PROFESE ONLINE
peer-reviewed journal for non-medical health professions

ISSN 1803-4330
DOI: 10.5507/pol.2017.006
volume 10 / 2 • November 2017

New Anticoagulants

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ABSTRACT

Background: Until recently, warfarin was the only oral anticoagulant. Due to its numerous side effects, especially various types of bleeding, new oral anticoagulants with the same or better safety and efficacy have been developed. Patients using new anticoagulant may be encountered at centers providing care in nearly all specialties and at various levels of healthcare. Therefore, it is advisable to know at least basic information on this issue as provided by this brief text.

Objective: The aim of this article is to briefly introduce new oral anticoagulants to health professionals at all levels of education and across disciplines.

Methodology: Data were obtained from recent publications, in particular the PubMed database, Czech State Institute for Drug Control website and summary of product characteristics (SPC) for particular drugs. Additionally, other Czech and foreign databases, manuals and clinical trial outcomes were used.

Results: Large clinical studies have shown that all new oral anticoagulants are as effective as or more effective than warfarin in preventing stroke and systemic embolism. They also proved to be relatively safe or even safer compared to warfarin in terms of the risk of serious bleeding complications. A big step forward was the approval of idarucizumab as a specific antidote for dabigatran. The other anticoagulants are still lacking specific antidotes.

Conclusions: This group of drugs should be monitored over the longer term to better characterize their activity, side effects, develop other specific antidotes and optimize their monitoring during treatment. It is necessary to continue education in this area.

KEY WORDS

NOAC, new oral anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, idarucizumab

LITERATURE REVIEW

Since patients using new oral anticoagulants (NOACs) are a relatively varied group, they may be encountered at most centers providing care in various specialties and at various levels of healthcare. This brief insight into NOACs aims is aimed for all levels of health education and everyday, for example nursing, practice.

INTRODUCTION

For 60 years, warfarin was the only oral anticoagulant. However, despite its undoubted clinical efficacy, particularly in preventing stroke and reducing the risk of death in patients with atrial fibrillation, warfarin has numerous adverse effects. Therefore, and for other reasons, NOACs were developed and introduced that are as effective and safe as, but easier to administer than, warfarin. Today, two groups of agents are available, oral direct thrombin inhibitors (gatrans) and oral direct factor Xa inhibitors (xabans). Based on large clinical trials, the following drugs to prevent stroke and other systemic embolic events in patients with atrial fibrillation have been approved so far (in the order as listed): dabigatran (Pradaxa®), rivaroxaban (Xarelto®) apixaban (Eliquis®) and edoxaban (Lixiana®) (1, 2, 3, 4).

DESCRIPTION OF SEARCH STRATEGY

Data were obtained from recent publications, in particular the PubMed database, Czech State Institute for Drug Control website and summary of product

characteristics (SPC) for particular drugs. Additionally, other Czech and foreign databases, manuals and clinical trial outcomes were used. The key words in both Czech and English languages were as follows: new anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, idarucizumab, and names of trials, that is, RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy Trial), ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial) and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48). The highest numbers of publications were on dabigatran, followed by rivaroxaban, apixaban and, finally, edoxaban, the newest drug. The oldest resources were results of large clinical trials published in 2011.

TEXT OF LITERATURE REVIEW

All NOACs were approved based on results of phase III large clinical trials comparing the efficacy and safety of NOACs with warfarin in large samples of patients with nonvalvular atrial fibrillation (NVAF). Those were RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban) and ENGAGE AF-TIMI (edoxaban). The AVERROES trial was the only one comparing apixaban, as the only NOAC in patients with atrial fibrillation who, for various reasons, could not use warfarin, with acetylsalicylic acid (ASA). The trials (1, 2, 3, 4) on individual NOACs are summarized in Table 1.

