Rules for using reduced doses of non-vitamin K antagonist oral anticoagulants in the prevention of thromboembolic complications in patients with atrial fibrillation. The expert opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society

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ABSTRACT

Non-vitamin K antagonist oral anticoagulants (NOACs) are commonly used in stroke prevention in patients with atrial fibrillation. Although the rules for using standard and reduced doses of NOACs are defined, there is a significant percentage of patients with AF treated with incorrect doses of NOACs. This expert opinion provides a summary of appropriate NOAC dose selection and an algorithm that facilitates it.

Key words: apixaban, dabigatran, rivaroxaban, reduced dose

INTRODUCTION

Prophylaxis of thromboembolic complications is an integral part of the care of patients with atrial fibrillation (AF) [1]. Currently, drugs that are non-vitamin K antagonist oral anticoagulants (NOACs) are commonly used. Their effectiveness and safety have been confirmed in numerous studies [2–4]. NOACs are registered in standard and reduced doses, and the criteria for dose reduction are precisely defined. Using NOAC doses in accordance with the indications is crucial to ensure the effectiveness and safety of therapy, and the selection of NOAC dose depends on age, body weight, kidney function, risk of bleeding, and the drugs used [1, 5]. Using NOAC doses that are not consistent with the indications may lead to lower effectiveness of anticoagulant prophylaxis or an increased risk of bleeding complications [6]. The ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) study showed that overdosing or underdosing of NOACs were associated with an increased risk of thromboembolic complications, myocardial infarction, bleeding, and death compared to patients treated with recommended doses of NOACs [6]. The use of incorrectly reduced doses of NOACs is particularly unfavorable as it significantly lowers stroke prevention.

Table 1. Indications for NOAC dose reduction in patients with AF. Based on [1, 5], modified

	Dabigatran	Rivaroxaban	Apixaban
Standard daily dose	2 × 150 mg	1 × 20 mg	2 × 5 mg
Lower daily dose	2 × 110 mg		
Reduced daily dose[a]		1 × 15 mg	2 × 2.5 mg
Indications for dose reduction	• Age ≥80 years • Concomitant treatment with verapamil • High risk of bleeding complications: — especially in patients with CrCl 30–49 ml/min — in patients with HAS-BLED score ≥3 receiving concomitant antiplatelet drugs	• CrCl 15–49 ml/min • In patients with HAS-BLED score ≥3 receiving concomitant antiplatelet drugs	• CrCl 15–29 ml/min • At least 2 of the 3 following: — Age ≥80 years — Body weight ≤60 kg — Serum creatinine ≥1.5 mg/dl

[a]The dose reduction criteria defined in the summary of product characteristics, not in the phase III inclusion criteria

Abbreviations: CrCl, creatinine clearance

REDUCED NOAC DOSES IN CLINICAL TRIALS

NOACs in large clinical trials were found to be at least as effective as vitamin K antagonists (VKAs) and had a better safety profile. However, the studies on the basis of which NOACs were registered in the prevention of thromboembolic complications in AF patients differed methodologically in terms of the use of reduced doses. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study [2], dabigatran was used at a dose of 150 mg twice daily and 110 mg twice daily, and the endpoints were assessed independently for two doses. However, in the ARISTOTLE study (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) [4] and 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) [3], patients received full doses of apixaban and rivaroxaban, which were reduced according to the established criteria. The differences in the protocols of the above-mentioned studies affect the recommended nomenclature. In the case of dabigatran, the notion of a "lower dose" should be used, and in the case of apixaban and rivaroxaban, the "reduced dose".

Indications for using reduced doses of NOACs according to the guidelines of the European Society of Cardiology (ESC) and the guidance of the European Heart Rhythm Association (EHRA)

Indications for the use of reduced doses of NOACs in patients with AF follow the criteria adopted in the conducted clinical trials [2–4]. Reduction of NOAC doses in situations other than those specified below is not supported by scientific data and is not recommended [1, 5]. The criteria for NOAC dose reduction in AF are summarized in Table 1.

