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EXPERT OPINION

New EHRA guidelines on anticoagulant therapy in patients with atrial fibrillation: comments of Russian experts

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The experts of the European Heart Rhythm Association prepared new guidelines on oral anticoagulant therapy in patients with atrial fibrillation. These guidelines included a wide spectrum of practical aspects of the use of anticoagulant therapy. This document provides comments of the leading Russian experts on four main directions: general aspects of the use of new oral anticoagulants (NOA), control of NOA efficiency, NOA adverse effects and management of complications of NOA therapy, and practical aspects of NOA therapy in several groups of patients.

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The Congress of the European Heart Rate Association (EHRA) was held in Barcelona (Spain) on March 18–20, 2018, within the framework of which new guidelines on oral anticoagulant therapy in patients with atrial fibrillation were presented [1]. The document consists of 20 chapters that can be combined into 4 main areas: general aspects of the use of new oral anticoagulants (NOAC), monitoring of NOAC effectiveness, NOAC side effects, the elimination of complications, and practical aspects of the use of NOAC in certain groups of patients.

The leading Russian experts gave their comments on topical issues of NOAC use in patients with atrial fibrillation (AF) that are listed here below.

General aspects of NOAC use in patients with atrial fibrilation

Sergei G. Kanorskii (Krasnodar)

The process of NOAC expansion in the field of thromboembolism prevention, in particular, in AF patients is unfolding before our eyes. It can be expected that in the near future, the use of NOAC will be impossible only in patients with AF and mechanical valve prostheses, moderate/severe rheumatic mitral stenosis [2]. In the new edition of the EHRA guidelines, it is allowed to use NOAC in patients with AF and bioprosthetic heart valves, after surgical correction of mitral defect, and transcatheter implantation of the aortic valve.

The indication on the necessity of regular (at least once per year) monitoring of patients taking NOAC (assessment of haemoglobin levels, liver and kidney function) should attract physicians' attention. Laboratory blood tests should be carried out even more frequently in patients with reduced kidney function, in elderly and old people. At the same time, in daily work, clinical practitioners evaluate patients' kidney function by calculating glomerular filtration rate, whereas during large randomized NOAC-dedicated studies, renal function was determined by the creatinine clearance (using the Cockroft-Gault formula). Neither NOAC can be prescribed in case of creatinine clearance < 15 mL/min due to its accumulation in the body and consequently high risk of the haemorrhage. Reduced doses of rivaroxaban (15 mg once per day) or apixaban (2.5 mg twice per day) can be used in case of creatinine clearance of 15-30 mL/ min. Dabigatran cannot be used with creatinine clearance <30 mL/min, but within the values of 30-50 mL/min, its prescription in doses of 110 or even 150 mg is acceptable (depending on the risk of bleeding) 2 times per day (Figure 1).

It is necessary to withdraw NOAC 24-48h before any surgical intervention depending on bleeding risk.

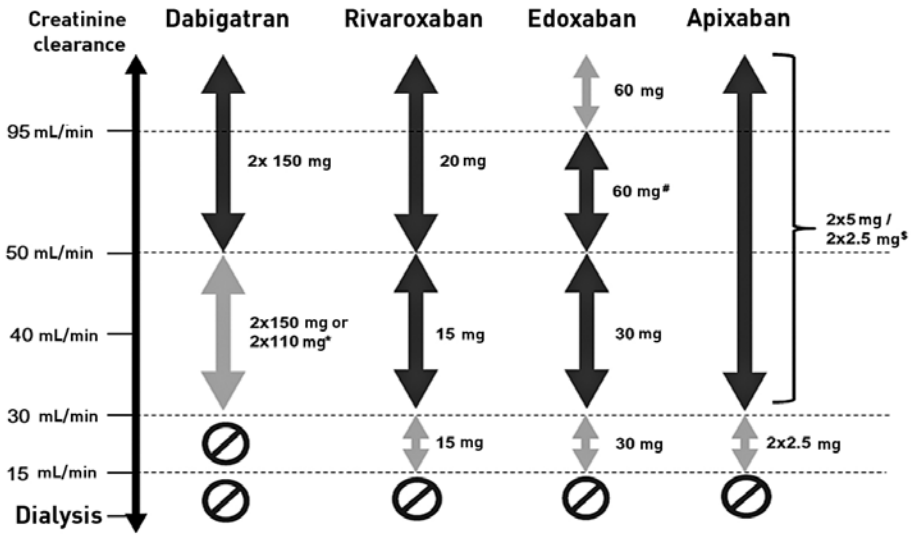


Figure 1. NOAC use depending on creatinine clearance

Meanwhile, in patients with chronic kidney disease (CKD) receiving dabigatran, the period between its cancellation and the surgical procedure should be, 48-96h, depending on the creatinine clearance.

In case of acute coronary syndrome (ACS) in a patient taking NOAC, percutaneous coronary intervention can be performed immediately, preferably using radial access. The duration of dual antiplatelet therapy after percutaneous coronary intervention in patients receiving NOAC should be reduced (no more than 3 months). After a period of dual therapy (NOAC + clopidogrel up to 12 months after percutaneous coronary intervention), which can also start directly after percutaneous coronary intervention, patients should be transferred to NOAC monotherapy.

NOAC therapy should be considered for resumption 3-14 days after ischemic stroke, depending on the degree of neurological deficiency and after exclusion of haemorrhagic transformation according to the results of computed tomography scan of the brain.

By now NOAC use in several clinical situations has not been well studied in major randomized clinical studies. Therefore, the updated European Heart Rhythm Association practical guidelines for the use of NOAC in patients with AF allow practitioners to make decisions in accordance with the consistent opinion of leading experts.

