

REVIEW

Endoscopic Procedures In Patients Taking Novel Oral Anticoagulants

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Abstract

The use of direct oral anticoagulants (DOAC) for the treatment of atrial fibrillation and prevention of strokes is encouraged by their superior properties compared to vitamin K antagonists: predictable anticoagulant effect, greater patient compliance, few drug interactions, low risk of intracranial hemorrhages. Although practicing gastroenterologists may never prescribe a DOAC, they are likely to encounter DOAC-related GI adverse events (gastrointestinal bleeding), and they will need to manage DOACs around the time of endoscopy. The present paper aims to present the management possibilities of the patient treated with DOAC undergoing endoscopy, most studies performed so far focusing on the risk of spontaneous bleeding in this category of subjects. The current guidelines provided by the British Society of Gastroenterology and the European Society of Gastrointestinal Endoscopy orientate us, but endoscopic maneuvers should be preceded by a detailed analysis of the risks of secondary bleeding and thrombosis associated with DOAC users.

Keywords: novel oral anticoagulant, gastrointestinal bleeding, time of endoscopy.

Rezumat

Utilizarea anticoagulantelor orale directe (DOAC) pentru tratamentul fibrilației atriale și prevenția accidentelor vasculare cerebrale este încurajată de proprietățile superioare ale acestora, comparativ cu antagoniștii de vitamina K: efect anticoagulant predictibil, complianța mai mare a pacientului la tratament, interacțiuni medicamentoase puține, risc scăzut al hemoragiilor intracraniene. Deși gastroenterologii nu prescriu în practica curentă NOAC, se pot confrunta cu reacțiile adverse ale acestora (sângerare gastrointestinală) și în consecință vor trebui să gestioneze administrarea lor în momentul endoscopiei. Lucrarea de față are ca scop prezentarea posibilităților de management al pacientului aflat sub tratament cu DOAC și supus unor gesturi endoscopice, cele mai multe studii efectuate până în prezent axându-se pe riscul hemoragiilor spontane la această categorie de subiecți. Ghidurile actuale oferite de Societatea Britanică de Gastroenterologie și Societatea Europeană de Endoscopie Gastrointestinală ne orientează, însă manevrele endoscopice ar trebui precedate de o analiză detaliată a riscurilor de hemoragie secundară, respectiv tromboza, asociate pacienților cu DOAC.

Cuvinte cheie: anticoagulant oral nou, sângerare gastrointestinală, endoscopie.

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New oral anticoagulants, also known as direct oral anticoagulants (NOAC/DOAC) are drugs used in patients with non-valvular atrial fibrillation to prevent stroke. They have some advantages compared to vitamin K inhibitors: a predictable anticoagulant effect, eliminating the need to monitor coagulation parameters, fewer drug interactions and a substantially lower risk of intracranial bleeding. However, DOAC therapy carry a higher risk of digestive bleeding compared to warfarin¹. Numerous studies have been carried out on the risk of spontaneous digestive bleeding in patients treated with DOAC or vitamin K antagonists. Apixaban is associated with the lowest risk of digestive bleeding, rivaroxaban being placed at the end of the ranking²⁻⁴.

There is an increasingly number of studies related to the risk of hemorrhage secondary to an endoscopic gesture in patients treated with DOAC, respectively to the thrombotic risk that may occur by short-term anticoagulant cessation in order to perform an urgent or an elective endoscopic maneuver. Any endoscopic intervention carries an intrinsic risk of hemorrhagic complication and bleeding is considered clinically significant if serum hemoglobin decreases by at least 2g/dL, if requires blood transfusion and symptoms like melena or hematemesis occur.

For the anticoagulated patients, this risk is higher, depending on the endoscopic maneuver practiced, as well as the type of DOAC. Simple diagnostic procedures like gastroscopy, colonoscopy, or sigmoidoscopy with biopsy have a low risk of intra-procedural bleeding. Current guidelines recommend skipping the DOAC dose in the morning of the procedure⁵. Probably a simple biopsy in these patients is safe, but more data are needed to confirm⁶ and herefore, it is probably safer to comply with the recommendations.

