Chapter 5

The Importance of Non-vitamin K Antagonists (NOAC) in Their Current Use

Veysel Tosun[1]

Abstract

Non-vitamin K oral anticoagulants are new drugs that are used in the treatment of atrial fibrillation and venous thromboembolism. There are 4 NOACs in use today; dabigatran is a direct thrombin inhibitor, while rivaroxaban, apixaban, and edoxaban are Factor Xa inhibitors. NOACs can be used safely in AF patients, except for patients with moderate to severe rheumatic mitral stenosis, and metallic prosthetic valves. In studies where NOACs were evaluated in terms of effectiveness and safety, similar or better results were obtained with VKAs. With the new two antidotes (idaricuzimab and andexanet alfa) approved for use in NOAC-related bleeding, the potential for use of NOACs in patients with high bleeding risk is expected to increase.

1. Introduction

Protecting patients with atrial fibrillation (AF) from stroke is very important, and vitamin K antagonists (VKA) have long been used for this purpose (1). However, non-vitamin K oral anticoagulants (NOAC) are now considered by AF guidelines worldwide as the preferred choice of anticoagulants to prevent stroke in patients with AF (2-4). NOACs have an efficacy/safety ratio and a predictable anticoagulant effect that does not require routine coagulation monitoring as required with VKAs (5, 6). In recent years, NOACs have begun to be widely used as an alternative to VKA in our country, as well as around the world, to protect against stroke and systemic embolism in AF. There are four preparations used as NOAC today. Of these, dabigatran is a direct thrombin inhibitor, rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors.

1 M.D, Department of Cardiology, T.C. SBU. Van Education and Research Hospital, Van, Turkey, veyseltosun8810@gmail.com, ORCID ID: 0000-0001-7629-2108

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2. NOAC eligibility and dosage

2.1. NOAC eligibility

NOACs are approved especially for stroke prevention in non-valvular AF. In previous guidelines, the term non-valvular AF emphasized AF without a mechanical prosthetic heart valve or with moderate to severe mitral stenosis (especially rheumatic origin) (2, 7, 8). There is no randomized controlled trial (RCT) demonstrating that NOACs are less efficacious in rheumatic mitral stenosis patients. The INVICTUS program investigating the use of VKA, rivaroxaban or acetylsalicylic acid, in patients with rheumatic heart disease is currently ongoing. In patients with mechanical valve replacement, NOACs should not be considered unless there is new evidence reversing existing data that NOACs may be better than VKA in preventing stroke (9, 10). In patients with bioprosthetic valves, in the 'Rivaroxaban for Valve Disease and Atrial Fibrillation' (RIVER) trial, it was non-inferior to warfarin for the median time to the composite endpoint of death, major cardiovascular events or major bleeding (11). Similarly, edoxaban was non-inferior in the 'Efficacy and Safety of Edoxaban in Patients Following Heart Valve Repair or Bioprosthetic Valve Replacement (ENAVLE) study. Observational data showed that early thromboembolic and bleeding events and all-cause mortality were lower with NOACs after TAVI compared with VKA (12, 13).

A summary of the above and other indications and contraindications for NOAC use are listed in Table 1. Additionally, NOACs are contraindicated in pregnancy and women of childbearing age must have reliable contraceptive methods before initiating NOAC therapy (14). Pediatric patients have been excluded from stroke prevention RCTs because AF requiring oral anticoagulation (OAC) is rare in this population (14). It can be considered in fully adult adolescents. Patients with non-valvular AF and antiphospholipid syndrome should be treated with VKAs rather than NOACs as a higher rate of thromboembolic events and major bleeding has been observed with rivaroxaban compared with VKA (15).

Table 1. Selected indications and contraindications for NOAC therapy in AF patients (16).