Control of NOAC efficiency

Sergei R. Gilyarevskii (Moscow)

Transfer of patients to another regimen of anticoagulant administration

When transferring patients from the use of one anticoagulant to the use of another one, one should be convinced of the continuity of anticoagulant therapy minimizing the risk of bleeding at the same time. Pharmacokinetic and pharmacodynamic features of various anticoagulants therapy regimens should be interpreted considering individual patient's characteristics [1].

Transfer from vitamin K antagonist (VKA) to a new oral anticoagulant (NOAC)

NOAC can be prescribed immediately if international normalized ratio (INR) is less than 2.0. If the INR corresponds to a range of 2.0-2.5, NOAC therapy can be started immediately or (preferably) the next day. If the INR is above 2,5 it is necessary to take into account both the INR values and the half-life of VKA in order to calculate the period during which the INR drops below the threshold level (the half-life of acenocoumarol, warfarin, phenprocoumon is 8-24, 36-48 and 120-200h, respectively).

The suggested scheme of transfer based on data from the patient information leaflets for these drugs is present on Figure 2. Briefly, NOAC administration may be started with the INR of 3.0 or less for rivaroxaban, 2.5 or less for edoxaban, and 2.0 or less for apixaban and dabigatran.

Transfer from NOAC to VKA

Given the slow onset of VKA action, it may take 5–10 days to reach the therapeutic range of INR; and this period can have significant individual variability. Therefore, NOAC and VKA should be administered contemporaneously until the INR reaches adequate therapeutic range. This approach is similar with the one used for administration of low molecular weight heparin (LMWH) together with the start of VKA treatment. Administration of the saturating dose of acenocoumarol and warfarin is not recommended, but such a method is acceptable when using fenprocoumone.

It should be remembered that NOAC administration may affect the results of INR measurement, therefore, it is important to follow these conditions: 1) The INR should be measured immediately before taking the next dose of NOAC during the combined therapy with VKA and NOAC; 2) The INR should be remeasured at early period after the cessation of NOAC therapy (in order to evaluate exclusively the effects of VKA administration) to prove the efficiency of anticoagulant treatment. Additionally, it is recommended to carefully monitor the INR levels during the first month until stable results are obtained (for example, INR in the range between 2,0 and 3,0 according to 3 consecutive analyses).

If combined use of NOAC during the start of VKA therapy is supposed to be inappropriate, during the initial period of VKA administration it is possible to temporally transfer the patients from NOAC to LMWH, that can be considered in several occasions, particularly in patients with high risk of developing thromboembolic complications.

Transfer from NOAC parenteral administration of anticoagulants

Parenteral administration of anticoagulants (unfractionated heparin – UFH) and LMWH can be started at the moment of suggested administration of another NOAC dose.

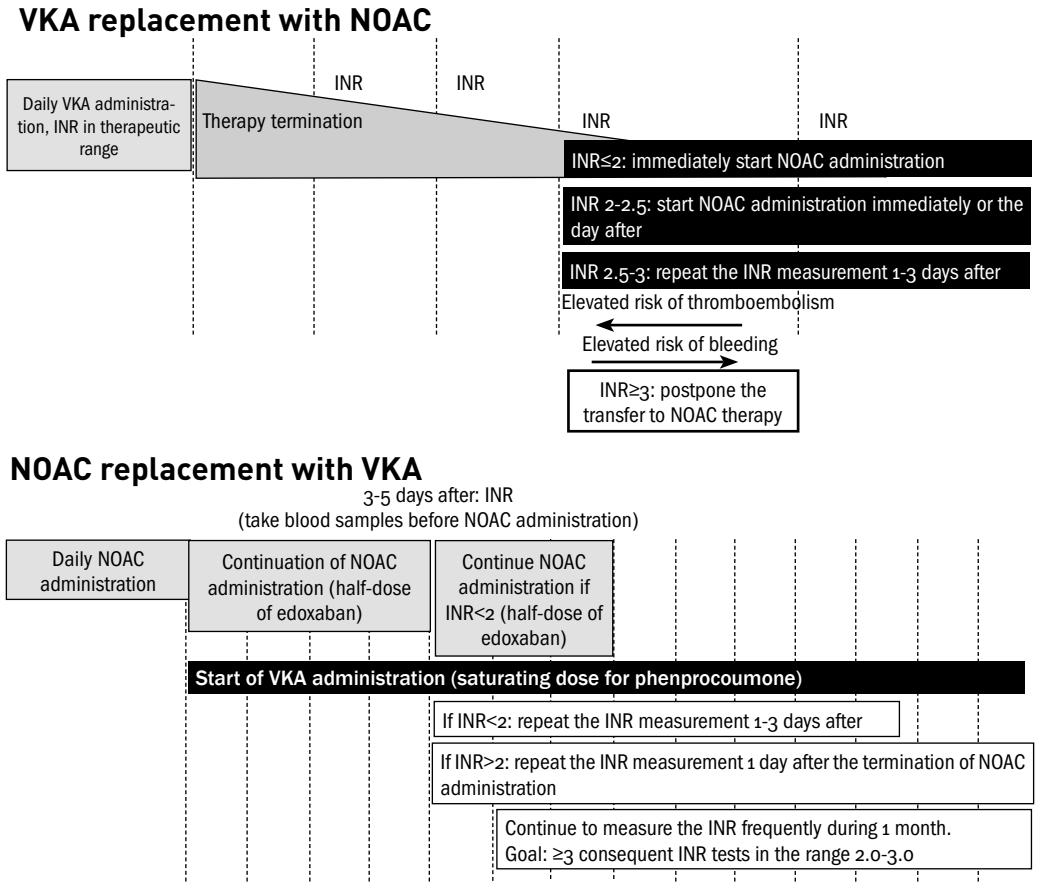


Figure 2. The scheme of NOAC replacement with VKA and vice versa.

Transfer from parenteral administration of anticoagulants to NOAC

Intravenous administration of UFH: NOAC administration normally may be initiated 2h (up to 4h after) after termination of UFH intravenous administration (half-life period of 2h).

