful in controlling bleeding in the most severe and urgent situations. Idarucizumab is available for clinical use for dabigatran and andexanet is currently being reviewed by drug agencies for rivaroxaban, apixaban and edoxaban. It is important to assess the bleeding risk associated with the planned procedure, and the patient's renal function before withholding DOAC therapy for a scheduled intervention. It is mandatory to strengthen the local hemostasis strategies in DOAC-treated patients undergoing a therapeutic endoscopic procedure. Resuming or not resuming anticoagulation with a DOAC after bleeding or a risky procedure depends on the thrombotic and bleeding risk as well as the procedure involved. This discussion should always involve the cardiologist and decisions should be taken by a pluridisciplinary team.

Keywords: apixaban, dabigatran, digestive bleeding, direct oral anticoagulants, edoxaban, endoscopy, gastrointestinal bleeding, hemostasis, rivaroxaban

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Introduction

Providing direct oral anticoagulants (DOACs) was an important therapeutic advance in nonvalvular atrial fibrillation (NVAF) and venous thromboembolic disease care. Four pivotal randomized controlled trials studying 71,863 patients with atrial fibrillation (AF) showed that DOACs are equal, if not superior, to vitamin K antagonists (VKAs) in preventing stroke with a survival benefit.[1] In these settings, treatment with DOACs is associated with a lower overall bleeding risk and especially a lower risk of intracranial hemorrhage.

In the management of deep vein thrombosis (DVT) and pulmonary embolism (PE), six randomized controlled trials have been conducted with 26,997 patients and have shown that DOACs are as efficient as heparin treatment relayed by VKA in preventing recurrence of thromboembolism, while being associated with a risk reduction in overall bleeding.[2] However, DOACs have been associated with a higher incidence of gastrointestinal bleeding in most of the pivotal trials available. The goal of this work, born from a pluridisciplinary reflection of experts in gastroenterology, cardiology, intensive care medicine and

Table 1. CHADS2 and CHA2DS2-VASc: scores for Atrial Fibrillation Stroke Risk.

	CHADS2	CHA2DS2-VASc
Congestive heart failure (or left ventricular systolic dysfunction)	+1	+1
Arterial hypertension	+1	+1
Age ⩾75 years	+1	+2
Age 65–74 years	–	+1
Diabetes mellitus	+1	+1
Stroke or transient ischemic attack or thromboembolism history	+2	+2
Vascular disease history (myocardial infarction, peripheral artery disease, aortic plaque)	–	+1
Female sex	–	+1

hematology, was to focus on the risk and management of gastrointestinal bleeding and scheduled endoscopy in patients receiving DOACs.

DOACs: characteristics, indications, uses

Indications of DOACs

Arterial and venous thromboembolism (VTE) are common and can be severe.[3] These conditions represent a burden for the patient and for society. Prevention and treatment of thrombosis relies on anticoagulation. In July 2014, a report from the French drug safety agency (ANSM) showed that 3.12 million patients, 13.7% of whom were over 65 years old, were treated with an anticoagulant in 2013. Clinically available oral anticoagulants are VKAs and DOACs, with a growing part of new prescriptions prioritizing DOACs: 30% at the end of 2014.[4] DOACs include the thrombin inhibitor dabigatran and the anti-Xa agents rivaroxaban, apixaban and edoxaban. They are prescribed for stroke prevention and systemic embolisms in adults with NVAF, associated with one or more risk factors (stroke risk assessed by CHADS2 and CHA2DS2-VASc scores, shown in Table 1). The use of a DOAC rather than a VKA has shown a reduction of ischemic [relative risk (RR) 0.92] or hemorrhagic stroke (RR 0.49), and a reduced all-cause mortality (RR 0.90).[1] A DOAC is also indicated in the secondary prevention and treatment of VTE, and in the prevention of VTE after a major elective orthopedic surgery.[4] Its use in patients with acute coronary syndrome is still being investigated.

Characteristics of DOACs

DOACs have a common rapid onset of action: between 30 min and 4 h (T_{max} between 1.5 and 4 h). A detailed description of pharmacokinetics parameters is shown in Table 2.

