

## **Direct oral anticoagulants – a new chapter in anticoagulation therapy**

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### **Summary**

Thromboembolic events are the leading cause of morbidity and mortality worldwide. From the second half of the 20<sup>th</sup> century, vitamin K antagonists (VKAs), warfarin and acenocoumarol, were the only anticoagulants taken orally. The major reform in anticoagulation therapy was made by the advent of direct oral anticoagulants (DOACs), about 10 years ago. Direct thrombin inhibitor (dabigatran) and direct inhibitors of factor Xa (rivaroxaban, apixaban, edoxaban, and betrixaban) have demonstrated favorable risk/benefit ratio. Compared to warfarin, DOACs are associated with a predictable pharmacokinetic profile, lower severe bleeding complications, particularly intracranial hemorrhages, and minimal drug interactions. Moreover, DOACs achieve a rapid onset of action and have shown comparable efficacy with warfarin and low molecular weight heparin (LMWH) in clinical trials. As a result, DOACs are now replacing VKAs and LMWH for many indications including stroke and systemic embolism prevention in nonvalvular atrial fibrillation, prevention, and treatment of venous thromboembolism and thromboprophylaxis following total knee/hip replacement surgery. In addition, rivaroxaban (in combination with aspirin alone or aspirin and clopidogrel) is used in the prevention of atherothrombotic events following acute coronary syndrome with elevated cardiac biomarkers. In case of severe bleeding complications under DOACs treatment, antidotes are available; idarucizumab for dabigatran reversal and andexanet alfa for rivaroxaban and apixaban.

**Key words:** direct oral anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban

## Introduction

Nonvalvular atrial fibrillation (NVAf) and acute venous thromboembolism (VTE) are associated with significant morbidity and mortality. Atrial fibrillation is the most prevalent treated arrhythmia, with 33.5 million patients worldwide, and its prevalence is increasing, making this a global epidemic (1). Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), comes right after a heart attack and stroke as a leading cardiovascular diagnosis (2). It is estimated that one in four deaths worldwide comes as a result of thrombosis (3).

Therefore, given the burden of these diseases, the treatment of thromboembolic events is a great medical challenge. Anticoagulation therapy is a mainstay for the prevention and therapy of VTE and prevention of cardioembolism in AF or patients with valvular heart disease. Rapidly acting parenteral anticoagulants have been used for prevention and initial treatment of thrombosis, whereas oral agents have been used for long-term therapy (4).

For more than 50 years, warfarin and acenocoumarol, vitamin K antagonists (VKAs) have been the gold standard in oral anticoagulation therapy. Albeit they are effective, VKAs have numerous limitations. These drugs have a narrow therapeutic range, slow onset and offset of action, predisposition to drug and dietary interactions and need for frequent monitoring of the international normalized ratio (INR) (5). These disadvantages of VKAs led to the development of new oral anticoagulants (non-vitamin K antagonists or direct oral anticoagulants) (6).

Direct oral anticoagulants (DOACs) represent novel direct-acting medications that directly inhibit one activated coagulation factor, which is thrombin for dabigatran and factor Xa for rivaroxaban, apixaban, edoxaban, and betrixaban (7). Compared with VKAs and low molecular weight heparin (LMWH), non-vitamin K antagonists are more convenient for administration. Unlike VKAs, they can be given in fixed doses with no necessity for routine monitoring of coagulation and are not invasive as LMWH (8, 9). Moreover, DOACs were found to be at least as effective as VKAs with less serious bleeding events compared to warfarin in the treatment of NVAf and for the treatment of VTE (10, 11).

Owing to their convenience of use, safety profile, comparable efficacy with VKAs, and LMWH, DOACs are changing the landscape of anticoagulation therapy. However, as the market is supplied with a wide variety of agents, it could be quite challenging to choose the most appropriate DOAC. Therefore, in this work, representatives of DOACs, their clinical indications, advantages/disadvantages, and differences will be discussed.

## Indications for the DOACs

The approved indications and dosage regimens of DOACs are listed in Table I.