LMWH: NOAC therapy may be started at the time of suggested administration of the next dose of LMWH. This requires particular caution in patients with impaired kidney function, since the time of LMWH elimination in these patients may be extended.

NOAC use in patients with CKD

Cinical decision on the tactics of treating a patient with AF in the presence of CKD, who needs to receive anticoagulants, should be based on the results of renal function assessment [3]. Several formulas are used for evaluation of kidney function, and each of them has distinct advantages and disadvantages. The CKD-EPI formula is recommended for calculating glomerular filtration rate (GFR) by the experts of the National Kidney Foundation, since its use provided reliable results for different stages of CKD. In case of NOAC administration it is more preferable to evaluate kidney function through creatinine clearance calculated with the Cockroft-Gault formula that has been used in numerous clinical studies. It is worth to highlight that it is possible to establish CKD diagnosis and to define its severity only in case of stable renal function but not in case of acute renal failure. In the latter case, creatinine level in the blood and calculated creatinine clearance may indicate only moderately reduced (or even normal) kidney function not reflecting the real severity of existing abnormalities. In case of acute renal failure NOAC therapy should be discontinued, and parenteral anticoagulant therapy should be prescribed (after careful comparison of risk and benefits).

Patients taking NOAC should be carefully monitored for renal function that should be evaluated not less frequently than once per year to detect changes in kidney function and perform adequate dose correction. If kidney function is impaired (if creatinine clearance is 60 mL/min and less) it is recommended to estimate renal function more often (the minimal frequency of these tests can be calculated using the following formula: creatinine clearance/10). Renal function should be assessed more frequently if additional risk factors (elderly age, weakness, several concomitant diseases, etc) are present, particularly

in case of treatment with dabigatran. Development of concomitant diseases (infections, acute heart failure, etc) may temporarily influence the kidney function, and it should be evaluated in such cases. Patient should know about the necessity of medical consultations in these situations.

It is worth to mention possible decrease of edoxaban (60 mg once per day) efficiency comparing with warfarin in patients with creatinine clearance ≥ 95 mL/min. Moreover, the results of secondary data analysis in patients included in studies dedicated to rivaroxaban and apixaban showed a similar pattern.

NOAC use in patients with mild or moderate CKD (creatinine clearance 30 mL/min or more)

According to the analysis of the main clinical trials of NOAC, the use of all 4 NOAC in patients with mild or moderate CKD is associated with stable efficiency and safety comparing with warfarin, similar with the treatment in the absence of CKD.

Moreover, the results of the ARISTOTLE study suggest a lower risk of bleeding when using apixaban compared with warfarin in these patients; and such benefits of apixaban became significantly more evident in case of lower creatinine clearance while maintaining benefits in reducing the risk of stroke [4]. On the contrary, the advantages of using 110 mg dabigatran compared with warfarin disappeared in patients with creatinine clearance less than 50 mL min while maintaining a similar risk of developing stroke compared with warfarin.

Using an appropriate dose of NOAC is particularly important for CKD patients. Despite the fact that rivaroxaban, apixaban and edoxaban doses were reduced according to kidney function in major randomized clinical trials (RCT), the RE-LY study randomized patients into the groups receiving dabigatran in dose of 150 mg twice per day or 110 mg twice per day without dose reduction in case of absence of renal failure [4]. It is recommended to use dabigatran in the dose of 110 mg twice per day in patients with creatinine clearance below 50 mL/min and high bleeding risk. Given the availability of 3 inhibitors of Xa factor, which are less excreted by the kidneys, the use of these drugs is preferable in patients with impaired renal function. NOAC use in doses not corresponding to indications correlates with worse prognosis. In particular, apixaban use in patients with normal renal function or its mild impairment was associated with decreased efficiency (increased frequency of stroke) and lack of information about higher safety in group of patients with AF, that are supported by some clinical evidences.

Use of anticoagulants in patients with creatinine clearance 15-29 mL/min

There are no RCT data on the effectiveness of NOAC for the prevention of stroke in patients with AF and severe CKD or in patients who use kidney replacement therapy, since the main NOAC-dedicated RCT did not include patients with creatinine clearance less than 30 mL/ min (except for a small number of patients with creatinine clearance 25-30 mL/min, who used apixaban). However, it be noted that warfarin has never been prospectively studied in RCTs, in which such patients would be included.

Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved for using for treatment of patients with severe CKD (stage 4 with creatinine clearance 15-29 mL/min) in Europe, considering appropriate dose reduction.

NOAC use in patients with creatinine clearance less than 15 mL/min and in hemodialysis patients

Safety and efficacy of NOAC use in patients with terminal CKD and in hemodialysis patients remains unclear and is actively investigated in ongoing studies. The results of the analysis of these registers showed a higher incidence of admission to hospital or death from bleeding in patients receiving hemodialysis, that began taking dabigatran or rivaroxaban in absence of registered indications, compared with VKA.

In the USA, but not in Europe and not in Russia, apixaban (5mg, twice per day) is currently approved for use in patients with chronic CKD receiving hemodialysis. It is worth to mention some recent results indicating that in this case (apixaban dose 5mg, twice per day) blood concentration of apixaban is higher than therapeutic one.

In patients with these characteristics, the concentration of NOAC in the blood corresponded to that in patients with normal renal function if they received apixaban (2.5 mg 2 times a day, in a small number of hemodialysis patients), edoxaban (15 mg once a day, severe renal failure, Japanese study), and rivaroxaban (10 mg once a day, in patients with terminal CKD). Notably, blood concentration of a drug can be considered just an indirect indicator of its efficiency of safety. In the absence of specific RCT data assessing clinical outcomes, NOAC use should be avoided as a

standard tactic in patients with severe renal dysfunction (creatinine clearance less than 15 mL/min) and in patients receiving hemodialysis. However, given the lack of convincing data on the efficacy and safety of VKA use in this situation, the decision on the choice of anticoagulant can be individual and should be made after discussion with colleagues and considering patient's preferences.