Oral bioavailability of DOACs is very variable. Dabigatran etexilate is a prodrug that is rapidly converted to an active substance by hydrolysis in the intestine and liver. Therefore, this drug has direct contact with the gastrointestinal mucosa. The main difference between the two subtypes of DOACs is the renal excretion of the drug, which is significant with dabigatran and negligible with rivaroxaban, apixaban and edoxaban. Concomitant treatment with a cytochrome P450 3A4 (CYP3A4) or Permeability-glycoprotein (P-gp) inducer or inhibitor can be associated with a decrease or increase in exposure to the DOAC, and can increase the risk of thrombosis or hemorrhage. The main drug interactions are with azole agents, rifampicine and some antiviral drugs. There is no known pharmacological interaction between DOACs and proton pump inhibitors (PPIs). There is also no contraindication to *Helicobacter pylori* eradication with doxycycline–metronidazole–bismuth subcitrate triple therapy. There is no clinical impact of the known pharmacological interaction between DOAC and clarithromycin, a CYP3A4 inhibitor.

Uses of DOACs

The recommended doses for the different DOACs are shown in Table 2. A dose reduction should be

Table 2. Main features of DOAC.

Features	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	Yes	No	No	No
Bioavailability	6.5%	<15 mg: 80–100% ⩾15 mg: 66% when fasting, 100% after food intake	50%	62%
Effect of food on absorption	No	⩾15 mg: bioavailability +39% if taken with food <15 mg: no difference if taken with or without food	No	No
T_{max} (h)	0.5–2	2–4	3–4	1.5
Half life (h)	12–14 Longer if renal impairment	5–9 in young patients 11–13 in older patients	12	10–14
Metabolism	Very low	High	High	Low
Excretion	Renal: 85% of absorbed drug Fecal: 6% of absorbed drug	Renal: 33% excreted unchanged 33% excreted as metabolites Fecal: 33% excreted as metabolites	Renal: 27% of absorbed drug Fecal: 50% of absorbed drug	Renal: 35% of absorbed drug Fecal: 60% of absorbed drug; 70% excreted unchanged
Dialyzability	Possible	No	Poorly efficient	Poorly efficient
Usual dose	2 × 150 mg or 2 × 110 mg	AF: 1 × 20 mg DVT-PE: 2 × 15 mg for 21 days and then 1 × 20 mg Post-ACS: 2 × 2.5 mg	2 × 5 mg or 2 × 2.5 mg	1 × 60 mg
Dose adjustment for renal impairment	CrCl 30–50 ml/min: 2 × 110 mg	CrCl 15–30 ml/min: 1 × 15 mg	CrCl 15–30 ml/min: 2 × 2.5 mg	CrCl 15–50 ml/min: 1 × 30 mg

AF, atrial fibrillation; DOAC, direct oral anticoagulant; DVT-PE, deep vein thrombosis pulmonary embolism; post ACS, post acute coronary syndrome; CrCl, creatinine clearance.

considered for patients with bleeding risks (older people, those with low body weight or impaired renal function). Hepatic impairment affecting coagulation and risk of active clinically significant bleeding are contraindications for using DOACs. In view of their pharmacokinetics, DOACs should never be used in association with other anticoagulants [unfractionated heparin, low molecular weight heparin (LMWH), among others].

There is no need for routine coagulation test surveillance while patients are treated with DOACs, as they have been developed to be used without any biological monitoring.

In the event of a major bleed, or if an urgent surgery or intervention with high bleeding risk is required, some specific coagulation tests can be used. Routine coagulation tests, such as activated partial thromboplastin time (aPTT) or prothrombin ratio (PR), cannot be used in this setting because of a lack of sensitivity. Therefore, normal aPTT or PR is not sufficient to exclude therapeutic blood levels of DOACs.[5] However, a normal thrombin clotting time (TCT) is related to the absence of clinically active blood levels of dabigatran. The plasma anti-Xa assay, used to monitor the effect of heparin, is useful to exclude clinically active blood levels of rivaroxaban or apixaban when anti-Xa activity is below 0.1 IU/ml.

Specific coagulation tests, correlated with the measurement of the plasma concentration of DOACs, have been developed. For instance, a

diluted thrombin time is used for dabigatran and an anti-Xa activity assay calibrated to the specific drug is used for rivaroxaban and apixaban. A threshold of 30 ng/ml has been proposed for dabigatran and rivaroxaban, under which there is no increase in the bleeding risk associated with therapeutic management of a major bleed or with an unscheduled invasive procedure with a risk of bleeding. These tests are unfortunately not broadly available yet.[6–8]

DOACs are administered in fixed doses for the long term without routine coagulation monitoring.