**Table I** Indication and dosage regimens of DOACs (12,13)

**Tabela I** Indikacije i režim doziranja DOAK-a (12,13)

	<b>Dabigatran</b>	<b>Rivaroxaban</b>	<b>Apixaban</b>	<b>Edoxaban</b>
<b>Brand names</b>	Pradaxa	Xarelto	Eliquis	Lixiana
<b>Prevention of stroke and systemic embolism in NVAf</b>	150 mg bid;  110 mg bid in patients with moderate renal impairment (CrCl 30-50 mL/min), age ≥ 75yr or with P-gp inhibitors	20 mg od;  15 mg od in patients with moderate renal impairment (CrCl 15-49 mL/min);  <i>Taken with the evening meal</i>	5 mg bid;  2.5 mg bid in patients with at least 2 of 3: age ≥ 80yr, weight ≤ 60kg; SCr ≥ 15 mg per 100 ml;  2.5 mg in patients with severe renal impairment (CrCl 15-29 mL/min) or with strong CYP3A4/P-gp inhibitors	30 mg od in patients with weight < 61 kg or with cyclosporin, erythromycin, or in patients with renal impairment (CrCl 15-50 mL/min);  60 mg od in patients with weight ≥ 61 kg
<b>Treatment of DVT and PE and prevention of recurrent DVT and PE</b>	150 mg bid;  110-150 mg bid in patients with age: 75-79 yr or moderate renal impairment;  110 mg bid in patients with age ≥ 80yr; with P-gp inhibitors  <i>after 5 days treatment with a parenteral anticoagulant</i>	15 mg bid for 21 days, then 20 mg od (reduction to 15 mg after evaluating for bleeding risk and renal impairment)  <i>Taken with the evening meal</i>	10 mg bid for 7 days, then maintenance 5 mg bid	30 mg od in patients with weight < 61 kg or with cyclosporin, erythromycin or in patients with renal impairment (CrCl 15-50 mL/min);  60 mg od in patients with weight ≥ 61 kg  <i>after 5 days treatment with a parenteral anticoagulant</i>
<b>Prevention of VTE following knee/hip replacement surgery</b>	110 mg 1-4h after surgery, then 220 mg od (10 days for knee, 28-35 days for hip);  75 mg 1-4h after surgery, then 150 mg od (10 days for knee, 28-35 days for hip) in patients with moderate renal impairment or age ≥ 75yr or with P-gp inhibitors	10 mg od 6-10h after surgery (5 weeks for hip, 12-14 days for knee);  <i>Taken with the evening meal</i>  <i>not recommended in patients with severe renal impairment</i>	2.5 mg bid 12-24h after surgery (32-38 days for hip, 10-14 days for knee)	NI
<b>Prevention of atherothrombotic events following an ACS</b>	NI	2.5 mg bid with ASA or ASA + clopidogrel or ticlopidine	NI	NI

ACS = acute coronary syndrome, CrCl = Creatinine clearance, bid = twice daily, od = once daily, SCr = serum creatinine, NI = not indicated, ASA = acetylsalicylic acid

## **Dabigatran Etexilate**

Dabigatran etexilate was the first approved DOAC; it was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in 2008 and 2010, respectively (14, 15). It is a small molecule, prodrug of dabigatran, competitive and reversible direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin, thereby preventing clot formation (16).

**Pharmacokinetic profile.** After oral administration takes place, dabigatran etexilate is rapidly absorbed and completely converted to dabigatran via esterase-catalyzed hydrolysis in plasma and liver. The absolute oral bioavailability of dabigatran is approximately 3-7% with no impact from food intake. It is formulated as a hard capsule filled with pellets coated with dabigatran etexilate mesylate. When the pellets are administered without the capsule shell, the oral bioavailability of dabigatran is increased by 75% (13,16). Therefore, patients should be advised not to take medication without the capsule shell. Dabigatran plasma protein binding is relatively low (35%). Its elimination is occasioned predominantly via renal excretion of the unchanged drug (80%) (17). Pharmacokinetic characteristics of dabigatran etexilate are displayed in Table II.

**Potential drug interactions.** Dabigatran does not inhibit cytochrome P450 (CYP), but it is a substrate for P-glycoprotein (P-gp) (16). Hence, there is a potential for interaction when it is coadministered with P-gp inhibitors/inducers. Concomitant use of dabigatran and some strong inhibitors of P-gp (e.g. cyclosporin, itraconazole) may increase plasma dabigatran concentrations to a clinically relevant degree, which may lead to an increased bleeding risk. Thus, these combinations are contraindicated (13). Mild to moderate inhibitors of P-gp (e.g. amiodarone, posaconazole, ticagrelor, and verapamil) and dabigatran ought to be administered with caution. Dosage adjustment of dabigatran etexilate is required when it is used with verapamil. Concomitant use of dabigatran etexilate with P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, hypericum) should be avoided (16).

**Efficacy of dabigatran etexilate.** In the RE-LY (prospective, randomized, open-label, multicenter study including 18113 patients), dabigatran etexilate (110 mg or 150 mg twice daily intake), confirmed efficacy in the prevention of stroke and systemic embolism in patients with NVAF compared to warfarin. Higher dose significantly reduced risk of stroke and systemic embolism by 35% compared to warfarin (the incidence was 1.11% with dabigatran vs 1.71% with warfarin). Intracranial haemorrhage was significantly lower with dabigatran 150 mg in comparison to warfarin but major gastrointestinal (GI) bleeding was increased by 50% compared to warfarin. A lower dose of dabigatran was shown to be non-inferior compared to warfarin in reducing stroke and systemic embolism with a 20% lower incidence of major bleeding events whilst the risk of major GI bleeding was similar to that of warfarin (18,19). The major bleeding is defined as a bleeding event resulting in death, symptomatic bleeding in a critical

area/organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome), or a hemoglobin fall of 2 g/dL (1.24 mmol/L) or more (20). Both dabigatran doses resulted in a non-significant numerical increase in the rate of myocardial infarction (MI) (18, 19). Although this has not been confirmed in real-world data, it might not be the best option for patients with an increased risk of MI (21). The safety outcomes of RE-LY study are listed in Table III.