For apixaban, dose reduction is recommended if at least 2 of the 3 following criteria are met: age ≥80 years, body weight ≤60 kg, and/or serum creatinine ≥1.5 mg/dl. An important factor to consider when assessing the indications for NOAC dose reduction is renal function (see below). In the case of dabigatran, a dose lowering is recommended in patients ≥80 years of age, as well as in patients treated concomitantly with verapamil (but no dose reduction is required in patients receiving diltiazem). It is worth emphasizing that NOAC drugs should not be used during treatment with itraconazole or ketoconazole, as well as in people infected with human immunodeficiency virus (HIV) taking HIV protease inhibitors. Concomitant use of dronedarone and dabigatran is contraindicated, and the combination of dronedarone and rivaroxaban should be avoided [4, 5]. The authors of the EHRA guidance propose that in patients who do not meet the standard criteria for NOAC dose reduction, the possible interactions between drugs that alter NOAC levels, and the risk of bleeding should be additionally analyzed [5].

Patients taking antiplatelet drugs, non-steroidal anti-inflammatory drugs, systemic glucocorticosteroids, amiodarone, clarithromycin, or selective serotonin reuptake inhibitors or with other risk factors for bleeding (e.g. frailty syndrome, previous bleeding, anemia) may be at higher risk of bleeding complications during NOAC therapy, however, none of the above-mentioned factors, as a single factor, allows physicians to reduce the NOAC dose [1, 5]. Patients with increased risk of bleeding complications should have their risk factors identified and more frequent follow-up visits should be performed (including assessment of e.g. renal function); modifiable risk factors for bleeding should be monitored instead of introducing unjustified NOAC dose reduction (unless the patient meets the NOAC dose reduction criteria) [1]. In the case of potential drug interactions, change of a given NOAC to a NOAC with a lower risk of interactions (e.g. replacement of dabigatran with rivaroxaban in patients treated with verapamil) should be considered [5]. Although the 2020 ESC guidelines [1] do not rank individual NOACs, apixaban has a lower risk of serious bleeding complications (including gastrointestinal bleeding) compared to dabigatran and rivaroxaban and may be preferred in patients at high risk of these complications (including the standard dose of 5 mg twice a day in patients who do not have the usual indications for dose reduction) [1, 4, 5, 7, 8]. In exceptional cases, in selected patients with a disproportionately high, unmodifiable risk of bleeding complications, a lower dose of dabigatran (110 mg twice daily) may be considered as an alternative because this dose (as opposed to a reduced dose of rivaroxaban or apixaban) was tested in a clinical trial [1, 5]. An in-depth analysis of the criteria for dose