Gastrointestinal bleeding and other bleeding risks under DOACs

Overall bleeding risk under DOACs

Clinically relevant bleeding events under DOACs are mainly intracranial hemorrhage and gastrointestinal bleeding. These bleeding complications, well known under VKA treatment, are relevant because they constitute the leading cause of iatrogenic hospitalization and are considered to be responsible for approximately 5000 deaths in France each year.[4] The one-year risk of major bleeding in patients anticoagulated for AF is assessed by the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalized Ratio, Elderly > 65 years, Drugs/Alcohol concomitantly). The bleeding risk under DOACs is increased in patients over 75 years of age, with severe renal function impairment, low body weight (<60 kg), hepatic impairment, diabetes, previous gastrointestinal bleeding, known arterial hypertension, or receiving concomitant systemic treatment by strong inhibitors of CYP3A4 and P-gp.

Phase III studies evaluating the efficacy and safety of DOACs in NVAF and VTE have shown a significant decrease in overall bleeding, in particular in preventing intracranial hemorrhage, compared with VKA (RR 0.49).[1,2,9–12] However, there is no difference in bleeding risk between DOACs and LMWH in patients with VTE in phase III studies.[2]

Some real-life observational studies have shown a similar overall bleeding risk in patients treated with DOACs compared with VKAs, whereas others have suggested a decrease in overall bleeding in those receiving DOACs. This effect was mainly related to a decrease in the risk of intracranial hemorrhage.[13,14]

Gastrointestinal bleeding risk under DOACs

The risk of gastrointestinal bleeding for patients treated with anticoagulants is estimated to be 1.5–5% a year. It is higher for older people because of associated comorbidity as well as polymedication, including treatment with antiplatelet drugs and nonsteroidal anti-inflammatory drugs (NSAIDs). In patients with NVAF, cumulative incidence rates of bleeding over 24 months of hospitalization have recently been estimated to be 53.1 in 1000 patients in France, 26% of whom experienced gastrointestinal bleeding.[15,16] Meta-analyses of randomized controlled trials available in patients with NVAF have suggested that treatment with DOACs could increase the risk of gastrointestinal bleeding by 25% compared with VKAs.[1,9,10,17] However, almost all of the analyses of individual studies available in patients with NVAF and VTE did not find an increase in this risk (Table 3).[18–20] The rate of lower gastrointestinal bleeding seems to increase in patients treated with DOACs compared with VKAs, but the mechanism remains unclear.[21]

Gastrointestinal contraindications to the use of DOACs

A clinically significant active bleed is a formal contraindication to anticoagulant therapy with a VKA as well as with a DOAC. Gastrointestinal contraindications to the use of DOACs are the same as with VKAs: active bleeding, active ulcers, hemorrhagic angiodysplasia and recurrent bleeding with need of iterative transfusion. These contraindications are mostly temporary. Other gastrointestinal contraindications are potential gastrointestinal bleeding lesions that are inaccessible to endoscopic or surgical treatments, and patients with Child-Pugh C cirrhosis. If a patient has had gastrointestinal bleeding in the past, there is a risk of recurrence under anticoagulant therapy, but it does not make it formally and definitively contraindicated.

Most gastrointestinal contraindications to the use of DOACs are temporary.

Table 3. Gastrointestinal bleeding risk in randomized controlled trials.

	DOAC	Compared	*n* (DOAC/ comparator)	Indication	Mean CHADS2	Treatment duration (months)	Gastrointestinal bleeding RR (95% CI) or %
RE-LY	Dabigatran	VKA	6076 + 6015/6022	NVAF	2.1	24	1.5 (1.19–1.89)
RE-LY ABLE	Dabigatran 150 mg	Dabigatran 110 mg	2937 + 2914			27.6	0.99 (0.75–1.31)
ROCKET-AF	Rivaroxaban	VKA	7131/7133	NVAF	3.5	22	1.39 (1.19–1.61)
ARISTOTLE	Apixaban	VKA	9120/9081	NVAF	2.1	20	0.89 (0.70–1.15)
ENGAGE AF-TIMI48	Edoxaban	VKA	7035 + 7034/7036	NVAF	2.8	34	1.23 (1.02–1.50)
AMPLIFY	Apixaban	Enoxaparin/VKA	2691/2704	VTE	N/A	6	0.3% *versus* 0.7%
RE-COVER I	Dabigatran	UFH-LMWH/VKA	1274/1265	VTE	N/A	6	1.50 (0.99–2.29)
RE-COVER II	Dabigatran	UFH-LMWH/VKA	1279/1289	VTE	N/A	6	1.47 (0.95–2.27)
EINSTEIN-PE	Rivaroxaban	Enoxaparin/VKA	4151/4131	VTE (PE)	N/A	3–12	0.04% *versus* 0.08%
HOSUKAI	Edoxaban	Enoxaparin/VKA	4143/4149	VTE	N/A	12	1% *versus* 0.8%
Meta-analysis (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF TIMI 48)	DOAC	VKA	42411/29272	NVAF	2.6	26.4	1.25 (1.01–1.55)
RECORD I	Rivaroxaban	Enoxaparin	2209/2224	VTE prophylaxis (after hip arthroplasty)	N/A	33.4 days	0.1% *versus* <0.1%
AVERROES	Apixaban	Aspirin	2808/2791	NVAF	2.0–2.1	13.2 (mean)	0.86 (0.40–1.86)

