

Management of bleeding or urgent interventions in patients treated with direct oral anticoagulants: 2017 recommendations for Poland

Piotr Pruszczyk¹, Anna Tomaszuk-Kazberuk², Agnieszka Słowik³, Rafał Drwiła⁴, Grażyna Rydzewska⁵, Krzysztof J. Filipiak⁶, Zbigniew Gaciong⁷, Jarosław Kaźmierczak⁸, Wojciech Marczyński⁹, Jerzy Windyga¹⁰, Adam Kobayashi¹¹, Janina Stepińska¹²

1 Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland

2 Department of Cardiology, Medical University of Białystok, Białystok, Poland

3 Department of Neurology, Jagiellonian University Medical College, Kraków, Poland

4 Department of Anesthesiology and Intensive Care, Jagiellonian University Medical College, Kraków, Poland

5 Department of Internal Diseases and Gastroenterology, Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Warsaw, Poland

6 1st Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

7 Department of Internal Diseases, Arterial Hypertension and Angiology, Medical University of Warsaw, Warsaw, Poland

8 Department of Cardiology, Pomeranian Medical University, Szczecin, Poland

9 Department of Orthopedics, Centre of Postgraduate Medical Education in Otwock, Otwock, Poland

10 Department of Hemostasis Disorders and Internal Diseases and Division of Hemostasis and Metabolic Disorders, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

11 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

12 Department of Cardiac Intensive Care, Institute of Cardiology, Warsaw, Poland

KEY WORDS

bleeding, direct oral anticoagulants, urgent intervention

ABSTRACT

Direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban are mainly used in the prevention of thromboembolic complications in patients with atrial fibrillation (AF) and in the treatment of venous thromboembolism. As compared with vitamin K antagonists (VKAs), they are characterized by at least similar efficacy and better safety profiles, especially with respect to intracranial hemorrhages. Moreover, they are more convenient therapeutic agents. The 2016 European Society of Cardiology guidelines clearly favor DOACs over VKAs in patients with AF. However, DOAC therapy is also associated with the risk of bleeding complications. The aim of this review was to provide recommendations for the management of bleeding complications during DOAC therapy in the Polish setting. The recommendations were based on the most important documents concerning this issue and were developed by representatives of different medical specialties. Experience in managing cases of bleeding on DOAC therapy is still limited. Therefore, we hope that this publication will be helpful in everyday clinical practice and that it will be useful for developing in-hospital recommendations for the management of patients with DOAC-related bleeding.

Introduction Direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban are mainly used in the prevention of thromboembolic complications in patients with atrial fibrillation (AF) and in the treatment of venous thromboembolism. As compared with vitamin K antagonists (VKAs), DOACs are characterized by at least similar efficacy and better

safety profile, especially with respect to intracranial hemorrhages. They are also more convenient therapeutic agents. The 2016 European Society of Cardiology guidelines clearly favor DOACs over VKAs in patients with AF.¹ However, DOAC therapy is also associated with bleeding complications. The aim of this paper was to provide recommendations for the management

Correspondence to:

Anna Tomaszuk-Kazberuk, MD, PhD,
Klinika Kardiologii, Uniwersytet
Medyczny w Białymstoku,
ul. M. Skłodowskiej-Curie 24A,
15-276 Białystok, Poland,
phone: +48 85 746 8656,
e-mail: a.tomaszuk@poczta.fm

Received: December 15, 2016.

Revision accepted: March 13, 2017.

Published online: March 15, 2017.

Conflict of interest: see page 350.

Pol Arch Intern Med. 2017;

127 (5): 343-351

doi:10.20452/pamw.3995

Copyright by Medycyna Praktyczna,

Kraków 2017

TABLE 1 Risk of procedure-associated bleeding (modified from Pernod et al)⁵

High (≥2%)	Two-day risk of major bleeding	
	Low (<2%)	Minimal
Epidural anesthesia, subarachnoid anesthesia, lumbar puncture; major surgeries: neurosurgical, cardiosurgical, thoracic, orthopedic, vascular; abdominal and oncological procedures; prostate resection, including transurethral; bladder surgery; liver, kidney, prostate, and bladder biopsy; lithotripsy; removal of colon polyps (especially of >2 cm in size); reconstructive plastic surgery; arterial puncture at noncompressible site	Arthroscopy, skin/lymph node biopsy, arm/shoulder/foot surgeries, endoscopic biopsy, hysterectomy, laparoscopic cholecystectomy, inguinal hernia repair, hemorrhoid removal, endoscopic biopsy, electrophysiology study/ablation, pacemaker or implantable cardioverter-defibrillator implantation	Minor skin procedures (excision of squamous cell and basal cell carcinomas, moles), cataract surgery, most dental procedures (eg, uncomplicated extraction of 1–3 teeth ^a), coronary angiography, nonsurgical endoscopy

a The risk of bleeding associated with dental procedures is described in detail in Kardiol Pol.⁷

of bleeding complications or urgent or elective procedures during DOAC therapy in the Polish setting. The recommendations were based on the most important documents concerning this issue¹⁻⁵ and were developed by representatives of different medical specialties, including cardiologists, gastroenterologists, neurologists, anesthesiologist, surgeons, orthopedic surgeons, and others. Our recommendations were adjusted to the Polish setting in terms of the availability of the drugs, their price, and summary of product characteristics which is obligatory in Poland. Our document is targeted at practitioners; therefore, it is brief and concise without unnecessary details.