High-risk procedures including polypectomy, endoscopic retrograde cholangio-pancreatography (ERCP) with sphincterotomy, ampullectomy, submucosal endoscopic dissection (ESD), endoscopic mucosal resection (EMR), stricture dilation, band ligation or gastric varices glue therapy, endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS with FNA), percutaneous endoscopic gastrostomy (PEG), requires more careful handling of DOAC administration.

The recommendation of the British Society of Gastroenterology and the European Society of Gastrointestinal Endoscopy is to administer the last dose of DOAC at least 48 hours before a high-risk endoscopic procedure; for patients treated with dabigatran,

the measurement of the glomerular filtration rate is mandatory to decide the optimal time to discontinue DOAC (at RFG between 30 and 50 mL/min/1.73 m² cessation of treatment with dabigatran is done 72 hours before a high-risk endoscopic intervention to reduce the risk of secondary bleeding)⁵. Switching to low-molecular-weight heparin therapy (LMWH) is not necessary, considering the rapid action of DOAC. It has been shown that in patients treated with rivaroxaban, switching to LMWH has led to a much higher frequency of gastrointestinal bleeding (up to 6.5%), but thrombotic risk analysis is mandatory, especially in patients at high cardiovascular risk^{7,8}.

Post-polypectomy bleeding (PPB) is a common but sometimes can be massive and a life-threatening complication. It can be immediate (intraprocedural), which is usually self-limited and could be controlled during endoscopy, or delayed, much more worrying, bearing in mind that the patient is already discharged. The associated risk factors are represented by the size of the polyp (>1 cm), the pedunculate appearance, the endoscopic technique used, the advanced age (>65 years), the chronic renal or cardiovascular diseases, the use of anticoagulant, anti-inflammatory treatment (NSAID), inadequate preparation for colonoscopy^{9,10}. With regard to DOAC, the risk of PPB is not well known. The frequency of polypectomy complications was compared in a group of 218 anticoagulated patients, of whom 73 were DOAC users and 218 patients without anticoagulant treatment¹¹; a similar bleeding rate between DOAC and warfarin was observed, but much higher compared to subjects who did not receive anticoagulant treatment (13.7% vs 13.7% vs. 0.9%, $P < 0.001$).

Similarly, newer data from the literature (2019) show a frequency of 0.6% of gastrointestinal bleeding within 30 days of polypectomy among patients treated with DOAC (n=1.950), and this frequency was not much higher than in the control group (0.2%)¹². The study included 1590 patients under DOAC, 3471 patients treated with warfarin and 599.983 patients in the control group. However, a higher frequency of bleeding was observed in the group of patients treated with warfarin compared to the control group (1.2%), as well as thromboembolic complications. Recently a Japanese study reported the frequency of gastrointestinal bleeding within 30 days of endoscopic gesture in patients under DOAC, most of the lesions analyzed being those at the colonic level (82.1%)¹³ 389 and 383 patients were receiving direct oral anticoagulants (DOACs). The study

included 772 subjects, of whom 389 were in treatment with DOAC. The average bleeding rate was 9.5%, the apixaban and edoxaban being the most incriminated (the frequency of bleeding of about 13%); contrary to the data from specific literature, rivaroxaban presented the best safety profile (bleeding rate of 6.4%). The highest risk techniques were represented by ESD and EMR (bleeding rate of 16% and 10.9%, respectively). However, the researchers noted a lower need for endoscopic hemostasis in patients treated with DOAC compared to patients treated with warfarin, which demonstrates a much better safety profile of DOAC.