There are no data on the use of NOAC in patients who underwent kidney transplantation. If NOAC are used in such patients, the dose should be selected in accordance with the calculated indicators of renal function; moreover, caution should be exercised due to the possibility of drug interactions between NOAC and concomitant immunosuppressive therapy.

NOAC use in patients with severe liver diseases

The use of all 4 NOAC is contraindicated in patients with liver diseases, associated with coagulopathy and clinically significant bleeding, including patients with cirrhosis, the severity of which corresponds to class C of the Child-Turcotte-Pugh classification. Rivaroxaban should also not be used in patients with AF and Child-Pugh class B cirrhosis, due to more than a double increase of blood drug concentration in such cases. Dabigatran, apixaban, and edoxaban can be used with caution in patients with class B cirrhosis. Both hepatologist and haematologist should prescribe therapy and control its effects in the conditions of specialized medical centres. None of the NOAC studies showed an increase in the risk of liver damage. According to experts, this risk may be even less than in case of VKA use.

Algorithm of NOAC dose choice considering drug interactions

A possible algorithm of the choice of NOAC dose considering drug interactions presented on Figure 3.

How to measure the anticoagulant effect of NOAC?

Aleksei V. Tarasov (Moscow)

In routine clinical practice, NOAC do not require monitoring coagulation: neither dose nor treatment intervals should not be corrected in response to the change of coagulation parameters for the registered indications. However, laboratory tests evaluating drug influence on anticoagulant effect may help clinical practitioners in case of emergency or in particular clinical situations [1].

Long-term laboratory monitoring may be considered for patients with particular characteristics (severely overweight or underweight patients, high risk

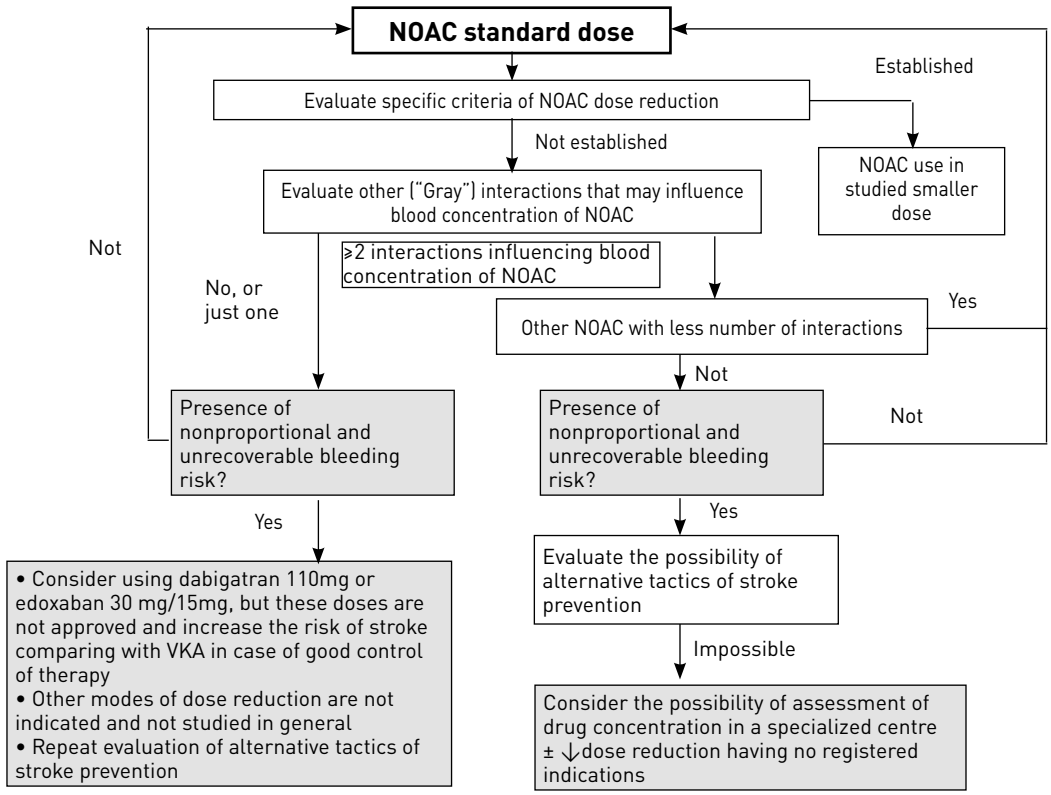


Figure 3. A possible algorithm of the choice of NOAC dose considering drug interactions

of bleeding, evaluation of compliance to treatment). Common tests of coagulation (prothrombin time (PT), activated partial thromboplastin time (APTT)) do not give a precise estimation of NOAC effects, since it can be measured just with specific anticoagulation tests developed for quantitative evaluation of NOAC in blood serum. Therefore, considering emergency situations, it is recommended to consider the opportunity of 24h-availability of these tests in all hospitals.

Chromogenic analysis of anti-Xa factor are available for measuring concentrations of inhibitors of Xa factor in blood plasm, using proved test calibrators of diluted thrombin time (dTT), and using ecarin clotting time (ECT). They demonstrate direct linear correlation with dabigatran concentration and are suitable for quantitative estimation of dabigatran concentration.

The review of expected values of maximal and minimal NOAC concentrations is presented in Table 1. It is important to know the time of NOAC administration in relation to blood sampling time for correct interpretation of the analysis of coagulation. Maximal effect of NOAC on clotting test occurs when its concentration in plasm is maximal, and it corresponds to the time interval of 1-3h after administration of each of these drugs (Figure 3).