CI, confidence interval; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism; RR, relative risk; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Prevention of gastrointestinal bleeding in patients treated with DOACs

When an increase in the risk of bleeding is identified in a patient treated with a DOAC, a pluridisciplinary discussion with the cardiologist is required and the DOAC dosage should be temporarily reduced. Concomitant therapy with NSAIDs, aspirin and other antiplatelet drugs is associated with a higher risk of bleeding and should be avoided whenever possible. A prophylactic antisecretory treatment with a PPI should be added when the patient has a history of gastroduodenal ulcer or gastrointestinal bleeding.[22] This prophylaxis could also be discussed individually in older patients with concomitant exposure to an antiplatelet drug, even if there are no proven benefits in this indication yet. Systematic eradication therapy for *H. pylori* prior to administration of DOACs is not recommended but can be discussed. An annual surveillance program looking for clinically visible bleeding and including a complete blood count and dosage of serum creatinine is required.

Management of gastrointestinal bleeding in patients treated with DOACs

In the case of gastrointestinal bleeding, DOAC treatment must be withheld, the time of the last intake must be noted and the renal function estimated. The Rockall risk scoring system is used to predict outcomes in patients with upper gastrointestinal bleeding. If a major bleed occurs, the priority is to restore hemodynamic stability, mainly by fluid resuscitation, whether or not the patient is anticoagulated. A red blood cell transfusion should be considered when hemoglobin levels are below 7 or 9 g/dl for patients with severe comorbidities. Indications for emergency endoscopies are no different for DOACs than for other anticoagulants. An endoscopy should be performed within 24 h after the bleeding has started. An observatory, which took place in 2001, showed that the time between a patient's first onset of bleeding and his arrival at the emergency room was 33 $\pm$ 42 h, and the time between his arrival in the emergency room and the performing of the endoscopy was 14 $\pm$ 16 h. In these settings, the short half lives of DOACs become advantageous. If there was no further intake of the DOAC since the diagnosis of gastrointestinal bleeding, the state of hypocoagulability will often be over by the time the patient reaches the gastroenterologist. However, this statement is only true if renal function is normal. The management of gastrointestinal bleeding must take the plasma half life of the DOAC used into account, knowing that it takes four half lives to regain normal coagulation characteristics. In the case of a life-threatening gastrointestinal bleed, uncontrolled by endoscopy and with recent intake of a DOAC, a reversal strategy should be considered depending on circulating levels of anticoagulants and the availability of specific antidotes.

In this case, administration of nonspecific procoagulant drugs, such as activated or nonactivated prothrombin complex concentrate (aPCC or PCC) or tranexamic acid can be considered.[8,23,24] FEIBA (Factor Eight Inhibitor Bypassing Activity), which is an aPCC, is considered the first choice in this situation and is administered intravenously at a dosage of 30–50 IU/kg (maximum flow rate 2 IU/kg/min).[25,26] A nonactivated PCC is also an option and is given at a dosage of 50 IU/kg (maximum flow rate 2–3 ml/min), which is twice the dosage used in VKA-related bleedings.[25,27] Another infusion of a PCC can be administered 8 h after the first one if needed.

Specific antidotes for DOACs have been recently developed: idarucizumab, a humanized monoclonal antibody fragment (Fab) for dabigatran, and andexan*et alf*a, a decoy recombinant factor Xa molecule with no action on hemostasis for rivaroxaban, apixaban and edoxaban.

Idarucizumab (Praxbind, Boehringer Ingelheim Pharma, GmbH & Co KG, Biberach, Germany) has been given US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2015 and is now authorized in France after an initial temporary use authorization from November 2015 to February 2016. It is restricted to hospital use in emergency situations, such as life-threatening bleeding or bleeding in a critical organ, and perioperative management of an emergency surgery at high risk of bleeding that cannot be delayed by more than 8 h. The recommended dose of idarucizumab is 5 g, administered as two consecutive infusions over 5–10 min each of 2.5 g (no more than 15 min apart) or as a bolus injection.