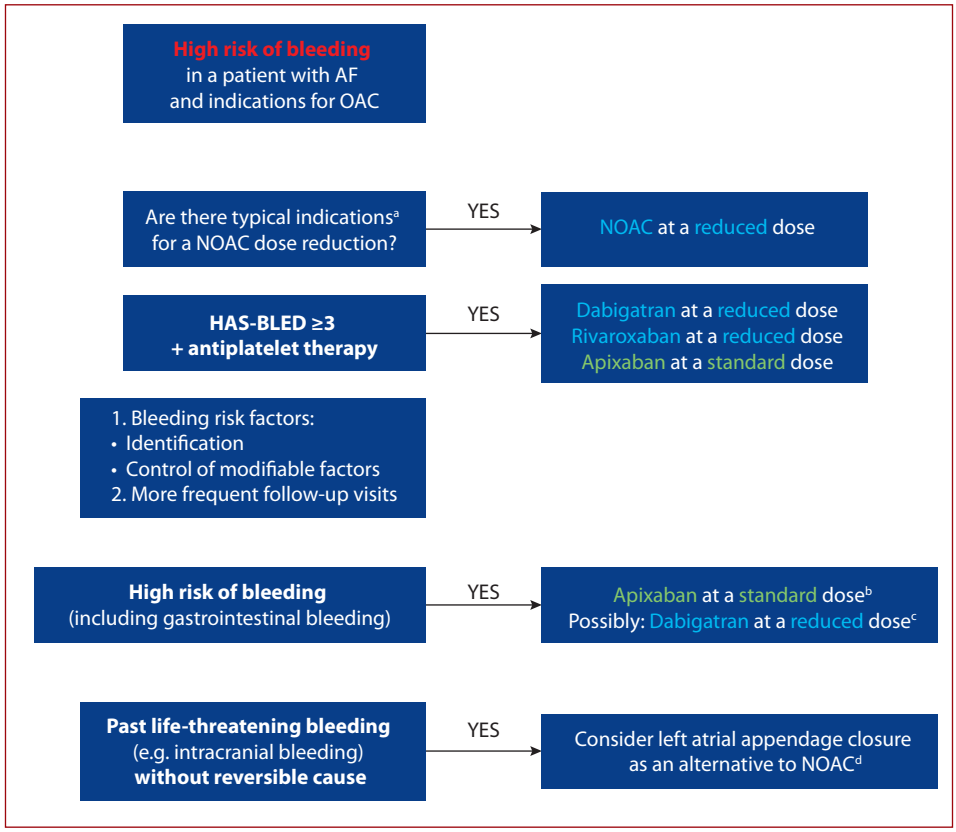

Figure 1. Proposed scheme for evaluation and management of patients with AF, indications for anticoagulant therapy and high risk of bleeding complications — the opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society
[a]According to Table 1. [b]Unless there are typical indications for dose reduction (Table 1). [c]In selected patients with a disproportionately high, unmodifiable risk of bleeding complications. [d]After transcatheter closure of the left atrial appendage, there is a need for antiplatelet therapy
Abbreviations: AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation

reduction in patients treated with NOACs is necessary, as well as regular evaluation of the parameters influencing the NOAC dose choice. The proposed scheme for evaluation and management of patients with AF, indications for NOACs, and high bleeding risk is presented in Figure 1.

In a nationwide Danish study comparing the effectiveness and safety of a reduced NOAC dose and warfarin in patients with AF, a reduced dose of apixaban was associated with a trend towards higher rates of ischemic stroke/systemic embolism compared to warfarin, while a reduced dose of rivaroxaban and dabigatran showed a trend towards lower thromboembolic rates. However, these results were not significantly different [9]. It should be emphasized that it is not recommended to routinely reduce NOAC doses in patients receiving antiplatelet therapy (e.g. after acute coronary syndrome or after planned elective coronary angioplasty with stent implantation; see below) [10]. Routine determination of NOAC levels to select a dosage regimen is also not recommended; however, in rare cases, it may be necessary to measure the concentration of the drug in the blood. This applies to the following situations: the need for immediate surgery, ischemic stroke in a person receiving NOAC, complex drug interactions, severe obesity, or underweight [1, 5].

Difficulties in implementing the guidelines for using reduced doses of NOACs

The reduced dose of NOACs in the prevention of thromboembolic complications is used in a significant percentage of patients with AF. In the Polish population of patients with AF included in the POL-AF Registry (POLish Atrial Fibrillation Registry), NOACs at a reduced dose were used in 36% of patients [11]. Although the rules for using standard and reduced doses of NOACs are defined, there is a significant percentage of patients with AF treated with incorrect doses of NOACs. Those are both patients with indications for the standard dose treated with the reduced dose of NOACs and patients with indications for the reduced dose receiving the standard dose of NOACs. A Korean study showed that in the group of 53 649 patients with AF treated with NOACs, 60% of them were administered the correct dose of NOACs, 31% received an incorrectly reduced dose of NOACs, and 8% obtained the standard dose of NOACs despite the indications for the reduced dose [12]. Patients treated with the non-recommended NOAC dose were older and had a higher CHA2DS2-VASc score than patients treated with NOACs at the appropriate dose. In a group of patients with AF who received anticoagulant treatment, Rodriquez et al. [13] showed that 76.9% of them received the appropriate

dose of NOACs: 84% of patients treated with rivaroxaban, 75% with apixaban, and 74% with dabigatran. The incorrectly reduced dose of NOACs was most often used in patients treated with apixaban (22%), and the standard dose of NOACs in patients with indications for the reduced dose was most often administered in patients treated with dabigatran (17%) [13]. The authors of the study noted that improper dosing was more common with apixaban and dabigatran, which are administered twice a day.