In the RE-COVER and RE-COVER II (two double-blind randomized, multicenter studies including 5153 patients) dabigatran was used in patients with acute VTE and was proved to be equally efficacious compared to warfarin in the prevention of recurrent VTE or VTE related to death. The rate of major bleeding was 0.9% with dabigatran in comparison to 1.8% with warfarin (22).

In the large, randomized, double-blind trials, RE-MODEL, RE-NOVATE and RE-NOVATE II (including 2076, 3494 and 2055 patients respectively) dabigatran etexilate and enoxaparin were found to be equally efficacious in patients undergoing hip/knee replacement surgeries. In addition, there were no significant differences in terms of the bleeding complications between the groups. Furthermore, the cost-utility analysis indicated that dabigatran etexilate 220 mg once daily intake was not only effective but also economically more favorable in comparison to enoxaparin (23).

***Adverse effects and contraindications.*** Dabigatran etexilate is generally well tolerated. The most common adverse effects of dabigatran are dyspepsia (>10%), dizziness, dyspnea, and peripheral oedema (13,16). However, the rate of GI bleeding is significantly higher with dabigatran compared to warfarin (16). General contraindications for all antithrombotic drugs are active bleeding and risk factors for major bleeding. Manufacturers advise for all DOACs to be avoided during pregnancy/breastfeeding. DOACs are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular, for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy. Besides, caution is needed if DOACs are used with other anticoagulants or drugs affecting bleeding, including NSAIDs and antiplatelet drugs (13). In particular, dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) < 30 mL/min) (13). In 2015, idarucizumab, a specific reversal agent for dabigatran was approved by EMA in case of life-threatening bleeding or before emergency surgery (24).

## **Rivaroxaban**

Rivaroxaban was the first direct oral factor Xa inhibitor receiving the authorization for clinical use in 2008 by EMA (25). It is the only DOAC which has as official indication prevention of atherothrombotic events following an acute coronary syndrome with

elevated cardiac biomarkers (in combination with aspirin alone or aspirin and clopidogrel) (26).

**Pharmacokinetic profile.** Rivaroxaban is absorbed rapidly and almost completely. The absolute bioavailability is relatively high (80-100%) with the 10 mg tablet dose, independently on fasting or fed conditions. In contrast, the rate of absorption and bioavailability of higher doses decrease without food (25). Therefore, tablets of rivaroxaban higher doses (15 or 20 mg) should be administered with food. Binding to the plasma proteins reaches about 92-95% (27). Approximately 28% of the drug is excreted in the feces and about 66% via the kidneys; 33% as unchanged drug and the remainder as inactive metabolites (28). Pharmacokinetic characteristics of rivaroxaban are listed in Table II.

**Potential drug interactions.** Rivaroxaban is metabolized in the liver by CYP-P450 isoenzyme CYP3A4 and is a substrate for P-gp (27). Therefore, concomitant use with drugs interfering with CYP3A4/P-gp may influence exposure to rivaroxaban. Coadministration of rivaroxaban with strong CYP3A4 and P-gp inhibitors (e.g. itraconazole, HIV-protease inhibitors) is not recommended due to significantly increased exposure to rivaroxaban and consequently increased bleeding risk (13). Concomitant use of rivaroxaban with strong P-gp and CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, hypericum) ought to be used with caution (27). In patients with renal failure, coadministration of P-gp and weak/moderate CYP3A4 inhibitors (e.g. verapamil, amiodarone, diltiazem, azithromycin, and erythromycin) should be considered using only if benefits outweigh the possible risks (29).

**Efficacy of rivaroxaban.** In the ROCKET-AF (double-blind, prospective, multicenter study including 14264 patients with NVAF), rivaroxaban was compared with warfarin in the prevention of stroke and systemic embolism in patients with NVAF. Rivaroxaban reduced stroke or systemic embolism by 21% compared to warfarin (the incidence was 2.1% with rivaroxaban vs 2.4% with warfarin). There was a significant reduction in intracranial haemorrhage (the rates were 0.5% vs 0.7%) but an increase in major GI bleeding events (the rates were 2.0% vs 1.24%) compared to warfarin (30). The safety outcomes of ROCKET-AF study are listed in Table III.

In EINSTEIN DVT and EINSTEIN PE (randomized, open-label multicenter studies including 3449 and 4845 patients, respectively), the efficacy and safety of rivaroxaban were compared to LMWH/VKA for the acute treatment of symptomatic DVT and PE, respectively. Rivaroxaban demonstrated similar efficacy (the rate of VTE recurrence was 2.1% with rivaroxaban vs 2.3% with LMWH/VKA) compared to traditional treatment of VTE and was associated with significantly less major bleeding events (the incidence was 1.0% vs 1.7%) (28).