Dabigatran plasma concentration should be measured before administration of idarucizumab and 12–18 h after if rebleeding occurs. A second 5 g infusion of idarucizumab is possible if dabigatran plasma concentration is above 30 ng/ml in this situation.

Idarucizumab has shown a median maximum percentage reversal of 100% and a normalization of hemostasis tests in 88–98% of patients within minutes.[28]

Phase III studies of andexan*et al*fa have shown a rapid onset of action (within 2–5 min), restoring thrombin generation and normal coagulation in patients treated with rivaroxaban, apixaban and edoxaban. Preliminary results of an ongoing multicenter prospective study (ANNEXA-4) of patients with acute major bleeding after the administration of a factor Xa inhibitor have recently been presented at the European Society of Cardiology Congress in 2016. An initial bolus and subsequent 2 h infusion of andexanet reduced anti-factor Xa activity with effective hemostasis by 79%. The final results of ANNEXA-4 are to be published in 2022. So far, andexan*et al*fa is not yet available for clinical use in Europe or the USA and is still awaiting approval from both the EMA and the FDA.[29,30]

The arrival of these antidotes will facilitate the management of bleeding complications in patients treated with DOACs. However, their position in the therapeutic strategy of bleeding events in patients receiving DOACs is not well defined yet. Restarting anticoagulation or not should be evaluated as soon as the bleeding is over, ideally right after a control endoscopy. Restarting anticoagulation therapy with a DOAC is possible except in patients with renal function impairment. In this case, weighing the benefits of preventing thromboembolism against the risk of recurrence of bleeding is essential. This must take into account the patient's risk factors and medical history, and the decision must ideally be taken by a pluridisciplinary team.

DOACs and scheduled endoscopy: risk stratification of endoscopic procedures, modality of discontinuation and restart of anticoagulation, surveillance after endoscopic procedures

Bleeding risk of a scheduled endoscopy in patients treated with DOACs

The management of a scheduled endoscopy in patients treated with DOACs is easier, even if there is still a risk of provoked bleeding. Diagnostic procedures are associated with a low risk of bleeding, even in a patient treated with a DOAC. However, most therapeutic procedures are associated with a high risk of bleeding and justify precautions to be taken (Table 4). For therapeutic procedures with a moderate 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, among others). The duration of a patient's hospital stay when treated with DOACs is no different than with another anticoagulation therapy: for an ambulatory endoscopic procedure, a 6 h observation is required, and thus a potentially risky endoscopic procedure should be performed in the morning. Finally, we should not underestimate the risk of delayed bleeding, especially in the case of excessive coagulation.

The modality of discontinuation of DOACs depends on the endoscopic procedure

The pharmacokinetic profile of DOACs varies a lot between individuals (higher peak levels 2–6 h after oral administration) and makes it impossible to predict accurately their anticoagulant effect. Currently there is no simple test to assess the anticoagulant activity of a DOAC and until 2015–2016 there were no specific antidotes available in clinical practice, which made the management of DOAC-related gastrointestinal bleeding difficult.

Therefore, recent European guidelines for the management of endoscopy in patients on DOAC therapy were published in March 2016 by the British Society of Gastroenterology (BSG) and the European Society of Gastrointestinal Endoscopy (ESGE), even though there is little evidence. For low-risk endoscopic procedures, the guidelines suggest that the morning dose (sometimes even the evening dose of the previous day) is omitted, whatever treatment regimen is used. For high-risk endoscopic procedures, it is recommended that the last dose of DOACs be taken at least 48 h before the procedure, or 72 h prior to the procedure for patients taking dabigatran with a creatinine clearance of 30–50 ml/min.[31]

These new guidelines are mostly the same as the latest American guidelines published in 2016 by the American Society for Gastrointestinal Endoscopy (ASGE). The only important difference is that the BSG/ESGE recommends withholding the DOAC on the morning of a low-risk endoscopic procedure whereas the ASGE allows continuation of the DOAC in this situation.[32] They are also in line with the guidelines published

Table 4. Risk stratification of endoscopic procedures based on the risk of hemorrhage (European Society of Gastrointestinal Endoscopy guidelines 2016).