Kidney function is an important confounding factor in choosing the correct NOAC dose. Firstly, in clinical trials, whose results were the basis for NOACs registration, in the registration documents, kidney function was determined using the Cocroft-Goult formula that should be used in the assessment of kidney function. Secondly, in patients treated with dabigatran with creatinine clearance (CrCl) <50 ml/min, routine dose reduction is not recommended, but it should be reduced when there is a high risk of bleeding complications [1, 5]. Ono et al. [14] showed that impaired renal function and advanced age were predictors of using an incorrectly reduced dose of NOACs. On the other hand, Yao et al. [15] showed in a group of 14 865 patients that 43% of them received the full dose of NOACs despite renal indications for its reduction.

Another factor predisposing to using incorrect NOAC doses is a high risk of bleeding or previous bleeding complications. In clinical practice, frequent use of the reduced NOAC dose is observed despite no indications, e.g. in patients with epistaxis or gingival bleeding. According to the current guidelines, a high risk of bleeding assessed according to the HAS-BLED score should not be an indication to use reduced doses of NOACs. However, in the results of the studies by Ono et al. [14] and Jacobs et al. [16], the use of incorrectly reduced doses of NOACs was more frequent in patients with high bleeding risk than in patients with low bleeding risk. Also, in the SAFE-NOACS study, a history of hemorrhagic complications was a predisposing factor for the application of a reduced dose of NOACs [17]. Meanwhile, patients after past bleeding complications are also often characterized by increased risk of thromboembolism, which results, for example, from the fact that anticoagulant treatment is discontinued for the duration of the bleeding episode.

Indications for using a reduced dose of NOACs in elderly patients

Older age is considered the only independent criterion that authorizes dose reduction only in the case of dabigatran (the dose of 110 mg twice daily in patients ≥80 years of age). It should be emphasized that in patients aged 75–79, the decision to use a full or lower dose is made on an individual basis, mainly taking into account the assessment of bleeding risk and renal function. Older age is not a criterion for dose reduction for rivaroxaban and cannot be used as the sole criterion for dose reduction in the case of apixaban. It should be remembered that older age is one of the most important risk factors for thromboembolic events in patients with AF, and unjustified reduction of the dose of apixaban or rivaroxaban in elderly patients deprives them of adequate protection against ischemic stroke. In people aged ≥80 years, the apixaban dose should be reduced (to 2.5 mg twice daily) when low body weight (≤60 kg) or significantly impaired renal function (serum creatinine ≥1.5 mg/dl or CrCl <30 ml/min) are observed [1, 5]. Age also indirectly influences dosing of NOAC drugs as it is included in the Cockroft-Gault formula (see below) [18].

Indications for using a reduced dose of NOACs in patients with chronic kidney disease

In patients treated with NOACs, the Cockroft-Gault formula should be used to assess renal function [5]. The CrCl value obtained on the basis of this formula may be significantly overstated in comparison with the CrCl value calculated according to the formula most commonly used by laboratories — the MDRD (Modification of Diet in Renal Disease), especially in elderly patients and/or with low body weight [18]. In patients taking NOACs, CrCl should be regularly assessed — at least once a year, and in patients with CrCl below 60 ml/min — according to the principle: time to assessment (in months) — CrCl/10 (e.g. in a patient with CrCl 50 ml/min, its next evaluation should be carried out after 5 months) [5]. In elderly patients with frailty syndrome or other risk factors, more frequent CrCl assessment should be considered, especially if the patient is receiving dabigatran [5].