Condition	Eligibility for NOAC	Comment
-Mechanical prosthetic valve	Contraindicated	-Excluded from pivotal RCTs Data indicating worse outcome
-Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	-Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
-Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) -Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	-Data regarding efficacy and safety overall consistent with patients without valvular disease -Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA Patients without AF usually on ASA after 3-6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
-Severe aortic stenosis	Limited data (excluded in RE-LY study)	-No pathophysiological rationale for less efficacy and safety most will undergo intervention
-Trans catheter aortic valve implantation	Acceptable	-Single RCT and observational data
-Percutaneous transluminal aortic valvuloplasty	With caution	-No prospective data
-Hypertrophic cardiomyopathy	Acceptable	-No rational for less efficacy and safety vs. VKA (observational data positive for NOACs)

Abbreviations: NOAC: non-vitamin K antagonist oral anticoagulant; RCT: randomized clinical trials; VKA: vitamin-K antagonist; AF: atrial fibrillation;

2.2. NOAC dosage

Four types of NOACs are used and they have different dosages and different dose reduction criteria for different indications. Therefore, determining the correct dose has become more complicated. Figure 1 provides an overview of available NOACs and their dosages in different indications, including dose reduction criteria (16).

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction
Apixaban	5 mg BID	2.5 mg BID if two out of three fulfilled: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/L (1.5 mg/dL) (*or* single criterion: if CrCl 15–29 mL/min)
Dabigatran	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III trial[a]
Edoxaban	60 mg QD	30 mg QD if: weight ≤60 kg *or* CrCl 15–49 mL/min *or* concomitant therapy with strong P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)
Rivaroxaban	20 mg QD	15 mg QD if CrCl ≤15–49 mL/min

'SmPc' refers to European SmPc.
BID, twice daily; CrCl, creatinine clearance; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding.

NOAC dosing in AF patients post-ACS/PCI (see 'Patients with atrial fibrillation and coronary artery disease' section)

	Standard dose	Comments/dose reduction
Apixaban	5 mg BID	Dose reduction as for SPAF
Dabigatran	150 mg BID or 110 mg BID	110mg as for SPAF
Edoxaban	60 mg QD	Dose reduction as for SPAF
Rivaroxaban	15 mg QD	Dose reduction to 10 mg QD if CrCl 30–49 mL/min

In addition to single/dual antiplatelet therapy, where applicable. See 'Patients with atrial fibrillation and coronary artery disease' section for details.
BID, twice daily; CrCl, creatinine clearance; QD, once daily; SPAF, stroke prevention in atrial fibrillation.

Treatment of DVT/PE

	Initial therapy	Remainder of treatment phase
Apixaban	10 mg BID, 7 days	5 mg BID, no dose reduction
Dabigatran	Heparin/LMWH	150 mg BID, no dose reduction[a]
Edoxaban	Heparin/LMWH	60 mg QD, same dose reduction as for SPAF (see above)
Rivaroxaban	15 mg BID, 21 days	20 mg QD, no dose reduction[b]

BID, twice daily; GI, gastrointestinal; LMWH, low molecular weight heparin; QD, once daily; SPAF, stroke prevention in atrial fibrillation.
[a]Per SmPC: 110 mg BID if age ≥80 years, concomitant verapamil, increased risk of GI bleeding [based on pharmacokinetic/pharmacodynamic (PK/PD) analyses; not studied in this setting].
[b]Per SmPc: 15 mg if risk of bleeding outweighs risk for recurrent DVT and PE (based on PK/PD analyses; not studied in this setting).

Long-term prevention of recurrent DVT/PE

	Standard dose	Comments/dose adjustment
Apixaban	2.5 mg BID	
Dabigatran	150 mg BID	No pre-specified dose-reduction criteria in clinical trial[a]
Edoxaban	60 mg QD[b]	
Rivaroxaban	10 mg QD	[c]

BID, twice daily; QD, once daily.
[a]SmPC: 110 mg BID if age ≥80 years, concomitant verapamil (both based on pharmacokinetics/pharmacodynamics analyses; not studied in this setting).
[b]Not specifically studied, follow-up data available up to 12 months in phase III trial.
[c]SmPc: 20 mg QD in patients at high risk of recurrence.