Bleeding severity assessment Bleeding is a highly dynamic complication and its consequences depend not only on the site of bleeding but also on the presence of concomitant diseases. Therefore, the assessment of bleeding severity requires an individualized approach.⁷ As the basis for assessing bleeding severity, we recommend adopting the International Society of Thrombosis and Haemostasis criteria,^{4,6} which distinguish 3 groups of bleeding.

Life-threatening bleeding Life-threatening bleeding is major bleeding with a significant loss of blood and full or developing hemodynamic instability or symptomatic bleeding affecting critical organs, such as intracranial, spinal cord, intraocular, retroperitoneal, and intraarticular or intramuscular bleeding with compartment syndrome.

Major or moderate bleeding Major or moderate bleeding encompasses major bleeding that does not cause serious hemodynamic disorders (eg, gastrointestinal [GI] bleeding with hemoglobin concentrations reduced by 2 g/dl, although without hemodynamic destabilization) and more severe minor bleeding (eg, with moderate blood loss, but below 2 g/dl).

Minor bleeding This category refers to bleeding of low intensity and not affecting critical organs, as well as not directly life-threatening as assessed by the physician.

Bleeding risk factors and assessment of bleeding risk in patients on anticoagulation

Risk factors for bleeding include modifiable risk factors, abnormal laboratory test results, and clinical risk factors (Supplementary material online, *Table S1*).¹ Bleeding risk is assessed using scores developed mainly with the aim to support decisions on dosing in patients on anticoagulant therapy (Supplementary material online, *Table S1*). The most common score, HAS-BLED, has been developed on the basis of data from VKA-treated patients.⁸ According to the HAS-BLED score, the annual bleeding risk ranges from 0.6% to 19.6%. However, the use of this score in patients treated with DOACs is disputable, and other scores have been suggested for use in this patient group.⁹

As for surgery-associated bleeding risk, 3 categories of procedures associated with various levels of perioperative bleeding risk can be distinguished: minimal, low, and high (**TABLE 1**). Perioperative management is discussed in the “Urgent surgery” section.

Direct oral anticoagulants DOACs directly and specifically inhibit one coagulation factor. They belong to 2 drug classes: direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban). Full anticoagulant effect is achieved after approximately 2 to 3 hours from DOAC administration. The drugs differ in the extent of renal elimination, which is important for invasive procedure planning. In patients with significant renal impairment, anticoagulant effect may be largely extended due to prolonged half-life of the drug, especially in patients treated with dabigatran. The half-lives of rivaroxaban, apixaban, and edoxaban are only minimally prolonged in patients with end-stage renal disease. The use of DOACs is contraindicated in patients with serious renal impairment (estimated glomerular filtration rate <30 ml/min/1.73 m²).¹⁰

Identification of an anticoagulant effect of direct oral anticoagulants

The effect of DOACs on the results of coagulation assays is presented in **TABLE 2**. The most characteristic feature is a significant prolongation of thrombin time (TT) with dabigatran

TABLE 2 Effects of direct oral anticoagulants on the results of coagulation screening assays and laboratory tests used for monitoring of direct oral anticoagulant activity (based on Gosselin and Adcock)¹²

Coagulation test	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	Comments
Coagulation screening assays					
PT	-/↑	-/↑	↑/↑↑	-/↑	Result depends on the reagent and individual variability.
APTT	↑/↑↑	-/↑	-/↑	-/↑	
TT	↑↑↑	-	-	-	
Laboratory tests					
dTT	↑↑	-	-	-	Sensitive to dabigatran, insensitive to Xa inhibitors
ECT/ECA	↑↑	-	-	-	
Anti-Xa activity	-	↑↑	↑↑	↑↑	Sensitive to anti-Xa inhibitors, insensitive to dabigatran

Abbreviations: APTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; PT, prothrombin time; TT, thrombin time; ↑, significant prolongation; ↑↑, very significant prolongation; “-”, no change

(normal TT confirms that dabigatran is not present in the bloodstream). Direct factor Xa inhibitors do not have any effect on the TT assay. Prolongation of the prothrombin time is most pronounced with rivaroxaban, and prolongation of activated partial thromboplastin time (APTT)—with dabigatran (although the prolongation depends on the reagent used and on individual patient characteristics). None of the coagulation screening assays can be used for laboratory monitoring of DOAC activity with the aim to adjust the dose to ensure that a therapeutic effect is obtained. However, the measurement of an anticoagulant effect of these drugs is helpful in patients who present with serious bleeding or who require urgent surgery or intervention.

The coagulation screening assays do not provide clear evidence that a DOAC concentration in a given patient is normal, as different results in various patients receiving the same dose of the same DOAC have been observed. TABLE 2 lists laboratory tests that may be used for anticoagulation measurement. The results of these tests are better correlated with the anticoagulant effect of DOACs as compared with coagulation assays, but their availability is limited. Normal TT confirms that dabigatran is not present in blood, while normal APTT suggests, although does not fully confirm, a clinically insignificant effect of dabigatran. More precise tests for dabigatran measurement, such as dilute TT and ecarin clotting time, are currently used only in highly specialized centers. Direct factor Xa inhibitors cause a significant prolongation of the prothrombin time and no change in TT; they may slightly prolong APTT. An anti-Xa activity assay, performed differently for individual direct factor Xa inhibitors, is used for precise assessment of their concentrations.^{11,12} However, since the therapeutic range of DOACs is largely unknown, dose adjustments are generally not recommended.