According to the current guidelines, all NOAC drugs are contraindicated in patients on dialysis or with CrCl <15 ml/min. Reports have confirmed that in comparison with warfarin, using NOACs, especially factor Xa inhibitors (rivaroxaban or apixaban), showed at least similar effectiveness and safety outcomes in AF patients on dialysis [19]. Dabigatran, with the highest degree of renal excretion (80%), is contraindicated in patients with CrCl <30 ml/min [1, 5, 20]. With a higher CrCl, the use of reduced vs. standard doses of NOACs depends on whether the indication for NOACs is AF or venous thromboembolism [1, 5, 20]. The below-presented dose reduction rules for NOACs available in Poland apply to patients with AF. In patients with CrCl <50 ml/min, the dose of rivaroxaban should be reduced (to 15 mg once daily). For apixaban, which is eliminated to the least extent (27%) via the kidneys, the standard dose (5 mg twice daily) should be used for CrCl up to 30 ml/min unless the patient meets at least 2 of the following 3 criteria: serum creatinine ≥1.5 mg/dl, age ≥80 years of age, and/or body weight ≤60 kg. The reduced dose of apixaban (2.5 mg twice daily) should be used only in patients with CrCl 15–29 ml/min, and in those patients who meet 2 of the 3 criteria mentioned above [1, 5]. It is therefore worth noting that when assessing the indications for apixaban dose reduction, not only CrCl should be taken into account but also creatinine concentration unless the patient is less than 80 years old and weighs more than 60 kg. In the case

Table 2. Non-vitamin K antagonist oral anticoagulant dose reduction criteria in atrial fibrillation depending on CrCl Based on [1, 5], modified

CrCl, ml/min	Dabigatran	Rivaroxaban	Apixaban
>50	2 × 150 mg	1 × 20 mg	2 × 5 mg[b]
30–49	2 × 150 mg or 2 × 110 mg[a]	1 × 15 mg	
15–29	**Do not use**		2 × 2.5 mg
<15 or dialysis therapy	**Do not use**	**Do not use**	**Do not use**

[a]2 × 110 mg, in the case of high bleeding risk. [b]2 × 2.5 mg if at least 2 of the 3 following criteria are met: creatinine concentration ≥1.5 mg/dl, age ≥80 years of age, and/or body weight ≤60 kg

Abbreviations: see Table 1

of dabigatran, it is not recommended to routinely reduce the dose in patients with CrCl 30–49 ml/min (unless they are at high risk of bleeding), but according to the EHRA guidance and ESC guidelines, dabigatran in this group of patients should be used with caution [1, 5]. In this patient group, the use of other NOACs may be preferable. In the United States, based on pharmacokinetic analyzes, the use of dabigatran at a dose of 75 mg twice daily was allowed in patients with CrCl 15–29 ml/min. Table 2 shows the NOAC dosage in AF depending on CrCl. These NOAC dose reduction criteria do not apply to patients with deep vein thrombosis or pulmonary embolism [5, 20].

It should be emphasized that chronic kidney disease is associated not only with increased risk of bleeding complications but also with increased risk of thromboembolic complications. Unjustified reduction of the NOAC dose (e.g. apixaban in patients with CrCl 30–50 ml/min, who do not meet 2 of the 3 above-mentioned criteria for dose reduction) exposes patients to increased risk of ischemic stroke. Moreover, in patients with mildly reduced or normal renal function, an unjustified reduction of the apixaban dose was not associated with a reduction in the risk of serious bleeding complications, while increasing the risk of stroke [14].

Indications for using a reduced NOAC dose in patients concomitantly treated with an antiplatelet drug/drugs

The use of NOACs with antiplatelet therapy is necessary in patients with AF and after percutaneous coronary interventions (PCI) and/or acute coronary syndrome (ACS) to prevent ischemic events and thromboembolic complications. After the decision to initiate combined anticoagulant therapy, its duration should be estimated taking into account the risk of thromboembolic complications, coronary ischemic events, and bleeding associated with anticoagulant therapy.

According to the ESC recommendations, NOACs are the preferred anticoagulants in combination with antiplatelet therapy [1].

It should be emphasized that the following NOAC doses have been studied in clinical trials in patients with AF after ACS/PCI:

- apixaban 5 mg twice daily in the AUGUSTUS study [21],
- dabigatran 110/150 mg twice daily in the RE-DUAL study (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) [22],
- rivaroxaban 15 mg once daily in the PIONEER AF-PCI study (OPen-Label, Randomized, Controlled, Multicenter Study Exploring TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) [23].

In the PIONEER AF-PCI study, rivaroxaban 10 mg once daily (CrCl, 30–50 ml/min) and 2.5 mg once daily was also tested [23].