In 2016, edoxaban (Lixiana®), another member of the xaban group, was introduced to the market. Its efficacy and safety was compared with those of warfarin and enoxaparin in large clinical trials ENGAGE AF-TIMI 48 and ENSURE-AF. Edoxaban is used to prevent stroke and systemic embolism in adult patients with NVAF and one or more risk factors such as congestive heart failure, hypertension, age ≥ years,

Table 1 Overview of studies on individual NOACs (5)

Drug names	Indications	Study name acronyms
Dabigatran	atrial fibrillation	RE-LY
	primary prevention of TED	RE-NOVATE I, II RE-MOBILIZE RE-MODEL
	acute treatment of TED	RECOVER RECOVER II
	secondary prevention of TED	RE-MEDY RE-SONATE
Rivaroxaban	atrial fibrillation	ROCKET-AF
	primary prevention of TED in orthopedics, internal medicine	RECORD 1-4 MAGELLAN
	acute treatment of TED	EINSTEIN DVT EINSTEIN PE
	secondary prevention of TED	EINSTEIN EXT
	acute coronary syndrome	ATLAS ACS TIMI 51
Apixaban	atrial fibrillation	ARISTOTLE AVERROES
	primary prevention of TED in orthopedics, internal medicine	ADVANCE 1-3 ADOPT
	acute treatment of TED	AMPLIFY
	secondary prevention of TED	AMPLIFY EXT
	acute coronary syndrome	APPRAISE-2

Table 2 Summary of basic comparative characteristics of conclusive studies of NOACs (10)

Study characteristics	RE-LY	ARISTOTLE	ROCKET-AF
	dabigatran	apixaban	rivaroxaban
Mechanism of effect	factor IIa	factor Xa	factor Xa
Number of patients	18,113	18,201	14,264
Dosage	150 mg twice daily	5 mg twice daily	20 mg once daily
	110 mg twice daily	(2.5 mg twice daily)	(15 mg once daily)
Mean $CHADS_2$ score	2.1	2.1	3.5
Mean TTR	64%	62%	55%
Median TTR	67%	66%	58%
Discontinuation – study drug / warfarin	21.2% / 16.6%	25.3% / 27.5%	23.9% / 22.4%

Legend: $CHADS_2$ score – risk of thromboembolism; TTR – time in therapeutic range

diabetes mellitus, prior stroke or transient ischemic attack (TIA). Other indications for administration of edoxaban are treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent venous thromboembolism and PE (17, 18).

Dabigatran, rivaroxaban and apixaban are indicated for prevention of postoperative thromboembolic complications after orthopedic surgery, elective knee or hip replacements, prevention of ischemic stroke or systemic embolism in patients with NVAF, treatment of DVT and hemodynamically stable PE and for prevention of recurrent DVT and PE in adults. Additionally, rivaroxaban administered together with ASA alone or in the combination ASA plus clopidogrel or ticlopidine is approved for prevention of atherothrombotic events in adult patients after acute coronary syndrome (ACS) with increased levels of cardiac biomarkers (6, 7, 8, 9). Table 2 summarizes basic comparative characteristics of conclusive studies of NOACs.

These NOACs proved to be as effective as or even more effective than warfarin in preventing stroke and systemic embolism. They also proved to be as safe as or safer than warfarin with respect to serious bleeding complications. Additionally, the rates of dreaded hemorrhagic stroke were also dramatically reduced as compared with warfarin. The fixed-dose regimen requires no monitoring of the effect which is undoubtedly both beneficial and comfortable for patients. They also have only few drug interactions. Another clear advantage is that they have better pharmacokinetic properties than warfarin. Their onset of action is within few hours after the initial dose and the effect wanes much more rapidly than that of warfarin. Also beneficial is the fact that both physicians and increasingly informed patients are aware of the advantages of NOACs as they compared them with numerous limitations of warfarin (1, 5). Table 3 shows the pharmacological characteristics of dabigatran, rivaroxaban and apixaban and their doses for particular indications.