Management of bleeding Bleeding in DOAC-treated patients should be managed according to the recommendations developed for patients after

acute blood loss of varied etiology.^{5,13} Additional management procedures depend on the type of anticoagulation. Management steps in DOAC-treated patients should include bleeding severity assessment and, if relevant, stabilization of the patient's condition.¹³ If possible, the administered anticoagulant should be identified and its activity assessed. Medical history should be obtained from the patient or his or her family members regarding the type of an anticoagulant or other drugs potentially affecting hemostasis and the time of their administration, along with basic information on renal and hepatic function. Laboratory tests may be helpful in identifying the drug and assessing its anticoagulant effect (TABLE 2). Moreover, a decision should be made as to whether to continue anticoagulation (and if yes, what type) or whether to reverse anticoagulation (and if yes, by which method). Generally, in life-threatening bleeding, anticoagulation should be at least temporarily stopped. If the decision is made to discontinue anticoagulation, the timing of and procedure for restarting anticoagulation should be specified. These decisions influence bleeding severity, individual thromboembolic risk due to anticoagulation interruption, and the risk of recurrent bleeding on restarting anticoagulation.

Bleeding severity is not the only factor to be considered. In each patient, clinical status should be assessed, including arterial pressure, heart rate, and organ hypoperfusion. The following laboratory tests should be performed: peripheral blood count, creatinine concentration with estimated glomerular filtration rate (preferably with the Cockcroft–Gault formula), coagulation parameters with at least APTT, PT, international normalized ratio, and TT assessment, and transaminase activity. The site of bleeding has to be identified and compression therapy applied, if possible, or management procedures recommended in the particular clinical setting should be used.¹³ Normal diuresis should be maintained.

TABLE 3 Characteristics of the available products used in life-threatening bleeding

Product	Brand name	Ingredients	Dosing
Prothrombin complex concentrate	Beriplex	Concentrate of coagulation factors II, VII, IX, X and coagulation inhibitors protein C and S	50 U/kg (+ 25 U/kg, if needed) IV
	Octaplex	Concentrate of coagulation factors II, VII, IX, X and coagulation inhibitors: proteins C and S	50 U/kg (+ 25 U/kg, if needed) IV
	Prothromplex total NF	Concentrate of coagulation factors II, VII, IX, X and protein C	50 U/kg (+ 25 U/kg, if needed) IV
Activated prothrombin complex concentrate	FEIBA NF	Concentrate of inactivated and activated coagulation factors II, VII, IX, X	50 U/kg IV; max. 200 U/kg/d
Recombinant activated factor VII	NovoSeven	Coagulation factor VIIa	90 µg/kg IV
Idarucizumab (monoclonal antibody)	PRAXBIND	Idarucizumab	5 g IV via 2 consecutive infusions (2 × 2.5 g) lasting 5–10 minutes each, or as bolus injection

Management of acute minor bleeding In this clinical setting, it is best to follow the strategy of watchful waiting. Control tests are recommended. Previously undiagnosed exacerbation of renal dysfunction and anemia or thrombocytopenia may impact further management. The drug half-life is short in patients with normal renal and liver function; therefore, supporting measures and actions aimed at reversing anticoagulant effect are usually not necessary in these patients. The half-life of dabigatran is 12 to 15 hours, while that of Xa inhibitors, 9 to 11 hours. Typically, it is sufficient to omit 1 or 2 DOAC doses. In a population at a very high thromboembolic risk, attempts should be made at maintaining anticoagulant therapy.

Management of acute major or moderate bleeding If acute major or moderate bleeding is not associated with hemodynamic destabilization, fluid therapy and blood and blood product supplementation should be considered. Transfusion intensity depends on the severity of bleeding. In patients with thrombocytopenia of less than 50 000/mm³, platelet concentrate should be administered to a target value of 100 000/mm³ or higher. Fresh frozen plasma transfusion should be considered, but only to replenish vascular bed on account of blood loss (at a dose of 10–20 ml/kg of body weight), because the concentration of coagulation factors in plasma products is too low to reverse the anticoagulant effects of DOACs. Maintaining normal diuresis is important as DOACs are partly eliminated by the kidneys, and renal elimination is particularly important in the case of dabigatran. Renal replacement therapy may be used to increase the rate of dabigatran elimination due to its low protein-binding capacity; however, it is rarely used for technical reasons and owing to the availability of antidote.

As additional supportive treatment in the management of bleeding complications, slow intravenous administration of tranexamic acid may be considered (2–4 g/d in 2–4 divided doses). In patients with renal failure, dosing should be reduced depending on the serum creatinine concentration. Oral activated charcoal, administered preferably

1 hour after dabigatran use, 10 to 20 minutes after rivaroxaban use, and 2 to 6 hours after apixaban use, could be a potential method of reducing serum drug concentrations. However, considerable amounts of charcoal (approximately 1 g/kg of body weight) are required to achieve a significant effect, and clinical evidence for its effectiveness is very limited.