The four randomized, double-blind, multicenter trials including 12729 patients in the RECORD program compared the efficacy and safety of rivaroxaban and enoxaparin

for VTE prevention after total hip/knee arthroplasty. Rivaroxaban was proved to be as effective as enoxaparin with low major bleeding events indicating it may be used instead of traditional parenteral therapy in patients undergoing major orthopaedic surgeries (28).

SELECT-D trial (randomized, multicenter, open-label, pilot trial including 406 patients) compared the efficacy of rivaroxaban with dalteparin in patients with active cancer and VTE. Active cancer is defined as a diagnosis of cancer (excluding basal-cell or squamous-cell skin carcinoma) in the previous 6 months, recurrent or metastatic cancer, or cancer not in complete remission (hematologic malignancy). Rivaroxaban showed a beneficial effect with regard to VTE recurrence comparing to dalteparin, the rate was 4% with rivaroxaban and 11% with dalteparin. The major bleeding was 6% with rivaroxaban and 4% with dalteparin, followed by significantly higher clinically relevant non-major (CRNM) bleeding with rivaroxaban compared to dalteparin, 13% and 4%, respectively. CRNM bleeding is defined as any sign or symptom of bleeding that is not considered as major bleeding but does include one of the following: requirement for medical intervention, leading to hospitalization or need for a face to face evaluation (i.e. not just telephone or electronic communication) (20). Major bleeding was higher in patients with esophageal or gastroesophageal cancers with rivaroxaban than with dalteparin, 36% and 11% respectively. Therefore, in patients with GI cancer (particularly with esophageal or gastroesophageal cancers), LMWH remains the first-line option (31).

***Adverse effects and contraindications.*** The most common side effect is bleeding. Rates of major and CRNM bleeding were no different between warfarin and rivaroxaban, but there were more GI bleeds with rivaroxaban compared to warfarin. Nausea and increases in liver enzyme values may also occur; other GI effects, pruritus, rashes, and renal impairment have been reported but are uncommon (0.1% to 1%) (13). There are no data available for rivaroxaban use in patients with CrCl <15 mL/min, and it is not recommended in this patient group, it is also contraindicated in patients with hepatic disease and clinically significant active bleeding or conditions that constitute a major bleeding risk (28). In April 2019, EMA approved andexanet alfa for management of life-threatening or uncontrollable bleeding in patients taking rivaroxaban (32).

**Table II** Pharmacokinetic characteristics of DOACs (9,13,41)**Tabela II** Farmakokinetičke karakteristike DOAK-a (9,13,41)

Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
<b>Target</b>	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa	Factor Xa
<b>Bioavailability</b>	3-7%	15 mg/20 mg: 66% without food, 80–100% with food	50%	62%	34%
<b>Time to peak activity</b>	0.5-2 h	2-4 h	3-4 h	1-2 h	3-4 h
<b>Half-life</b>	12-17 h	7-11 h	12 h	10-14 h	19-27 h
<b>Protein binding</b>	35 %	92-95%	87%	55%	60%
<b>Dosing frequency</b>	Twice daily	Once or Twice daily	Twice daily	Once daily	Once daily
<b>Drug interactions</b>	P-gp	CYP3A4/P-gp	CYP3A4/P-gp	P-gp	P-gp
<b>Renal elimination</b>	80%	33% (66%)	27%	35%	17.8%

### Apixaban

Apixaban is the third DOAC approved by EMA in 2011 (33). It is a reversible direct factor Xa antagonist. In July 2020, generic versions of apixaban were approved by EMA (34).

**Pharmacokinetic profile.** Apixaban is rapidly absorbed after oral administration and its bioavailability is approximately 50% with a dose up to 10 mg (35). However, for oral doses  $\geq 25$  mg, absorption is dissolution-limited and bioavailability is reduced. Apixaban may be taken on an empty or full stomach (35). The plasma protein binding of apixaban is approximately 87%. Compared with other DOACs, apixaban is to a smaller extent eliminated by the kidneys (~27%) and might be an optimal choice by clinicians in patients with modest renal impairment (36). Pharmacokinetic characteristics of apixaban are listed in Table II.

**Potential drug interactions.** Apixaban is predominantly metabolized by CYP3A4 isoenzyme and is also a substrate for P-gp transporter proteins (13). Concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g. itraconazole, voriconazole, posaconazole, ritonavir or clarithromycin) increases apixaban exposure and risk of bleeding and is not recommended in the EU (35). Concomitant use of apixaban with strong inducers of CYP3A4 and P-gp (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone) is not recommended as may decrease the efficacy of the anticoagulant agent. Administration of activated charcoal can decrease apixaban concentration by 50% when given 2 hours after a single dose of apixaban and may be used in the management of apixaban overdose (35).