Endoscopic mucosal resection (EMR) presents a general risk of intraprocedural and delayed bleeding between 3.7% -11.3% and, respectively, 0.6% - 6.2%⁵. Risk factors associated with secondary hemorrhage EMR include proximal location of lesion, dimensions, endoscopic pattern, resection technique, anti-coagulant/anti-inflammatory treatment (NSAID)^{14,15}. Post-EMR delayed bleeding prediction scores (GSE-ED-RE2) were proposed, based on variables such as lesion size, proximal location, associated comorbidities and antithrombotic treatment, which could guide endoscopic therapies and be a useful tool in clinical trials to evaluate bleeding prevention strategies after broad EMR¹⁶. To reduce the risk of post EMR hemorrhages, prophylactic measures, such as the use of hemoclips or of Purastat, a hemostatic gel, may be useful. A retrospective study demonstrates much lower bleeding rates for lesions larger than 2 cm resected by EMR technique when hemoclips were used to close the defect (1.8% vs. 9.7%)¹⁷. However, the authors encourage prospective studies to address this topic for most reliable results and encourage a careful hemostasis during the procedure. In contrast to these data, other studies question the usefulness of these prophylactic measures, especially in the case of small lesions bearing in mind the associated higher costs^{18,19}. A multicenter study published in 2019 included a total of 2,062 subjects undergoing EMR for colonic lesions and analyzed the incidence of post-interventional bleeding in patients on antithrombotic treatment. The frequency of hemorrhage was highest in the DOAC users, despite the use of endoscopic clips as a hemostatic method (7.9% vs. 2.9% for warfarin, 3.2% for antiplatelets, 0.6% in the control group), without significant differences between DOAC subtypes. No thromboembolic events were reported in this category of patients. In view of these results, the procedure is considered of high risk and the recommendations of European guidelines should be followed.

Endoscopic submucosal dissection (ESD) is a more recent and complex technique, with increasing worldwide popularity and very good results in early gastric cancer treatment. The hemorrhagic risk is increased by the size of the resected specimen (fragments over 35 mm being considered at risk) according to a recent Korean study, independent of the presence of anticoagulant treatment²⁰. Post-endoscopic haemorrhage was less common in subjects treated with DOAC than in those treated with warfarin. Following the recommendations of the current guidelines, the study found 3 cases of post procedural bleeding, respectively one case of thrombosis (myocardial infarction) occurring 3 weeks after endoscopy. Endoscopic control was carried out one day after the ESD procedure, suggesting the need for further studies to clarify the necessity of an endoscopic second look in patients receiving DOAC when performing ESD. In addition, older data in the literature regarding this subject are contradictory, the results being limited to the category of subjects without DOAC treatment²¹⁻²³. Prevention of post-ESD bleeding is very important; the use of polyglycolic acid, fibrin adhesive, endoscopic coagulation, endoscopic clips being effective in different studies²⁴⁻²⁶.

Endoscopic procedures such as balloon dilation or gastrointestinal stenting may be associated with some risk of bleeding.

Endoscopic dilation is used for the treatment of benign strictures of various causes (peptic, post caustic, post surgical, post radiotherapy); the procedure is a safe one from the perspective of occurrence of intra-procedural hemorrhages²⁷. The technique was also applied for the treatment of post ESD stenosis after superficial esophageal cancer with an insignificant rate of secondary hemorrhage being (0.8%)²⁸. Endoscopic dilation of strictures secondary in inflammatory bowel diseases is also a safe maneuver, the frequency of bleeding being estimated at 1%²⁹.

Endoscopic stenting remains an important tool in the management of malignant diseases of the digestive tract, bleeding rates ranging between 2% and 13.4% in the case of esophageal lesions, up to 5% for gastro-duodenal and colonic lesions stented³⁰⁻³³. Unfortunately, there are currently very few data related to the hemorrhagic complications of this endoscopic technique in the anticoagulated patient.

Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is associated with a bleeding risk of up to 2%³⁴. This risk can be amplified by

factors such as male sex, advanced age (>80 years), low number of thrombocytes (<100.000/uL), anticoagulant use^{35,36}. With regard to DOAC, they have been proven to have a lower risk of endoscopic bleeding when compared to vitamin K antagonists; the possibility of thromboembolic events was analyzed, the results being encouraging for DOAC users³⁷. Masuda et al demonstrated that stopping the anticoagulant for at least 48 hours before ERCP is associated with a lower bleeding rate (5.6% vs. 20.8% in case of interrupting DOAC for less than 2 days prior to surgery); none of the study participants showed thromboembolic events³⁶. Considering that the study included a small number of patients treated with DOAC (n=42), although the results are encouraging in the group of subjects who have stopped taking anticoagulants for at least 48 hours, the thrombotic risk should be well weighed for an effective patient management.

Endoscopic ampullectomy is a minimally invasive method of treating superficial lesions of the ampulla Vater. With a careful patient selection and assessment of lesions, it is a safe and effective therapeutic procedure that can avoid the need for potentially major surgery. The associated risk of bleeding was approximately 8.5%³⁸. Currently, there are no data in the literature to guide us the situation of anticoagulated patients undergoing endoscopic ampullectomy so it is very important to analyze the individual hemorrhagic risk⁵.

Percutaneous endoscopic gastrostomy (PEG) can be complicated by an abdominal wall hemorrhage and hematoma or other bleeding complications with a recent prospective study estimating bleeding incidence at 1%³⁹. The incidence of secondary bleeding after PEG placement was estimated at 3.3% in a report published in 2011; the highest bleeding rates were seen in subjects treated with low-molecular-weight heparin (LMWH) and those with more than two antithrombotic drugs (7.9%, 6.3%); low bleeding rates were found in patients treated with clopidogrel (2.1%)⁴⁰. Probably stopping DOAC with at least 48 h before procedure and bridge with low molecular weight heparin in high risk of thrombosis patients is advisable.

The treatment of choice for esophageal varices bleeding is endoscopic band ligation (EBL); the technique is also used for prophylactic purposes. Data on anticoagulant patients with DOAC who have undergone EBL are missing, but, regarding the other categories of anticoagulants, the literature offers some directions for a safer management. In 2008 a retrospective analy-

sis of anticoagulated patients who underwent EBL for primary/secondary prevention of hemorrhage was carried out. Five out of 215 subjects required permanent anticoagulation, being diagnosed with cardiac cirrhosis, Budd Chiari syndrome, polycythemia vera and portal vein thrombosis, primitive sclerosing colangitis and cryptogenic cirrhosis. Anticoagulant treatment was maintained before and after EBL, with the preservation of INR values within therapeutic limits, and none of the patients developed gastrointestinal bleeding either immediate or within 2 weeks of endoscopic intervention⁴¹. These results support the possibility of practicing EBL for primary/secondary prophylaxis in patients treated with oral anticoagulants. However, given the small number of subjects who have experienced this procedure, additional data are needed for an optimized management. Same rule of 48 h stop of DOAC and transition to LMWH prior to endoscopic procedure in patients with high risk of thrombosis^{5, 42}.

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) has revolutionized the ability to diagnose and staging tumors of the gastrointestinal tract and neighboring organs, especially the pancreas. Although the procedure includes tissue puncture, the reported incidence of bleeding is low. A systematic review that included 51 articles with a total of 10,941 patients undergoing EUS-FNA, showed bleeding in 0.17% of procedures, most appearing after performing this procedure on pancreatic lesions⁴³. Data on patients treated with DOAC are missing, but the procedure is considered safe for patients on antiaggregant / anti-inflammatory therapy (NSAIDs) treatment⁴³.

As the population ages and the incidence of chronic diseases increases, the need for anticoagulant treatment is increasing; the widespread use of DOAC has increased in recent years. At present, the existing guidelines orientate us, but additional research should be encouraged in order to achieve an optimal risk-benefit ratio for our patients. A decision should be taken in every case after carefully balancing bleeding and thrombotic risks.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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