Importantly, patients with acute moderate or major bleeding should be treated in the intensive care setting and subjected to hemodynamic parameter monitoring. Diagnostic and therapeutic procedures for a specific type of bleeding, such as gastroscopy in a patient with GI bleeding, should be considered.

Management of life-threatening bleeding Hemodynamic stabilization usually determines the future status of the patient.¹⁴ Treatment should be conducted in the intensive care setting, and vital signs monitoring is necessary. Early packed red blood cell transfusion to replenish blood loss is recommended. Management should be complemented with actions aimed at a rapid reversal of the DOAC effect. For dabigatran, an immediate intravenous administration of idarucizumab, a specific antidote, is the option of choice (TABLE 3). If idarucizumab is not readily available for a dabigatran-treated patient or if the patient receives another DOAC, the use of prothrombin complex concentrate (PCC) or activated PCC (aPCC) should be considered (TABLE 3). An additional option is the use of recombinant activated factor VII. PCC contains coagulation factors II, VII, IX, and X, and lower amounts of inhibitory proteins C and S, with a small addition of heparin, while aPCC contains both inactivated and activated factors II, VII, IX, and X. PCCs supplied by various manufacturers differ slightly with regards to the content of coagulation factors and coagulation factor inhibitors.

Antidotes to direct oral anticoagulants Currently, the only available antidote to DOACs is idarucizumab, a reversal agent for dabigatran. However, studies are underway for an antidote to factor Xa inhibitors (andexanet alfa) and for

TABLE 4 Indications and contraindications to idarucizumab use

Indications
Life-threatening bleeding or bleeding affecting critical organs
Major bleeding despite local treatment or a high risk of bleeding recurrence due to dabigatran overdose or reduced elimination rate
Need of urgent surgery/intervention associated with a high risk of bleeding, which cannot be delayed
Contraindications
Treatment with an anticoagulant other than dabigatran, regardless of bleeding severity
Minor or major bleeding that can be managed with other methods (eg, gastrointestinal bleeding effectively controlled with endoscopic methods)
Elective surgeries, or surgery or intervention that can be delayed
High drug concentration or overdose with no signs of bleeding

a universal antidote acting on DOACs, heparins, and fondaparinux (ciraparantag).

Idarucizumab is a humanized antibody fragment that binds to dabigatran with a more than 350-fold higher affinity than dabigatran does to thrombin, which immediately, strongly, specifically, and permanently binds dabigatran circulating in the blood and quickly neutralizes its anticoagulant effects (TABLE 3). The dabigatran–idarucizumab complex is eliminated by the kidneys within several hours. Dabigatran therapy may be restarted after 24 hours from antidote administration. The efficacy and safety of idarucizumab were demonstrated in a group of 90 patients with severe bleeding or who required urgent surgery or invasive procedures.¹⁵ Adverse reactions were observed in no more than 5% of the patients and included headache and hypokalemia. No prothrombotic effect of idarucizumab has been reported so far.¹⁵ Idarucizumab should be used in patients with life-threatening bleeding or before urgent major surgeries (TABLE 4).^{16–18}

Andexanet alfa, an analogue of factor Xa, a potential antidote to rivaroxaban, apixaban, edoxaban, heparin, low-molecular-weight heparin, and fondaparinux, is currently under investigation. It is administered through a prolonged intravenous infusion and causes a significant decrease in blood anticoagulant concentration and reversal of anticoagulant effects. However, the drug has not yet been approved for clinical use. Moreover, some rare thrombotic events following its use have also been reported.¹⁷

Management of intracranial bleeding Intracranial hemorrhages (ie, intracerebral hemorrhages, subdural hematoma, epidural hematoma, and subarachnoid hemorrhage) are rare, but life-threatening, bleedings.⁴ Their incidence is 50% lower in DOAC-treated patients than in patients receiving VKAs.^{2,19} Immediate drug discontinuation is the fundamental approach to intracranial hemorrhage management. In each case, it is necessary to record previous anticoagulant dosing and the timing of the last dose, as well as assess the anticoagulant effect and expected timing of coagulation status normalization (TABLE 2). Drug therapy of all types of intracranial hemorrhages in patients receiving anticoagulants follows in

part the recommendations for the management of other life-threatening bleeds (FIGURE 1).

Management aimed at reversing the anticoagulant effect depends on the patient's clinical status and the timing of the last DOAC dose. In the case of intracranial hemorrhage in a patient treated with dabigatran, idarucizumab is recommended. It should be administered even if APTT or TT is only slightly prolonged. The second dose of idarucizumab may be considered, for example in the case of recurrent bleeding in a patient with prolonged APTT or TT. PCC or aPCC (TABLE 3) should be used in dabigatran-treated patients who cannot be administered idarucizumab and in those with intracranial hemorrhage receiving factor Xa inhibitors. There is no evidence for the beneficial effects of recombinant factor VIIa; therefore, its use in cases of intracranial hemorrhage is not recommended.²⁰