***Efficacy of Apixaban.*** In the ARISTOTLE (randomized, double-blind, multicenter, trial including 18 201 patients), apixaban (5 mg twice daily) reduced stroke or systemic embolism in patients with NVAF by 21% compared with warfarin (the rate of stroke and systemic embolism was 1.27% with apixaban compared to 1.6% with warfarin). On the other hand, the safety profile was also more favorable with apixaban, there was a 31% reduction in major bleeding compared to warfarin (the rate was 2.13% with apixaban vs 3.09% with warfarin), in particular with intracranial haemorrhage (0.33% vs 0.80%) and haemorrhagic stroke (0.24% vs 0.47%) (37,38). Additionally, one of the advantages over other DOACs was less GI bleeding events. Rates of major GI bleeding were similar between two treatments (0.76% with apixaban vs 0.86% with warfarin) indicating apixaban may be preferred over dabigatran and rivaroxaban in patients with the risk of GI bleeding (38). The safety outcomes of ARISTOTLE study are listed in Table III.

In AMPLIFY (randomized, double-blind, study including 5395 patients), apixaban demonstrated to be non-inferior to traditional anticoagulant therapy (enoxaparin overlapped with and followed by warfarin) in the treatment of adults with acute VTE over 6 months. Additionally, apixaban was shown to be safer compared with enoxaparin/warfarin with a significantly lower incidence of major and the CRNM bleeding (35).

In ADVANCE, randomized double-blind multicenter clinical trials, including 8464 patients undergoing knee/hip replacement surgery, apixaban was found to be more effective compared to enoxaparin without increased incidence of bleeding (39).

CARAVAGGIO trial (prospective, randomized, open-label clinical trial including 1168 patients) compared apixaban with dalteparin in patients with cancer and acute proximal DVT and/or PE. The recurrence of VTE was 5.6% with apixaban and 7.9% in dalteparin group. The rate of major bleeding was 3.8% in the apixaban group and 4.0% in the dalteparin group whereas the incidence of major GI bleeding was 1.9% with apixaban compared to 1.7% with dalteparin (40). This implies apixaban might be safe enough to be used in patients with GI cancer but further studies are needed to confirm this.

***Adverse effects and contraindications.*** The same as with other anticoagulants, the most serious and potentially life-threatening adverse effect of apixaban is bleeding. In clinical trials, apixaban has shown superiority to enoxaparin/warfarin concerning the risk of major bleeding (35). Other common side effects (with incidence 1% to 10%) besides bleeding include nausea, anemia, an increase in liver transferases/transaminases and skin reactions (33). In case of life-threatening or uncontrolled bleeding, EMA approved andexanet alfa in 2019 for apixaban reversal (32).

## Edoxaban

Edoxaban was the third approved oral direct factor Xa inhibitor, initially approved in Japan in 2011, following by EMA and FDA approval in 2015 (41,42). It has been approved for two indications in Europe: prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors and treatment/prevention of DVT and PE in adults (43). In Japan, edoxaban is also indicated for VTE prevention in patients undergoing hip fracture surgery (41).

**Pharmacokinetic profile.** Edoxaban demonstrated linear pharmacokinetics at the therapeutic doses. It is rapidly absorbed (1-3 hours) with an oral bioavailability of approximately 61.8% (41). It can be taken with or without food. The majority of the drug (73%) is eliminated unchanged via urine (35%) and feces (62%). Interestingly, edoxaban is associated with a lower relative efficacy in patients with NVAF compared with warfarin in patients with a CrCl > 95 mL/min. Because of this, EMA suggests using edoxaban in patients with high CrCl after a careful evaluation of the risk/benefit ratio (9). Pharmacokinetic characteristics of edoxaban are listed in Table II.

**Potential drug interactions.** In contrast with rivaroxaban and apixaban, edoxaban is minimally metabolized by CYP3A4 (<4%) (44). Therefore, the risk of potential interactions of edoxaban with other drugs is low. However, edoxaban is a substrate for P-gp and thus not completely devoid of potential drug interactions. Consequently, when administered with potent P-gp inhibitors (e.g. itraconazole, voriconazole, erythromycin) dose should be halved. By contrast, when administered with amiodarone or verapamil, no dose adjustment is required. Edoxaban can be safely taken with itraconazole or voriconazole (by halving the dose) (44).

**Efficacy of Edoxaban.** In the ENGAGE AF-TIMI 48 (a randomized, double-blind multicenter clinical trial including 21105 patients), edoxaban (60 mg and 30 mg once daily) was proved to be non-inferior compared to warfarin in the prevention of stroke and systemic embolism in patients with NVAF (the stroke and systemic embolism occurred in 1.29% patients with warfarin vs 1.00% and 1.79% with edoxaban, 60 mg and 30 mg, respectively). Moreover, the higher dose of edoxaban significantly reduced major bleeding events by 20% compared with warfarin, whilst the lower dose significantly reduced major bleeding events by 53% (45). The safety outcomes of ENGAGE AF-TIMI 48 study are listed in Table III.