Table 3 Pharmacological characteristics and doses of NOACs

	dabigatran	rivaroxaban	apixaban
Mechanism of effect	competitive inhibition of thrombin	competitive inhibition of factor Xa	competitive inhibition of factor Xa
Onset of effect	30–60 mins	30–60 mins	30–60 mins
Time of maximum effect	2–3 hrs	2–4 hrs	2–4 hrs
Half-life	12–14 hrs	7–11 hrs	12 hrs
Dosage	prevention of TED in orthopedics: 220 mg once daily or 150 mg once daily	prevention of TED in orthopedics: 10 mg once daily	prevention of TED in orthopedics: 2.5 mg twice daily
	prevention of embolism in AF: 150 mg twice daily or 110 mg twice daily	prevention of embolism in AF: 10 mg once daily or 15 mg once daily	prevention of embolism in AF: 5 mg twice daily or 2.5 mg twice daily
		treatment of acute vein thrombosis: 15 mg twice daily for the first 3 weeks then 10 mg once daily	
Renal clearance	80%	66%	25%
Interactions	P-gp inhibitors/inducers	CYP3A4 and P-pg inhibitors/inducers	CYP3A4 and P-pg inhibitors/inducers

Legend: TED – thromboembolic disease

Characteristics and indications of individual NOACs

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis in plasma and in the liver. Dabigatran is a potent competitive, reversible and direct thrombin inhibitor and is the main metabolite in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation (7). Table 3 shows doses for particular indications.

The indications of dabigatran (Pradaxa®) include:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement (75 mg, 110 mg).
- Prevention of stroke and systemic embolism in adult patients with NVAF and one or more risk factors such as prior stroke or TIA, age 75 years or more, cardiac failure (NYHA class II or higher), diabetes mellitus or hypertension (110 mg, 150 mg).
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients (110 mg, 150mg).

The most frequent adverse effect of dabigatran is dyspepsia present in 5–10% of patients. It is characterized as gastric and abdominal pains, dyspepsia or abdominal discomfort. They are typically more common in females than in males. Moreover, rectal hemorrhage and epistaxis may occur (7).

Dabigatran etexilate therapy is contraindicated with strong P-gp inhibitors such as systemic ketoconazole, cyclosporin, itraconazole or dronedarone; the concomitant use of tacrolimus is also not recommended. Caution should be exercised with mild and moderate P-gp inhibitors (e.g. amiodarone, posaconazole, quinidine, verapamil and ticagrelor). P-gp inducers (rifampicin, St John's Wort, carbamazepine or phenytoin) reduce exposure to dabigatran, so their administration to patients treated with dabigatran etexilate should be avoided.

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the coagulation cascade and inhibits both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated. Table 3 shows doses for particular indications.

The indications of rivaroxaban (Xarelto®) include:

- Co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, rivaroxaban is indicated for the prevention of atherothrombotic events in adult patients after ACS with elevated cardiac biomarkers (2.5 mg).
- Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery (10 mg).
- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors such as congestive heart failure, hypertension, age 75 years or more, diabetes mellitus, prior stroke or TIA (15 mg, 20 mg).
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (hemodynamically unstable PE patients) (15 mg, 20 mg) (8).

The most common serious adverse effects of rivaroxaban are bleeding and anemia. Gastrointestinal tract hemorrhage (including gingival and rectal bleeding), urogenital tract hemorrhage (including hematuria and menorrhagia), epistaxis, eye hemorrhage (including conjunctival bleeding) and postoperative hemorrhage have been identified as frequent. Moreover, commonly reported undesirable effects include nonspecific symptoms, with frequencies no higher than those seen in other common cardiovascular drugs: increased serum levels of liver enzymes, dizziness, headache, hypotension and syncope. Less common are intracerebral and intracranial hemorrhage, hemoptysis and hemarthrosis, cutaneous and subcutaneous hemorrhage. These adverse effects were found by the ROCKET-AF study. However, it must be taken into consideration that the cohort included in the study had a higher-than-average rate of bleeding risk factors; in lower-risk populations, bleeding was less frequent (5, 8). Table 3 shows doses for particular indications.

The concomitant administration of rivaroxaban and apixaban with strong CYP3A4 and P-gp inhibitors is not recommended; these drugs include azole antifungals (ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g. ritonavir). The concomitant use of CYP3A4 and P-gp inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort) should be avoided since the antithrombotic effect may be considerably reduced.