In patients with intracranial hemorrhage, including those taking DOACs, a surgery to remove hematoma and treat the source of hemorrhage may be necessary. Embolization or surgery of a bleeding vascular malformation and evacuation of intracerebral hematoma are interventions with proven therapeutic efficacy in cases of intracranial hemorrhage. In emergency situations requiring urgent intervention in DOAC-treated patients, therapy with idarucizumab, aPCC, or PCC should be used to achieve normal anticoagulation (TABLE 3).⁵ Surgery can be performed only when the anticoagulant effect of a DOAC has been reversed or minimized. Idarucizumab causes an immediate and full reversal of dabigatran effects and enables an urgent procedure of intracranial hematoma removal.¹⁵ The preparation for a surgical intervention in cases of intracranial hemorrhage is the same as for procedures associated with high bleeding risk (TABLE 1). The time for discontinuation of DOACs depends on creatinine clearance. For dabigatran, if idarucizumab has not been administered, the time ranges from at least 48 to 96 hours from the last dose intake, and for factor Xa antagonists, it is at least 48 hours (Supplementary material online, Table S2).

Management of upper and lower gastrointestinal bleeding In clinical trials, a slightly higher rate of GI bleeds was observed during treatment with

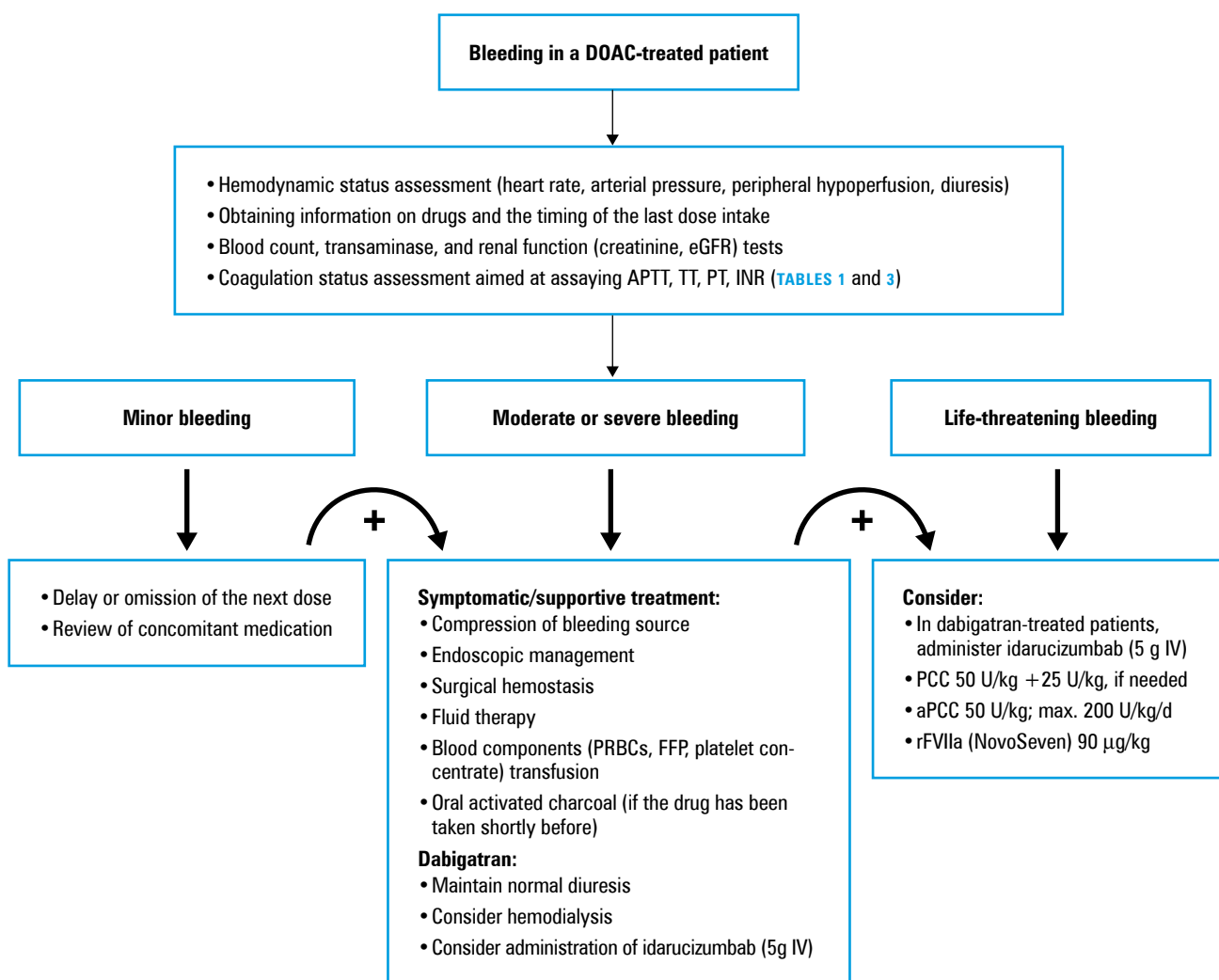


FIGURE 1 Management of bleeding in patients on direct oral anticoagulants (modified from Heidbuchel et al³)

Abbreviations: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; INR, international normalized ratio; PRBC, packed red blood cell; rFVIIa, recombinant factor VIIa

dabigatran (2 × 150 mg/d), rivaroxaban (1 × 20 mg/d and 1 × 15 mg/d), and edoxaban, 1 × 60 mg/d, as compared with VKA therapy. In addition, dabigatran at doses of 1 × 150 mg and 2 × 110 mg was associated with a higher rate of dyspeptic disorders.²¹