In general, the rules for NOAC dose reduction in patients with AF after PCI and/or ACS are the same as for the general population of patients with AF. If, according to the general principles, a patient has an indication to receive a reduced NOAC dose, it should be used in combination with antiplatelet therapy. If a patient is indicated for a standard NOAC dose, the risk of bleeding should be assessed according to the HAS-BLED score. In patients with high risk of bleeding, preferential use of rivaroxaban 15 mg once daily instead of rivaroxaban 20 mg once daily during antiplatelet therapy should be considered to reduce the risk of bleeding. Similarly, in patients at high risk of bleeding, consideration should be given to using dabigatran 110 mg twice daily instead of dabigatran 150 mg twice daily for the duration of antiplatelet therapy to reduce the risk of bleeding [1]. Apixaban in combination therapy with antiplatelet drugs should be used in the standard dose [1]. The principles for selecting the NOAC dose are the same when using NOACs with one or two antiplatelet drugs. According to the recommendations included in the EHRA guidance, if ticagrelor was used during hospitalization in triple treatment, it is preferable to switch to clopidogrel on discharge [5]. It should be emphasized that the duration of treatment with dual antiplatelet therapy has been significantly shortened and should normally be one week, and in exceptional cases, in patients at high risk of ischemia, it can be extended to one month [1]. Thus, the time of triple therapy is short, which significantly affects the safety of its use.