The Hokusai-VTE (randomized, double-blind, multicenter study including 8292 patients) examined the efficacy and safety of edoxaban for the treatment of VTE compared with warfarin after the initial course with heparin. This study found that edoxaban is as effective as warfarin with a better safety profile for the treatment of VTE (46).

Hokusai VTE Cancer trial (randomized, open-label, multicenter clinical trial including 1050 cancer patients) compared the efficacy and safety of edoxaban (60 mg

once daily) with subcutaneous dalteparin (200 IU/kg once daily for 1 month, then 150 IU/kg once daily) in cancer patients with proximal DVT, acute symptomatic or incidental PE for 6-12 months. Edoxaban has shown similar efficacy and safety compared to dalteparin. The incidence of VTE recurrence was 7.9% with edoxaban compared to 11.3% with dalteparin. The rate of major bleeding was 6.9% with edoxaban and 4% with dalteparin. This difference is mainly because of the higher upper GI bleeding with edoxaban, predominantly seen in GI cancer patients (47). Therefore, in patients with GI cancer, edoxaban should be avoided.

**Adverse effects and contraindications.** Besides bleeding, other common adverse effects (with incidence 1% to 10%) are anemia, nausea, skin reactions (12).

### **Betrixaban**

Betrixaban is the last DOAC, direct Xa inhibitor available, approved in 2017 by the FDA for extended thromboprophylaxis in hospitalized acute medically ill patients at risk of VTE; it has not been approved in the EU yet (48).

**Pharmacokinetic profile.** Betrixaban has rather different pharmacokinetic properties from other DOACs, particularly with regard to low renal clearance and minimal metabolism by CYP enzymes. Betrixaban is rapidly absorbed, with a bioavailability of approximately 34% and peak plasma concentration after 3–4 h. Bioavailability is lowered when taken with fatty food. The plasma protein binding of betrixaban is approximately 60%. It has the longest half-life compared with other DOACs, therefore it is administered once daily. Betrixaban is primarily excreted in the gut (85%), mostly unmetabolized (49). Pharmacokinetic characteristics of betrixaban are listed in Table II.

**Potential drug interactions.** Opposite to apixaban and rivaroxaban, betrixaban has a minimal metabolism by CYP enzymes (<1%) and does not induce/inhibit CYP-P450 activity. As betrixaban is a substrate for P-gp, concomitant use with P-gp inhibitors (e.g., amiodarone, azithromycin, verapamil, clarithromycin) carries increased bleeding risk and in that case, a dose of betrixaban should be reduced (48,49).

**Efficacy of Betrixaban.** Betrixaban has a long half-life, low renal elimination, and minimal metabolism by CYP enzymes making it especially convenient for the acute medically ill patients. Furthermore, it is not contraindicated in patients with severe renal impairment (dose reduction indicated) and has a low predisposition for drug interactions (dose reduction indicated for patients on P-glycoprotein inhibitors) (49).

In the APEX, randomized, multicenter clinical trial (including 7513 patients), betrixaban was compared with a standard enoxaparin regimen for thromboprophylaxis in patients hospitalized with an acute medical illness. Patients were included in the trial if they were 40 years of age or older, had been hospitalized for less than 96 hours for a specified acute medical illness, and had reduced mobility and other specific risk factors

for VTE. Oral betrixaban administered over approximately 40 days was found to be more effective comparing to subcutaneous enoxaparin administered over approximately 10 days. The risk of major bleeding was similar between the two drugs; however, the combined risk of major bleeding and CRNM bleeding was higher with betrixaban (48).

**Table III** Safety comparison of DOACs with warfarin in patients with NVAF (54)

**Tabela III** Bezbednost DOAK-a u poređenju sa varfarinom kod pacijenata sa NVAF (54)

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind		Randomized, double-blind		
No. of patients	18113			14264		18201		21105		
Duration (years)	2			1.9		1.8		2.8		
Randomized groups	warfarin vs. dabigatran (150 mg bid, 110 mg bid)			warfarin vs. rivaroxaban 20 mg od		warfarin vs. apixaban 5 mg bid		warfarin vs. edoxaban (60 mg od, 30 mg od)		
Adverse effects, %/ year										
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
MB	3.61	3.40	2.92	3.45	3.60	3.09	2.13	3.43	2.75	1.61
ICB	0.77	0.32	0.23	0.74	0.49	0.80	0.33	0.85	0.39	0.26
GI MB	1.09	1.60	1.13	1.24	2.00	0.86	0.76	1.23	1.51	0.82
MI	0.64	0.81	0.82	1.12	0.91	0.61	0.53	0.75	0.70	0.89
HS	0.38	0.10	0.12	0.44	0.26	0.47	0.24	0.47	0.26	0.16
Death from any cause	4.13	3.64	3.75	2.21	1.87	3.94	3.52	4.35	3.99	3.80