It is believed that antiplatelet or nonsteroidal anti-inflammatory drugs, esophagitis, and gastritis or gastroesophageal reflux requiring the use of proton pump inhibitors or histamine H₂-receptor antagonists increase the risk of GI bleeding. Bleeding in normal vessels in the lack of mucosal damage is rare. Therefore, *Helicobacter pylori* infection, history of peptic ulcer disease, concomitant steroid therapy, history of gastric and duodenal erosions, GI angiodysplasia, and diverticulosis are also important risk factors for GI bleeding. There are no effective methods for the prevention of lower GI bleeding.²² No studies have convincingly justified prophylaxis with the use of proton pump inhibitors or precisely determined their doses, although it seems that their use should be recommended in DOAC-treated patients at a high risk of upper GI bleeding.

Urgent endoscopy in patients with upper GI bleeding should be performed after cardiovascular stabilization. The next dose to be taken after the onset of bleeding symptoms should be omitted. In most cases, administration of prohemostatic agents is not justified. However, they should be considered in cases of massive, life-threatening bleeds or bleeds that cannot be controlled using endoscopic techniques (eg, bleeding associated with DOAC use and hemorrhagic gastritis). In the case of upper GI bleeding that requires surgery in a DOAC-treated patient, the decision on surgery should be made along with implementing procedures recommended in cases of urgent surgery in patients taking DOACs.²³

It should be noted that diagnostic procedures of the upper and lower GI tract, including biopsy, biliary and pancreatic stent (without simultaneous sphincterotomy), and enteroscopy, are associated with low or moderate bleeding risk. In other endoscopic procedures, the risk is considered high.²⁴ In the case of procedures at higher risk of bleeding, treatment should be discontinued (Supplementary material online, Table S2).

Even minor GI bleeding should be diagnosed. Diagnosis and removal of the cause of bleeding allow safe reinitiation of anticoagulation. In cases of prior life-threatening bleeding with no evident cause, the decision to restart anticoagulant therapy is difficult and requires an individualized approach. Of note, several analyses point to a lower risk of GI bleeding during treatment with dabigatran at a dose of 2×110 mg/d, apixaban at a dose of 2×2.5 mg/d, and edoxaban at a dose of 30 mg/d. Currently, it seems that these doses may be prescribed in patients with a history of major GI bleeding.^{20,21}

Neuraxial blockade (subarachnoid and epidural anesthesia) in patients on direct oral anticoagulants Neuraxial blockade (subarachnoid and epidural anesthesia) is a routine anesthesiologic technique. Spinal cord hematoma is one of the most serious possible complications of this procedure. Anticoagulated patients are at a 10-fold higher risk of spinal cord hematoma during neuraxial blockade. Therefore, spinal anesthesia should generally be avoided in patients taking rivaroxaban, apixaban, or edoxaban who require urgent surgery. However, it can be applied in patients taking dabigatran, because its anticoagulant effect can be reversed with idarucizumab.

Neuraxial blockade in patients receiving DOACs should be discussed separately for 2 populations. The first population includes patients undergoing orthopedic surgery, who take DOACs at prophylactic doses to reduce the rate of thromboembolic complications due to the surgery. For this indication, the use of DOACs is only temporary and is initiated only after anesthesia and surgery. The second population includes patients who take DOACs for internal diseases, in whom neuraxial blockade may be applied because of surgery or analgesic interventions. When preparing for neuraxial blockade, an anesthesiologist should particularly carefully weigh the benefits against the risks of the procedure, discuss this issue with the patient, and obtain his or her written consent.^{22,24}

Neuraxial blockade performed to administer anesthesia for various procedures and manage pain not associated with surgery requires an individualized approach in patients on DOACs. This approach should take into account the patient's age, organ function (especially renal function), spinal degeneration, coagulopathies, concomitant medication, possible technical problems, and history of regional anesthesia. DOAC discontinuation for at least 5 half-lives, like in the case of other procedures at a high risk of bleeding, is recommended before neuraxial blockade. Before puncture, APTT and TT tests in dabigatran-treated patients and PT tests in rivaroxaban-treated patients are recommended. Suggested time to restarting full anticoagulation after catheter removal varies between patients.^{22,24}

Direct oral anticoagulants in primary prevention of venous thromboembolism in patients after hip or knee surgery Usually, an epidural catheter is inserted or subarachnoid anesthesia is performed before hip or knee surgery. If the catheter is maintained in the perioperative period for analgesic therapy and DOACs at prophylactic doses (Supplementary material online, *Table S3*) are introduced, the removal of the epidural catheter may be safe provided it is performed with appropriate delay after the prophylactic therapy is stopped. Following catheter removal, safe DOAC therapy (if indicated) may be initiated after up to 10 to 20 hours (Supplementary material online, *Table S3*).²⁴