Measurement in emergency situations

In emergency situations, such as bleeding, urgent invasive interventions or acute stroke, available routine blood clotting tests can quickly inform the doctor about the anticoagulant effect at a given point in time; specific analyses can provide an accurate assessment of drug plasma levels. Coagulation tests can also detect associated bleeding disorders, and, in exceptional cases of a planned operation with a high risk of bleeding, they can help to determine the timing of the intervention.

Dabigatran

APTT can provide qualitative estimation of dabigatran anticoagulant activity. The correlation between dabigatran and APTT is curvilinear during the day. Clinically significant plasma levels of dabigatran have a small influence on PT and INR that makes them inappropriate for evaluation of dabigatran anticoagulative activity. Thrombin time (TT) is very sensitive to the presence of dabigatran, and normal TT values exclude the presence of very small doses of this drug. dTT and ECT tests allow measuring dabigatran levels in a clinically significant range.

Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Factor Xa inhibitors influence PT and APTT differently. But APTT cannot be used for any significant evaluation of Xa factor inhibition due to its restricted duration, high variability of analysis and paradoxal response to low concentrations. Even if factor Xa inhibitors demonstrate concentration-dependent increase of PT, this effect depends both on the inhibitor itself and on the analysis. More than that, PT is not specific and may be influenced by numerous factors (hepatic insufficiency, vitamin K deficiency, for example). PT cannot be used for estimation of anticoagulant effect of apixaban. PT may give some quantitative information for rivaroxaban and, to a lesser extent, for edoxaban, even if the sensitivity of different reagents is significantly different and may be insensitive to the effect of anti-Xa factor.

Adverse effects of NOAC and liquidation of complications

Vadim S. Zhuk (Saint-Petersburg)

Despite the absence of obligatory control and convenient therapeutic regimen of NOAC, it is impossible to exclude the errors of administration. The most frequent and the most "human" one is simple for-

Table 1. **NOAC plasma levels and appropriate clotting tests**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Expected plasma levels of NOAC in patients with AF (based on the diluted thrombin time (dTT) /ecarin coagulation test (ECT) for dabigatran and anti-Xa factor (for Xa factor inhibitors)				
Expected plasma variation (peak) for standard dose (ng/mL)*	64–443	69–321	91–321	184–343
Expected plasma level variation (lowest, "at the bottom") for a standard dose (ng/mL)*	31–225	34–230	31–230	12–137
Expected effects of NOAC on routine clotting tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
APTT	↑↑(↑)	(↑)	↑	↑
Activated clotting time	↑(↑)	↑	↑	↑
TT	↑↑↑↑	–	–	–

***** This variation in values is shown as P5/95 percentile for dabigatran, rivaroxaban, apixaban, and interquartile range for edoxoban

getfulness. Each patient should be informed how to proceed in case of a missed drug dose. The forgotten medication dose should be taken immediately if the half period before the next drug administration has not passed yet (12h or 6h is drug is taken once or twice a day, respectively). If this time has already passed, it is recommended to take the next dose and every effort should be made to prevent such a situation in future. Another possible mistake is taking a double dose. If drug is taken twice a day, it is recommended to skip the next administration, and if the medication regimen is once a day, treatment should be continued normally.

The situation related to increased concentration of drug in blood is potentially dangerous since it may lead to bleeding.

This is possible either if patient deliberately or not took more than three pills, or if he developed acute renal failure on the background of chronic administration, or if it was the result of drug interactions. In case of overdose, some coagulation tests may help. For example, normal APTT excludes high level of dabigatran, and normal PTT excludes overdose of rivaroxaban, apixaban, and edoxaban.

In general, NOAC are safe enough, however, their administration increases the absolute number of bleeding cases. The relevant sections of the guidelines are dedicated to evaluation of the risk of bleeding. If bleeding occurs, it is important to understand rapidly how much threatening it is for patient's life: if it is small and not dangerous or if it is large and life-threatening. In addition, it is necessary to obtain information about what particular drug and in which dose the patient is taking, the exact time of the last dose, renal function, and concomitant therapy. Remembering the relatively short NOAC half-life period, waiting strategy is adopted, otherwise the need to administer a specific drug inhibitor is considered.

Minor bleeding during NOAC therapy can be normally resolved by skipping one dose, at maximum. In case of recurrent bleeding, it is acceptable to reduce the dose or replace the drug with another NOAC with a different mechanism of action. However, in case of a larger but still not life-threatening bleeding some measures aiming to treat the underlying cause of bleeding, like mechanical compression, endoscopic or surgical hemostasis, etc, are required. Already at this stage, the possibility of dialysis or of administration of a specific antidote should be planned. In life-threatening situations, the use of antidotes and other specific medications can bring significant benefits and reduce potential danger. The detailed algorithm is presented at Figure 4.

NOAC therapy may be resumed in most of cases after stopping bleeding and eliminating its cause. All other bleeding cases, especially the life-threatening ones, require the re-evaluation of benefits and risks of repeated start of anticoagulant therapy. Especially