MB = Major bleeding; ICB = Intracranial bleeding; GI MB = Gastrointestinal major bleeding; MI = Myocardial infarction; HS = Haemorrhagic stroke; od = once daily; bid = twice daily

### Concomitant use of antiplatelet agents and DOACs in patients with NVAF and coronary artery disease

Given the fact that patients with AF often have an acute coronary syndrome (ACS) or are undergoing percutaneous coronary intervention (PCI), concomitant use of

antiplatelet agents and oral anticoagulants is often inevitable (50). Until recently, common guidelines for patients with AF and ACS or undergoing PCI, recommended the use of three medications in so-called triple therapy which include dual antiplatelet therapy (DAPT) – aspirin and clopidogrel combined with oral anticoagulation therapy, usually VKA for 6 months followed by a combination of VKA and one antiplatelet agent up to 12 months, after which lifelong therapy with VKA ought to be continued (50). Recently, there has been published four randomized controlled trial clinical trials (The PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PC trial) comparing DOACs (rivaroxaban, dabigatran, apixaban and edoxaban) with conventional treatment (VKA-based combination triple therapy) in patients with AF and recent ACS or undergoing PCI. The results of these studies showed the similar efficacy between dual therapy (one DOAC plus P2Y<sub>12</sub> inhibitor) and conventional triple therapy (VKA plus aspirin plus P2Y<sub>12</sub> inhibitor) with significantly less major bleeding (including intracranial haemorrhage) in patients with dual therapy (50,51,52,53). It should be noted that both, the PIONEER AF-PCI and the RE-DUAL PCI trial demonstrated a lower incidence of bleeding with DOACs (rivaroxaban and dabigatran) without aspirin than with VKA therapy that included aspirin, hence it was not clear whether this result was due to the use of DOACs or to the removal of aspirin in therapy (50,51). In the AUGUSTUS trial, placebo (vs aspirin) and apixaban (vs VKA) regimens were related to significant reduction in bleeding (52).

### **Overview of DOACs – their advantages and disadvantages**

As we mentioned above, DOACs have various advantages over VKAs. They have demonstrated equal or even greater efficacy in the treatment of NVAf compared with warfarin. In general, DOACs are equally / more effective compared to warfarin in the treatment of stroke and systemic embolism, but the main strength of DOACs over warfarin is the reduction of intracranial haemorrhage by approximately 50%. In general, DOACs significantly reduced events of stroke and systemic embolism by 19% comparing to warfarin but the main strength of DOACs over warfarin is the reduction of intracranial haemorrhage by approximately 50%. On the other hand, they increased major GI bleeding by 24% compared with warfarin (10). DOACs have also demonstrated non-inferior efficacy compared to LMWH in the treatment of VTE (11). As DOACs can achieve a rapid onset of action, they can be used in all-oral regimens, thus replacing parenteral anticoagulants and warfarin for initial treatment and prevention of VTE. Some guidelines (e.g. NICE guidance) suggest using rivaroxaban and apixaban in all-oral regimens, obviating the need for a parenteral anticoagulant at the outset, whereas dabigatran and edoxaban are administered 5 days after initial treatment with LMWH. In patients with VTE and active cancer, new guidelines (NICE 2020) consider DOACs instead of LMWH if there is no contraindication for their use (e.g. CrCl < 15 mL/min, antiphospholipid syndrome) (55, 56). In addition, it should be emphasized that DOACs ought to be avoided in patients with GI cancers owing to their increased bleeding risk in this population based

on the results of clinical trials. With this wealth of evidence, guidelines give preference to the DOACs over VKAs for stroke and VTE prevention/treatment in most patients with NVAF and VTE (54, 56).

One of the advantages of DOACs is that they do not request dose titration and requirement for therapeutic monitoring in most patients. However, in some situations, (e.g. renal impairment, geriatrics, taking concomitant interfering medications, obesity, the need for emergency surgery) laboratory monitoring may be necessary. Laboratory tests used for a global assessment of the coagulation (such as activated partial thromboplastin time [aPTT], prothrombin time (PT) and INR) can be affected by the DOACs, but their levels do not accurately reflect their plasma concentrations. Dabigatran preferentially affects the aPTT, while Xa inhibitors preferentially affect PT. However, these tests ought to be standardized for their wider clinical use. In addition, owing to their rapid onset/offset of action, it is important to correlate laboratory tests with the last drug intake. Unlike warfarin, the INR is not suitable for the measurement of the anticoagulant effect of the DOACs (8).

Although DOACs undoubtedly have numerous advantages over VKAs and LMWH, they also have some limitations. For example, DOACs are not licensed in patients with valvular heart diseases or prosthetic heart valves. The RE-ALIGN study was discontinued due to the increased occurrence of thromboembolic and bleeding complications in patients with mechanical heart valves taking dabigatran compared with warfarin patients (57). In addition, there is a need for avoidance or dose adjustment in patients with renal failure or with concomitant use with P-gp/CYP-3A4 inhibitors/inducers. The short half-life which is in most cases preferable sometimes can be undesirable as it requires strict patient adherence (9). A significant issue also remains the cost of DOACs. However, as EMA approved the first generics of Eliquis (apixaban) tablets, this problem will be solved with the advent of generic drugs on the market in the foreseeable future (34).