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombic activity. Apixaban inhibits free and clot-bound factor Xa and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved hemostasis. Table 3 shows doses for particular indications.

The indications of apixaban (Eliquis®) include:

- Prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery (2.5 mg).
- Prevention of stroke and systemic embolism in adult patients with NVAF and one or more risk

factors such as prior stroke or TIA, age 75 years or more, hypertension, diabetes mellitus or symptomatic heart failure (NYHA class II or higher) (2.5 mg, 5 mg).
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (hemodynamically unstable PE patients) (2.5 mg, 5 mg) (9).

The most common adverse effect of apixaban (bleeding) stems from the pharmacodynamic profile of its activity. Clinically relevant and major bleeding in the intraoperative and postoperative periods (10–35 days after the procedure) occurred in approximately 3–5% of patients receiving 5 mg of apixaban daily (ADVANCE study). In patients with atrial fibrillation receiving long-term therapy with 10 mg of apixaban daily in the AVERROES study, clinically significant and major bleeding was observed in 4–5% of cases annually (of which 0.5% had intracranial bleeding). The incidence rates for all types of bleeding were comparable to those seen in ASA therapy. The most frequent types of bleeding were epistaxis, gastrointestinal hemorrhage, hematuria, postprocedural hemorrhage, puncture site and catheter site hemorrhage. In more than 1% of cases, anemia is observed, often posthemorrhagic. The incidence of gastrointestinal problems is similar. Less common is an increase in liver enzymes; episodes of mild transient thrombocytopenia are rare. The other adverse effects, such as hypersensitivity, were of little importance and very rare (5, 9).

Edoxaban (Lixiana®) is a highly selective, direct and reversible inhibitor of factor Xa. Edoxaban inhibits free factor Xa and prothrombinase activity. Inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation. As mentioned above, the indications of edoxaban include:

- Prevention of stroke and systemic embolism in patients with NVAF with one or more risk factors such as congestive heart failure, hypertension, age 75 years or more, diabetes mellitus, prior stroke or TIA.
- Treatment of DVT and PE and prevention of recurrent DVT and PE.

The adverse effects mainly include various types of bleedings such as cutaneous hemorrhage, epistaxis or mucosal hemorrhage. Rash, nausea, pruritus and abnormal liver function tests may also appear (17, 18).

For all of the above anticoagulants, doses need to be adjusted in renal insufficiency and information on all potential interactions and contraindications must be obtained from relevant summaries of product characteristics.

Antidotes for NOACs

Idarucizumab – the first approved specific antidote for dabigatran

The first antidote for NOACs has been introduced into clinical practice. Idarucizumab (Praxbind®), a reversal agent for dabigatran, was approved by regulatory authorities for use in the European Union and USA at the end of 2015; since January 2016, the drug has also been available in the Czech Republic. Idarucizumab is a humanized antibody fragment that specifically binds to dabigatran. The binding affinity of idarucizumab for dabigatran is approximately 300-fold more potent than that of dabigatran for thrombin. Its administration neutralizes the anticoagulant effect of dabigatran, without affecting any other parts of the coagulation cascade. In studies, idarucizumab was able to reverse the effect of dabigatran immediately, within several minutes from administration of a 5 g dose. The reversal of the effect was complete and permanent in nearly all patients. No serious adverse effects associated with the use of idarucizumab were shown; moreover, no procoagulant effect was observed following the administration of idarucizumab. Idarucizumab is currently available in 74 Czech hospitals. Its use is indicated in adult patients treated with dabigatran etexilate (Pradaxa) in situations when the anticoagulant activity needs to be rapidly reversed such as surgical/emergency procedures or life-threatening or uncontrolled bleeding. The recommended dose is 5 g (2× 2.5 g / 50 mL). There are no contraindications to its use; the dosage does not need to be adjusted in either elderly patients or those with impaired kidney or liver function. The plasma half-life of idarucizumab is short (approximately 10 hours). The approval and introduction of idarucizumab into practice changed the prior approach to the management of bleeding and other emergencies in patients using NOACs.