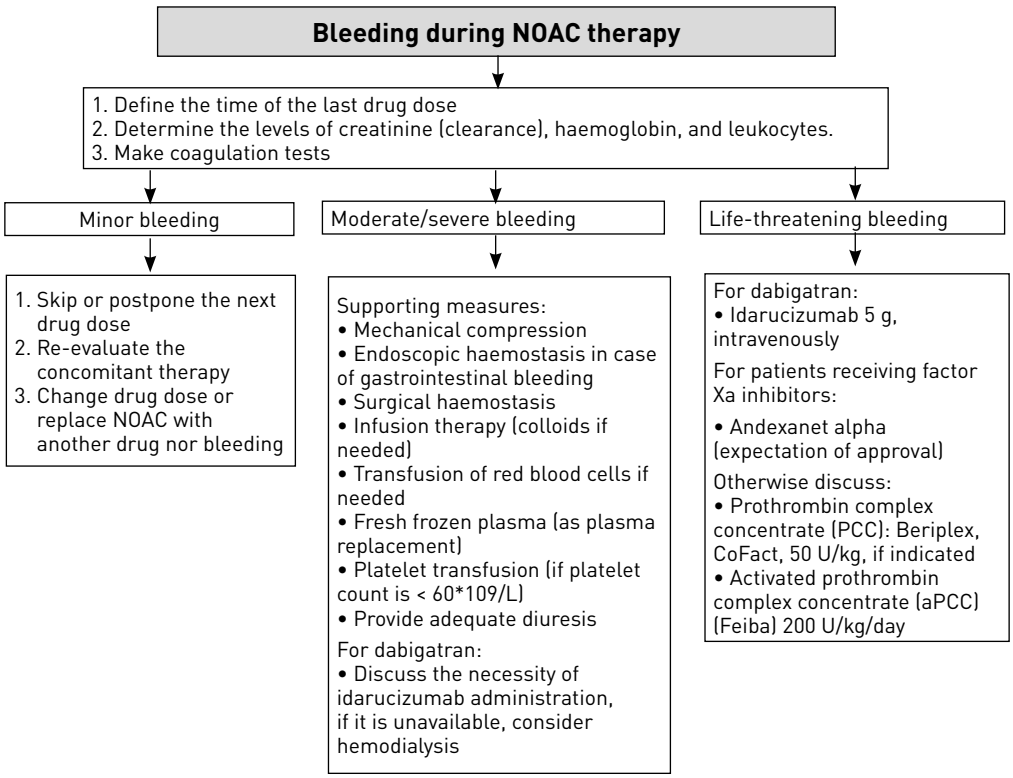


Figure 4. Algorithms of actions in case of bleeding during NOAC therapy

after severe and life-threatening bleeding, the risks of re-initiating anticoagulant therapy may outweigh the benefits. In such cases, implantation of the occluder into the left atrial appendage can be considered as a potential substitute for long-term anticoagulation.

Practical aspects of NOAC use in some groups of patients

Igor S. Yavelov (Moscow)

Percutaneous coronary interventions in patients with AFT taking NOAC

The approach to NOAC therapy of patients with stable coronary heart disease (CHD) undergoing transcutaneous coronary interventions (TCI, coronary stenting) is shown in Figure 5. It has few differences from the previous version of this guideline. The main difference is that it is recommended to check NOAC levels in blood and not routine clotting parameters when deciding on thrombolytic therapy and parenteral anticoagulant administration during thrombolysis.

Comments: ATT – antithrombotic therapy, ACT – activated clotting time, GP IIb/IIIa inhibitors – glycoprotein IIb/IIIa inhibitors; MI w– myocardial infarction; PPI – proton-pump inhibitors; LMWH – low molecular weight heparin; UFH – unfractionated heparin; DES – drug-eluting stents.

Many aspects of the use of combined antiplatelet therapy after PCI are unclear [1]. This concerns both its duration and its composition. The decision must be made individually, taking into account the characteristics of a particular patient. The algorithm proposed in this document assumes the use of triple antithrombotic therapy within 1-7 days after PCI (prior to discharge). In the future, after the implantation of modern DIS in patients with stable CHD, it is preferable to use double antithrombotic therapy (NOAC in combination with aspirin or clopidogrel) up to 1 year, then changing it for NOAC monotherapy. Such approach is acceptable for PCI in patients with ACS, but in this case also the triple antithrombotic therapy with duration of 3 months is considered (that is less than in guidelines of other expert groups recommending 6 months of triple antithrombotic therapy). The arguments favouring reduced duration of double/triple antithrombotic therapy are unavoidably high risk of bleeding and low atherothrombotic risk. The reasons for increased duration of double/triple antithrombotic therapy include implantation of first-generation drug-eluting stents, high atherothrombotic risk (stenting of the left coronary artery, proximal stenosis of the anterior interventricular branch, and proximal bifurcation, repeated MI history, history of stent thrombosis) together with the low risk of bleeding. In patients with a score on the scale CHA2DS2-VASc = 1 in men or =