Orthopedic injury and trauma A significant percentage of patients after orthopedic trauma are treated with DOACs for other reasons such as those related to internal diseases. Orthopedic procedures are usually elective, planned, and performed in patients who have discontinued DOACs in line with the recommendations for elective surgeries (Supplementary material online, *Table S4*). However, posttraumatic patients on DOAC therapy often require urgent surgeries. In the first place, manual compression with the use of bandage or dressing is necessary to stop bleeding. If the wound is large and there are multiple sources of bleeding, mechanical tamponade is indicated until the anticoagulant effect is reversed. Depending on bleeding severity, principles of management presented in **FIGURE 1** should be followed. Major surgeries should be avoided in the early posttraumatic period unless the patient had been treated with dabigatran and received idarucizumab. A broken leg or arm is usually managed using skeletal traction with ligamentotaxis, which does not generate additional bleeding risk. It is also necessary to assess risk factors for thrombosis and to implement preventive measures for venous thromboembolism, as well as ischemic stroke in patients with AF. Thromboembolic prophylaxis is implemented during the safe postoperative period, that is, when hemostasis has been achieved.

Bleeding in patients after coronary angioplasty who require extended direct oral anticoagulant therapy In DOAC-treated patients undergoing coronary angioplasty, the radial artery should be the preferred vascular access to reduce the risk of perioperative bleeding.²⁵ Long-term exposure of patients to triple therapy with the use of 2 antiplatelet drugs and 1 anticoagulant drug is associated with an increased risk of bleeding. According to the European Society of Cardiology guidelines, the duration of triple therapy depends on whether the angioplasty was elective or performed due to acute coronary syndrome (ACS) and on the risk of bleeding. Triple therapy after ACS should be maintained for 6 months in patients at low bleeding risk as compared with the risk of thrombosis or another ACS. If the risk of bleeding is high as compared with the risk of thrombosis or another ACS, triple therapy should be administered only

for 30 days. Triple therapy following elective angioplasty is administered for 30 days. In patients at a high risk of ACS or thrombosis and a relatively lower risk of bleeding, a DOAC in combination with 1 antiplatelet agent is recommended for up to 12 months, and if the bleeding risk is higher—up to 6 months.¹ DOACs in combination with antiplatelet drugs may be used at a lower dose—dabigatran at a dose of 110 mg twice daily and rivaroxaban at a dose of 15 mg.²⁶ Proton pump inhibitor is recommended for gastric protection in patients receiving dual antiplatelet therapy and a DOAC. A combination therapy with the use of DOACs and prasugrel or ticagrelor is contraindicated until the results of the ongoing studies become available.²⁷

Urgent surgery If urgent surgery is necessary, management strategy is based on expected DOAC concentrations. The basic information that needs to be obtained includes: 1) bleeding risk assessment based on the type of the procedure (TABLE 2); 2) patient's clinical data, including renal function, age, body weight, and concomitant medication; and 3) the dose and timing of the last DOAC intake.

Information obtained from the patient or his or her family or friends on the dose and timing of the last drug intake, and in the case of DOACs, the assessment of coagulation status (TABLES 3 and 4), may support determination of anticoagulant effects. If immediate surgical intervention associated with a high risk of bleeding is required and cannot be delayed, antidote administration is absolutely indicated.²⁸ If the antidote is unavailable for patients treated with dabigatran or if urgent surgery is necessary in a patient using direct factor Xa inhibitors, the availability of PCC or aPCC should be secured. If possible, the procedure should be delayed, especially because DOACs have a relatively short duration of action.²⁹

Postbleeding anticoagulation A decision to restart anticoagulation, including after a major bleeding event in a DOAC-treated patient, is always made on an individual basis and should take into account the risk of recurrent bleeding or bleeding associated with a recent surgery (considering postoperative hemostasis), as well as the risk of thromboembolic complications due to anticoagulation discontinuation.³⁰ Removing the cause of bleeding should not lead to prolonged interruption of anticoagulation, and the decision to restart anticoagulation should be consulted with other specialists (eg, with a neurosurgeon or an anesthesiologist).³¹

Restarting anticoagulation after intracranial hemorrhage A decision to restart anticoagulation after intracranial hemorrhage should be made on individual basis. In patients with identifiable and manageable bleeding risk factors, anticoagulant therapy may be restarted after 4 to 8 weeks from

hemorrhage.¹ In cases where the factor responsible for intracranial hemorrhage cannot be removed (eg, suspected amyloid angiopathy) or dual antiplatelet therapy is necessary, anticoagulation is contraindicated.^{1,3} Restarting oral anticoagulation is contraindicated in patients in whom bleeding occurred during treatment with appropriate doses of DOACs, during therapy interruption, or at nontherapeutic doses, in patients at older age, and in those with uncontrolled hypertension, cortical bleeding, major intracranial bleeding, numerous cerebral microbleeds on radiographic examination, and in those with alcohol abuse.