The following two drugs are under clinical investigation. **Andexanet alfa** is a recombinant derivative of factor Xa with no intrinsic catalytic activity; it binds to both direct and indirect factor Xa inhibitors. Only a partial effect is assumed in low-molecular-weight heparin as apart from factor Xa inhibition, these drugs, to a varying extent, act against thrombin. It has a shorter half-life so it should be administered as a bolus followed by continuous infusion. At the present time, a phase III clinical trial is under way. **Ciraparantag (Aripazine)** is a small synthetic molecule that noncovalently binds to unfractionated heparin, low-molecular-weight heparin, fondaparinux, dabigatran and xabans. Thus, it is a universal antidote. At present, a phase II clinical trial is under way (11, 12, 13).

Table 4 Interpretation and results of coagulation tests in patients treated with various NOACs

	Dabigatran	Apixaban	Rivaroxaban
Peak plasma concentration	2 hrs after administration	1-4 hrs after administration	2-4 hrs after administration
Minimum plasma concentration	12-24 hrs after administration	12-24 hrs after administration	16-24 hrs after administration
PT	unsuitable	unsuitable	prolonged PT may suggest an increased risk of bleeding; local calibration needed
INR	unsuitable	unsuitable	unsuitable
aPTT	> 2x ULN at a minimum concentration may suggest a higher risk of bleeding	unsuitable	unsuitable
dTT (Hemoclot)	at minimum: > 200ng/mL or >65 s: increased risk of bleeding	unsuitable	unsuitable
Chromogenic methods for determination of anti-Xa	unsuitable	quantitative, data on threshold levels for bleeding or thrombosis are not available	quantitative, findings should be compared with values in the rivaroxaban SPC
ECT	>3x ULN at a minimum concentration may suggest a higher risk of bleeding	unsuitable	unsuitable

Legend: PT – prothrombin time, INR – International Normalization Ratio used to express the Quick Test value, aPTT – activated partial thromboplastin time, dTT – diluted thrombin time, ECT – ecarin clotting time, ULN – upper limit of normal