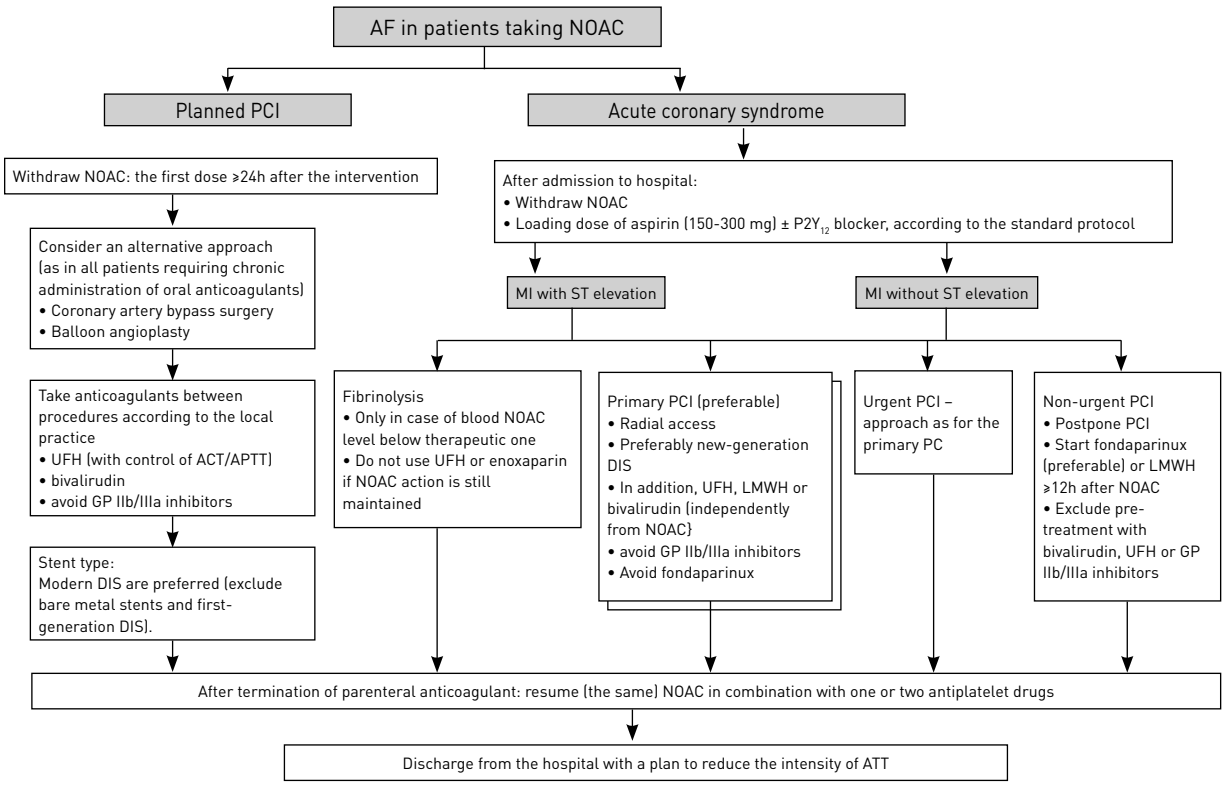


Figure 5. PCI in patients with AF taking NOAC

Table 2. **Timing of the last dose of NOAC before the start of planned invasive interventions.**

Creatinine clearance (mL/min)	dabigatran etexilate		Apixaban, rivaroxaban, edoxaban	
	In the absence of a significant risk of bleeding and / or adequate local hemostasis, a procedure is possible when minimal drug concentration in the blood is reached (in particular, 12 or 24 hours after the last dose)			
	Low bleeding risk	High bleeding risk	Low bleeding risk	High bleeding risk
≥80	≥24 h	≥48 h	≥24 h	≥48 h
50-80	≥36 h	≥72 h	≥24 h	≥48 h
30-50	≥48 h	≥96 h	≥24 h	≥48 h
15-30	Not indicated		≥36 h	≥48 h
<15	No official permission for use			
Bridge therapy using LMWH/UFH is not needed				
Resume taking full NOAC dose ≥24h after interventions with low risk of bleeding, and 48(-72h) after interventions with high risk of bleeding				
In case of planned operations patients should receive written instructions where the expected date and time of the intervention are mentioned together with the timing of the last NOAC dose (and other medications)				

2 in women, in combination with an increased risk of bleeding, it is suggested to refuse NOAC therapy limiting treatment to antiplatelet agents.

NOAC doses after PCI in patients with non-valvular AF: apixaban – dose will be defined after the results of the AUGUSTUS study (in which the standard doses for patients with non-valvular AF are used), dabigatran etexilate – 110 mg twice a day or 150 mg twice a day, rivaroxaban – 15 mg once a day (10 mg once a day in patients with creatinine clearance 30-49 mL/min), edoxaban – dose will be defined after the results of the ENTRUST-AF PCI study [5]. At the same time, it should be noted that for stroke prevention, the efficiency of the dose of rivaroxaban used in the PIONEER AF-PCI study (15 mg once a day) remains not fully studied due to the statistical limitations of this trial, at least comparing with the standard dose of VKA or rivaroxaban dose of 20 mg once a day in patients with normal creatinine clearance [6]. In case of combination of dabigatran and one antiplatelet agent (clopidogrel in this study), it is suggested to prefer the dose of 150 mg twice a day, leaving the dose of 110 mg twice a day for patients with elevated risk of bleeding.

Surgical interventions in patients taking NOAC

The data on optimal approaches for the use of NOAC in surgical interventions are limited. When deciding when to terminate and restart NOAC administration, one should consider patient's characteristics (age, history of bleeding, concomitant therapy, renal function) and operation-related factors (Table 2).

NOAC and restoration of sinus rhythm (cardioversion)

The possibilities of using NOAC in cardioversion are presented in the Figure 6.

NOAC and ischemic stroke

The details of treatment of acute ischemic stroke in patients taking NOAC are presented in the Figure 7.

Resuming NOAC therapy should be considered ≥1 day after transitory ischemic attack (TIA), ≥ 3 days after ischemic stroke with light neurologic deficit, ≥6-8 days after ischemic stroke with moderate neurologic deficit (in last two cases, it should be done after repeated CT or MRI during previous 24 h to exclude hemorrhagic transformation of ischemic stroke). Earlier start of NOAC therapy is suggested for patients with high risk of recurrent stroke (in particular, in case of left atrial appendage thrombus) without hemorrhagic transformation of ischemic stroke proved with the results of CT or MRI. These approaches correspond to the suggestions of other expert groups of the ESC.

NOAC after intracranial haemorrhage

It is recommended to consider the resumption of NOAC therapy 4-8 weeks after intracranial hemorrhage (after possible repeat of CT or MRI).

Arguments favouring refusal of NOAC therapy resumption:

- Severe intracranial hemorrhage;
- Multiple cerebral hemorrhages (in particular, > 10);
- Lack of reversible/treatable cause of bleeding;
- Elderly age;
- Bleeding during a break in taking anticoagulants;
- Bleeding occurred while taking adequate or reduced dose of NOAC;
- Uncontrollable arterial hypertension;
- Chronic alcohol abuse;
- The need for dual antiplatelet therapy after PCI.

In these cases, the possibility of the implantation of left atrial appendage occluder should be discussed.