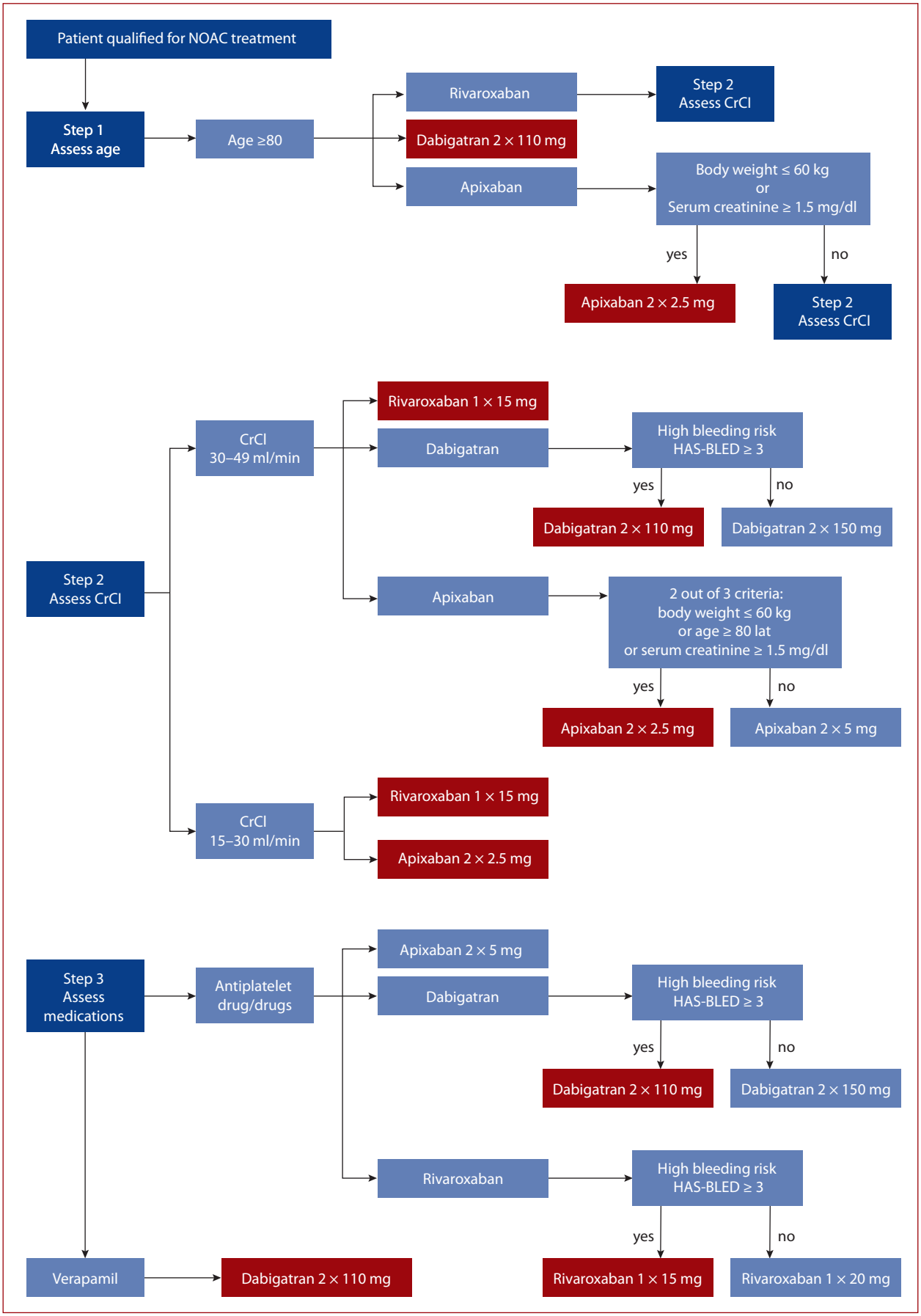

Figure 2. Algorithm for evaluation of indications for the use of a reduced dose of NOAC in patients with atrial fibrillation — the opinion of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society

Abbreviations: see Table 1 and Figure 1

Indications for using a reduced NOAC dose in patients after bleeding

Anticoagulant treatment in AF patients treated with NOACs who have bleeding raises many doubts in clinical practice. It should be emphasized that bleeding during the use of NOACs is not an indication for a reduction of the NOAC dose unless the criteria specified in Table 1 are met.

In most cases of mild bleeding, current anticoagulant therapy can be administered without delaying the NOAC dose. In the event of major or life-threatening bleeding, the decision to restart anticoagulant therapy should be preceded by careful risk-benefit analysis. Most of the bleeding is secondary (e.g. traumatic, due to alcohol abuse) or reversible (e.g. gastrointestinal bleeding caused by polyposis or peptic ulcer disease). In most bleeding events, re-treatment with NOACs is possible after the cause of the bleeding has resolved. The risk of recurrent bleeding and the possibility of eliminating factors that increase the risk of bleeding should be assessed, as well as the type and dose of the anticoagulant drug. Therefore, restarting NOACs after a hemorrhagic complication should be preceded by thorough analysis of indications for the use of a reduced dose of NOACs in accordance with specific indications. To do this, age, kidney function, body weight, and concomitant therapy should be assessed, and then the NOAC dose should be administered according to Table 1. In some patients after life-threatening bleeding without a reversible cause, closure of the left atrial appendage may be considered (Figure 1).

PROPOSED ALGORITHM FACILITATING NOAC DOSE SELECTION IN EVERYDAY CLINICAL PRACTICE

The dose reduction criteria for apixaban, dabigatran, and rivaroxaban are different. To make the selection of the recommended NOAC dose simpler, we propose an algorithm created by the Working Group on Cardiovascular Pharmacotherapy, on the basis of which an appropriate NOAC dose can be determined (Figure 2). The following data are necessary for the complete evaluation of the recommended NOAC dose:

- age;
- kidney function (CrCl estimated by the Cockroft-Gault formula and serum creatinine);
- body weight;
- bleeding risk assessed using the HAS-BLED score;
- medications used.

The algorithm involves three steps – assessing age, kidney function, and medications other than NOACs. We encourage readers to check step by step all factors listed in the criteria requiring a reduced dose of NOACs in accordance with the applicable guidelines. Particular attention should be paid to evaluation of all criteria in patients treated with apixaban, bearing in mind that meeting 2 out of 3 criteria or CrCl <30 ml/min are required to use a reduced dose of apixaban. We propose to use the presented algorithm not only in patients who initiate NOAC treatment but also in patients already treated with NOACs because all the factors constituting the criteria for dose reduction are variable.

CONCLUSION

The use of the correct dose of NOACs is important for the prognosis of patients with AF. The most common mistake in anticoagulant treatment is using reduced NOAC doses with no indication for dose reduction. In-depth analysis of the factors listed as the criteria for dose reduction in patients treated with NOACs is necessary, as well as regular evaluation of the parameters influencing the choice of the NOAC dose.

Article information

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