Risk stratification	Endoscopic procedure
Low risk	Diagnostic procedures with or without biopsy Biliary or pancreatic stenting Device-assisted enteroscopy without polypectomy
High risk	Endoscopic polypectomy ERCP with sphincterotomy Sphincterotomy plus large balloon papillary dilatation Ampullectomy Endoscopic mucosal resection or endoscopic submucosal dissection Endoscopic dilatation of strictures in the upper or lower gastrointestinal tract Endoscopic therapy of varices Percutaneous endoscopic gastrostomy Endoscopic ultrasound with fine needle aspiration Esophageal, enteral or colonic stenting

ERCP, Endoscopic Retrograde CholangioPancreatography.

Table 5. Thrombotic risk: based on HAS (French National Authority for Health) synthesis.

	Atrial fibrillation	VTE
Mild risk	CHADS 0–1 No stroke	Other VTE
High risk	CHADS 2–6 Stroke	PE < 3 months Proximal DVT < 3 months Recurrent VTE

Associated risk factors: atrial fibrillation, history of TIA or AIS, diabetes, heart failure, age over 75.
AIS, acute ischemic stroke; DVT, deep venous thromboembolism; PE, pulmonary embolism; TIA, transient ischemic attack; VTE, venous thromboembolism.

by the European Heart Rhythm Association in 2015, insisting on shorter duration of discontinuation depending on the thromboembolic (Table 5) and bleeding risk, and on the renal function.[33]

In any patient with rapidly deteriorating renal function, a hematologist should be consulted. There is no need for a bridging therapy with parenteral heparin in these settings. It is not recommended that plasma concentrations of DOACs are routinely monitored (working group on perioperative haemostasis, GIHP 2015 proposal).

When to restart anticoagulation with DOACs

The timing of restarting anticoagulation with a DOAC depends on the risk of thrombosis or hemorrhage, and on the kind of endoscopic therapy that has been carried out. There is no consensual strategy at this time. Creatinine clearance using the Cockroft and Gault equation or estimated glomerular filtration rate can be useful before restarting a DOAC therapy.

After a diagnostic procedure, treatment can be resumed after a rest of 6 h. After a therapeutic procedure, provided that hemostasis is achieved, treatment can be resumed with a delay of 12–48 h: 12–24 h in most cases (e.g. polypectomy) or 24–48 h in higher risk situations (e.g. deep gastroduodenal ulcer).

A period of discontinuation longer than 48 h is associated with a significant increase in the risk of thrombosis. For a procedure with a significant risk of delayed hemorrhage, such as endoscopic mucosal resection or endoscopic submucosal dissection, a longer period of discontinuation may be considered.[31] This risk of delayed hemorrhage

should be anticipated and adequate surveillance should be provided to well informed patients, considering their risk factors.

Alternatives to anticoagulation with DOACs

Switching from a DOAC to another anticoagulation therapy should be discussed case by case, depending on the indications, bleeding severity, a reversible cause of bleeding and renal function. In some situations, for example patients with AF at low risk of embolic events or beyond the first 3 months of treatment for VTE, restoring therapeutic intensity anticoagulation is not an emergency. It should always be discussed with the practitioner prescribing the DOAC.

Alternatives to anticoagulation should be considered after pluridisciplinary discussions: urgent vena cava filter placement for treatment of VTE, semi-urgent closure of the left atrial appendage followed by ablation for atrial fibrillation with embolism that could allow discussion of discontinuation of anticoagulation therapy with enough hindsight and in the absence of recurrence.

A temporary switch to heparin (unfractionated heparin or LMWH) or fondaparinux is possible, but should not be considered a standard of care in this situation.

Switching from a DOAC to a VKA, with the assumption of a lower rate of bleeding events, is also an option. Switching from a DOAC to another DOAC can be discussed depending on pharmacological features (lower peak plasma concentration), shorter half lives (which allows a quicker reversibility of the anticoagulant effect) or lower rates of gastrointestinal bleeding, described in the literature according to the chosen DOAC.

There is no information available regarding the prevention of recurrent gastrointestinal bleeding.

Conclusion

VTE prophylaxis, treatment and prevention of embolic events in patients with nonvalvular AF are greatly simplified by the use of DOACs, which are administered in fixed doses and do not require any biological monitoring.

Gastrointestinal bleeding could be more frequent with DOAC therapy than with VKA therapy. Gastroenterologists should know how to deal with an emergency such as a gastrointestinal bleeding and how to manage a scheduled procedure in patients treated with a DOAC.

Better knowledge of these situations and well defined protocols set up by gastrointestinal bleeding units should permit the minimization of morbidity and mortality associated with these adverse events.

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