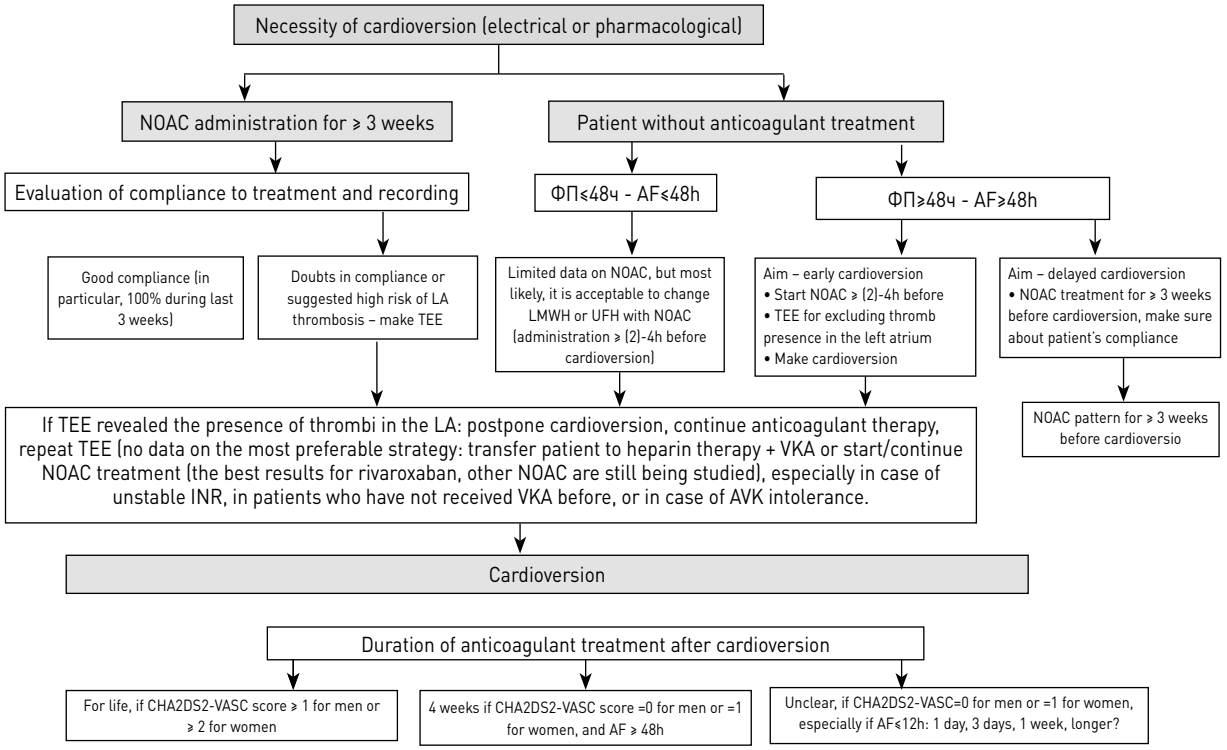
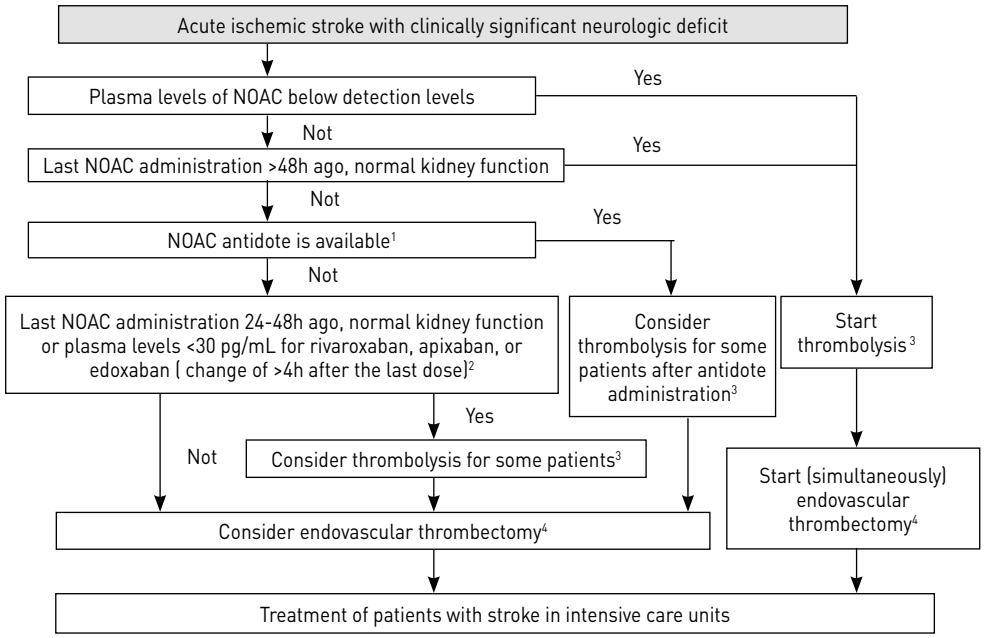


Figure 6. NOAC in cardioversion
Comments: LMWH – low molecular weight heparin, UFH – unfractionated heparin, TEE – transesophageal echocardiography, LA – left atrium.



Comments:
1 currently the antidote is available just for dabigatran (idarucizumab);
2 agreement of the experts;
3 in case of presence of necessary indications and absence of contraindications;
4 endovascular thrombectomy should be performed just in case of target vessel occlusion, presence of indications and acceptability of the procedure according to the existing evidences.

Figure 7. Treatment of acute ischemic stroke in patients taking NOAC

These approaches correspond to the suggestions of other expert groups of the ESC.

NOAC after gastrointestinal bleeding

It is recommended to consider the resumption of NOAC therapy 4-7 days after gastrointestinal bleeding. Arguments favouring refusal of NOAC therapy resumption:

- Undetected area of bleeding;
- Multiple angiodysplasia in the digestive tract;
- Lack of reversible/treatable cause of bleeding;
- Bleeding during a break in taking anticoagulants;
- Chronic alcohol abuse;
- The need for dual antiplatelet therapy after PCI;
- Elderly age.

In these cases, the possibility of the implantation of left atrial appendage occluder should be discussed.

Conflict of interests: None declared.

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