Monitoring the effects of NOACs

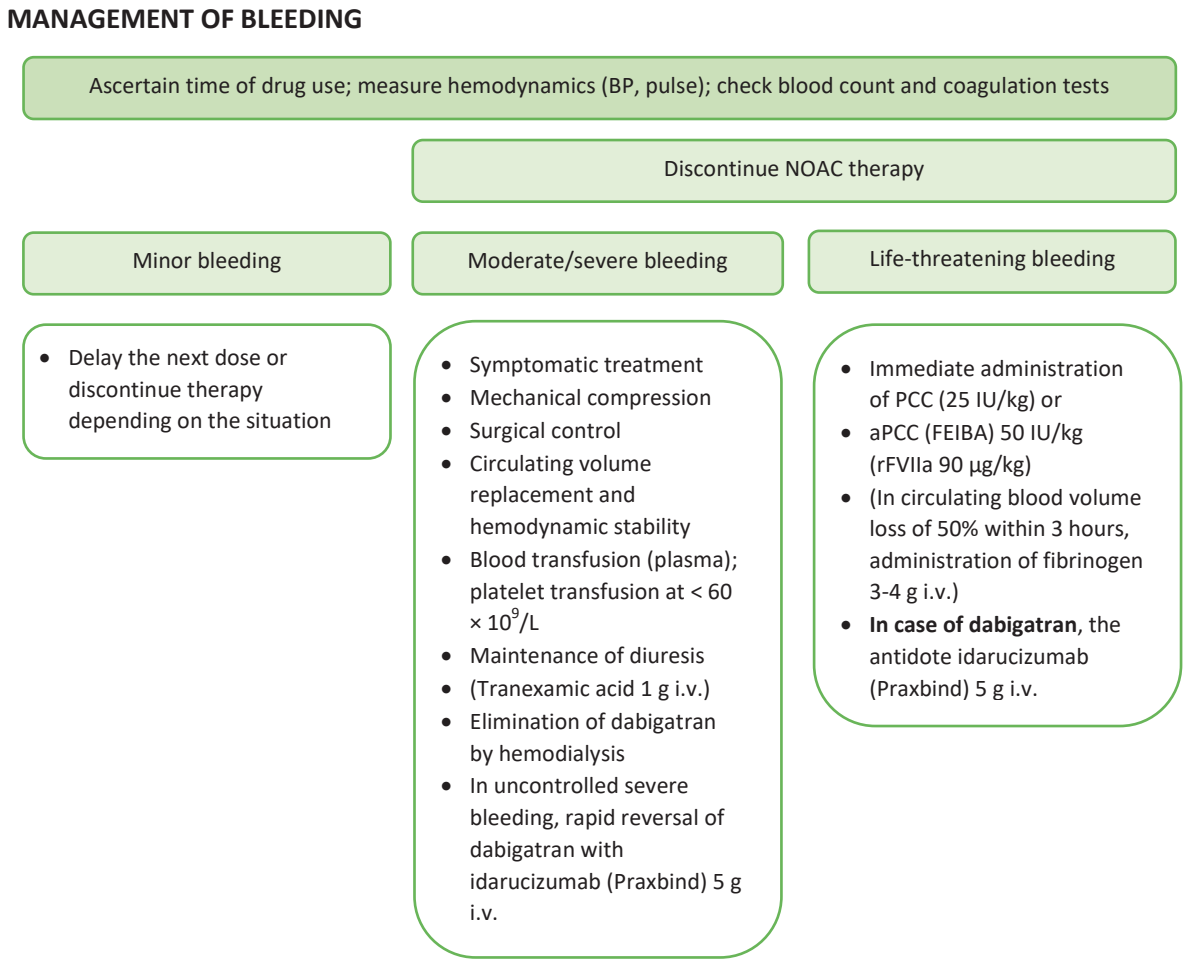
Table 4 summarizes tests currently recommended for monitoring treatment in probably the most common long-term applications of NOACs, that is, prevention of ischemic stroke and systemic embolism in patients with NVAF. However, they may also be used for monitoring NOACs in other indications. In any case, to assess the effect of a NOAC on hemostasis, it is essential to know when and in what dose the NOAC was last used by the patient. Given the short plasma half-life of the NOAC activity, this may suggest its concentration at a particular time and the impact on coagulation. In patients treated with NOACs, it is recommended to delay surgery until at least double the half-life. It means approximately 14–26 for patients treated with rivaroxaban, 20–30 hours for those treated with apixaban and up to 34 hours for those receiving dabigatran. Of importance are also kidney function, total clearance, other surgery-related bleeding risks, etc. (14) The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory tests. Unfortunately, a specific reversal agent for edoxaban is still unavailable.

Management of bleeding is shown in Figure 1. The updated guidelines of the Czech Society on Thrombosis and Hemostasis recommend administration of the specific antidote idarucizumab (Praxbind®) to patients treated with dabigatran in case of uncontrolled severe or life-threatening bleeding or in case of emergency procedures (15, 16).

OUTPUTS

NOACs have only been used for several years. Therefore, experiences with them will only gradually accumulate. Nevertheless, NOACs add to the anticoagulation treatment options, are undoubtedly beneficial in terms of treatment safety and efficacy and, last but not least, contribute to better patient comfort. On the other hand, certain questions arise that will only be answered with increasing clinical experiences with this therapy. These are mainly concerned with managing emergencies (bleeding, surgery), laboratory assessment of anticoagulation in certain situations and specific antidotes (11, 14). As already stated above, due to their older age and frequent comorbidities, patients may be encountered at most centers providing care in various specialties and at various levels of healthcare, from the general practitioner's office to specialized wards such as cardiology, diabetology or gerontology. Therefore, it is advisable to learn the basic facts concerning the issue that may be further used in common practice by both medical and non-medical health workers.

Figure 1 Management of bleeding in patients treated with NOACs according to the Czech Society on Thrombosis and Hemostasis guidelines



Legend: BP – blood pressure, aPCC – activated prothrombin complex concentrate, PCC – prothrombin complex concentrate, rFVIIa – recombinant coagulation factor VIIa

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