Conclusions Experience in managing patients with bleeding episodes on DOAC therapy is still limited. Therefore, we hope that this paper will be helpful in everyday clinical practice and that it will be useful in developing in-hospital management principles for this population of patients.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

Conflict of interest PP received honoraria for lectures from and sat on advisory boards for Bayer, Boehringer-Ingelheim, Pfizer, and Sanofi. RD provided sponsored lectures for Bayer, Boehringer Ingelheim, and CSL Behring. AT-K provided sponsored lectures and consultations for Boehringer Ingelheim and Bayer. AS received honoraria for lectures from Boehringer Ingelheim, Bayer, and BMS Pfizer, and was involved in consultation bodies for Bayer and Boehringer Ingelheim. ZG received honoraria for lectures from Adamed, Alpha Wasserman, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Krka, Merck Serono, MSD, Pierre Fabre, Sandoz, Sanofi Aventis, and Servier; sat on advisory boards for Amgen, Boehringer Ingelheim, and Polpharma; and received scientific grants from Sanofi Aventis. AK received honoraria for lectures from Boehringer Ingelheim, Bayer, and BMS Pfizer. JK sat on advisory boards for Boehringer Ingelheim and received honoraria for lectures from Pfizer. KF received honoraria for lectures from and was involved in consultation bodies for Bayer, Boehringer Ingelheim, MSD, and Pfizer. GR received honoraria for lectures from Bayer and Boehringer Ingelheim. JS received research grants, sat on advisory boards, and received honoraria for lectures from Astra Zeneca, Bayer, Boehringer Ingelheim, and Pfizer.

REFERENCES

- 1 Kirchoff P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2016; 37: 2893-2962.
- 2 Hart RG, Diener HC, Yang S, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke*. 2012; 43: 1511-1517.

- 3 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Eur Heart J*. 2016. doi:10.1093/eurheartj/ehw058
- 4 Schulman S, Kearon C; The Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (2005). Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005; 3: 692-694.
- 5 Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) – March 2013. *Arch Cardiovasc Dis*. 2013; 106: 382-393.
- 6 Schulman S, Angeras U, Bergqvist D, et al. On behalf of the Subcommittee on Control of Anticoagulation of The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010; 8: 202-204.
- 7 Pruszczyk P, Ciużyński M, Opolski G, et al. Dental cardio common position for dealing anticoagulation in patients undergoing dental procedures. *Kardiol Pol*. 2016; 74: 87-98.
- 8 Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012; 33: 2719-2747.
- 9 Hijazi Z, Oldgren J, Lindback J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet*. 2016; 387: 2302-3211.
- 10 Młodawska E, Tomaszuk-Kazberuk A, Łopatowska P, et al. Management of patients with atrial fibrillation and chronic kidney disease in light of the latest guidelines. *Pol Arch Med Wewn*. 2016; 126: 353-362.
- 11 Kitchen S, Gray E, Mackie I, et al. On behalf of the BCSH committee. Measurement of non-coumarin anticoagulants and their effects on tests of haemostasis: Guidance from the British Committee for Standards in Haematology. *Br J Haematol*. 2014;166: 830-841.
- 12 Gosselin RC, Adcock DM. The laboratory's 2015 perspective on direct oral anticoagulant testing. *J Thromb Haemost*. 2016; 14: 886-893.
- 13 Faraoni D, Levy JH, Albaladejo P, Samama CM; Groupe d'Intérêt en Hémostase Périopératoire. Updates in the perioperative and emergency management of non-vitamin K antagonist oral anticoagulants. *Crit Care*. 2015; 19: 203-208.
- 14 Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016; 20: 100-154.
- 15 Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med*. 2017; 377: 431-441.
- 16 Levy JH, Ageno W, Chan NC, et al. Subcommittee on Control of Anticoagulation. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016; 14: 623-627.
- 17 Connolly SJ, Milling TJ Jr, Eikelboom JW, et al. ANNEXA-4 Investigators. Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016; 375: 1131-1141.
- 18 Tomaszuk-Kazberuk A, Łopatowska P, Młodawska E, et al. Successful use of idarucizumab as a reversal agent for dabigatran in a patient with acute dissected aortic aneurysm. *Pol Arch Intern Med*. 2017; 127: 68-70.
- 19 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.
- 20 Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. *Thromb Haemost*. 2015; 113: 931-942.
- 21 Graham DJ, Reichman ME, Wernecke M, et al. Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med*. 2016; 176: 1662-1671.
- 22 Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the neurocritical care society and society of critical care medicine. *Neurocrit Care*. 2016; 24: 6-46.
- 23 Abraham NS, Castillo DL. Novel anticoagulants: bleeding risk and management strategies. *Curr Opin Gastroenterol*. 2013; 29: 676-683.
- 24 Narouze S, Benzon HT, Provenzano DA, et al. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: Guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med*. 2015; 40: 182-212.
- 25 Kolh P, Windecker S. ESC/EACTS myocardial revascularization guidelines 2014. *Eur Heart J*. 2014; 35: 3235-3236.
- 26 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016; 37: 267-315.
- 27 Dzeszka MS, Brown RA, Lip GY. Patients with atrial fibrillation undergoing percutaneous coronary intervention. Current concepts and concerns: part I. *Pol Arch Med Wewn*. 2015; 125: 73-81.
- 28 Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Perioperative management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost*. 2016; 14: 875-885.
- 29 Tafur A, Douketis JD. Perioperative anticoagulant management in patients with atrial fibrillation: practical implications of recent clinical trials. *Pol Arch Med Wewn*. 2015; 125: 666-671.
- 30 Sticherling C, Marin F, Birnie D, et al. Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). *Europace*. 2015; 17: 1197-1214.
- 31 Volk T, Kubulus C. New oral anticoagulants and neuraxial regional anesthesia. *Curr Opin Anaesthesiol*. 2015; 28: 605-609.