As there are several representatives available, choosing adequate medication may be demanding. When it comes to deciding which drug to choose, clinicians should take into consideration patient comorbidities and individual preferences (Table IV). In patients with a history of GI bleeding, apixaban may be the most appropriate choice as it has been shown to have a similar or lower incidence of GI bleeding as warfarin (38). Dabigatran should be avoided in patients with dyspepsia or peptic ulcer disease, as symptoms can get worse (18). If patients prefer once-daily dosing, rivaroxaban or edoxaban are better options especially in patients with poor adherence. In patients with a history of MI, dabigatran should be avoided (18). In patients with significant renal impairment, some clinicians prefer apixaban over other DOACs because renal elimination may be lower with this agent (36). On the other hand, in patients with very high CrCl, edoxaban should be avoided (9). Finally, potential drug interactions may determine which DOAC to select.

For instance, concomitant use with CYP3A4 inhibitors/inducers may prevail over dabigatran and edoxaban due to their more favorable pharmacokinetic profile (16, 44).

**Table IV** Suggestions for the choice of DOACs in patient eligible for them (9)

**Tabela IV** Preporuke za izbor DOAK-a u pacijenata kod kojih su indikovani (9)

Characteristic	Drug of choice	Rationale
Recent gastrointestinal (GI) bleed	Apixaban	More GI bleeding with dabigatran, rivaroxaban and edoxaban compared with warfarin.
Dyspepsia or upper GI symptoms	Rivaroxaban, apixaban or edoxaban	Dyspepsia may occur in 10% of patients treated with dabigatran.
All- oral therapy	Rivaroxaban or apixaban	They are the only DOACs evaluated in all-oral regimens.
Creatinine clearance 30-50 mL/min	Rivaroxaban, apixaban or edoxaban	Less affected by renal impairment than dabigatran which has a renal clearance of 80%.
Creatinine clearance 15-29 mL/min	Apixaban	It has lower renal elimination compared to rivaroxaban, edoxaban, and dabigatran.
Recent acute coronary syndrome (ACS)	Rivaroxaban	Rivaroxaban is the only DOAC indicated in the prevention of atherothrombotic events following ACS.
Poor compliance with twice-daily dosing	Rivaroxaban or edoxaban	They are once-daily used.
Concomitant use with CYP3A4 inducers/inhibitors	Dabigatran or edoxaban	Dabigatran is not metabolized by CYP3A4 while edoxaban is metabolized to a small extent.
Acute medical illness	Betrixaban	Promising results in patients hospitalized with an acute medical illness.

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# Direktni oralni antikoagulansi – novo poglavlje u antikoagulantnoj terapiji

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## Kratak sadržaj

Tromboembolijski događaji predstavljaju vodeći uzrok morbiditeta i mortaliteta širom sveta. Od druge polovine 20. veka, antagonisti vitamina K (VKA), varfarin i acenokumarol bili su jedini dostupni oralni antikoagulantni lekovi. Pojava direktnih oralnih antikoagulanasa (DOAK), od pre 10-tak godina, donela je veliku promenu u antikoagulantnoj terapiji. Direktni inhibitor trombina (dabigatran) i direktni inhibitori faktora Xa (rivaroksaban, apiksaban, edoksaban i betriksaban) su pokazali povoljan odnos koristi i rizika. U poređenju sa varfarinom, DOAK pokazuju predvidljiv farmakokinetički profil, nižu incidencu ozbiljnog krvarenja posebno intrakranijalnog krvarenja i stupaju u mali broj interakcija sa drugim lekovima. Pored toga, DOAK imaju brz nastup dejstva i pokazali su komparabilnu efikasnost u poređenju sa varfarinom i niskomolekularnim heparinima (LMWH) u kliničkim ispitivanjima. Posledično, DOAK postepeno zamenjuju VKA i LMWH u mnogim indikacijama uključujući prevenciju moždanog udara i sistemskog embolizma kod pacijenata sa nevalvularnom atrijskom fibrilacijom, prevenciju i terapiju venskog tromboembolizma, kao i tromboprofilaksu nakon ugradnje veštačkog kolena/kuka. Dodatno, rivaroksaban (sa aspirinom ili kombinacijom aspirina i klopidogrela) je indikovano u prevenciji aterotrombotičnih događaja posle akutnog koronarnog sindroma, kod pacijenata sa povećanim srčanim biomarkerima. U slučaju pojave ozbiljnog krvarenja, dostupni su antidoti; idarucizumab za dabigatran i andeksanet alfa za rivaroksaban i apiksaban.

**Ključne reči:** direktni oralni antikoagulansi, dabigatran, rivaroksaban, apiksaban, edoksaban, betriksaban