VTE prevention post-major orthopaedic surgery

	Standard dose	Comments/dose reduction
Apixaban	2.5 mg BID	
Dabigatran	220 mg QD/150 mg QD	[a]
Edoxaban	30 mg QD	Not approved in Europe (only studied in Asia)
Rivaroxaban	10 mg QD	

BID, twice daily; QD, once daily.
[a]SmPc: 1× 150 mg if CrCl 30–50 mL/min; concomitant verapamil, amiodarone, quinidine; age >75 years.

Secondary prevention of atherothrombotic events post-ACS in patients without AF (i.e. no OAC indication)

	Standard dose	Comments/dose reduction
Rivaroxaban	2.5 mg BID	In addition to aspirin ± P2Y12 inhibitor

BID, twice daily.

Secondary prevention of atherothrombotic events in patients with chronic coronary syndrome and/or symptomatic peripheral artery disease patients without AF (i.e. no OAC indication)

	Standard dose	Comments/dose reduction
Rivaroxaban	2.5 mg BID	In addition to aspirin

AF, atrial fibrillation; BID, twice daily; OAC, oral anticoagulation.

Figure 1. NOACs and approved/studied doses across indications.

3. Pharmacokinetics of NOACs

Treatment with VKAs requires careful consideration of multiple food and drug-drug interactions. These interactions are less in NOACs. Nevertheless, physicians need to consider the pharmacokinetic interactions of concomitant medications and comorbidities when prescribing NOACs. The absorption, distribution, metabolism, and excretion of the different NOACs, are summarized in Figure 2 (17).

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (In part dialysable)	14% (Not dialysable)	NA (Not dialysable)	NA (Not dialysable)
Metabolism	Glucoronic acid conjugation	CYP3A4 (25%), CYP1A2, CYP2J2, CYP2C8, CYP2C9 CYP2C19	CYP3A4 (<4% of elimination)	CYP2A4 (18%)[519], CYP2J2
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	−12% to 30% (not clinically relevant)	No effect	No effect	No effect
Time to peak levels (h)	3	3	2–4	2–4
Elimination half-life (h)	12–17	12	10–14	5–9 (young) 11–13 h (elderly)

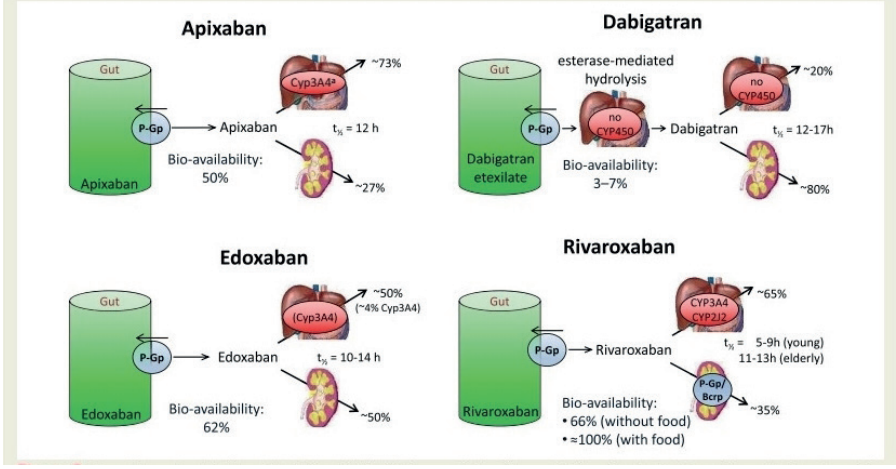

Figure 2. Absorption and metabolism of different NOACs. There are interaction possibilities at the level of absorption or first transformation and at the level of metabolization and excretion. Also via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19.

4. NOACs in patients with chronic kidney disease or advanced liver disease

4.1. Atrial fibrillation and chronic kidney disease

Both bleeding and thrombotic risks are increased in patients with chronic kidney disease (CKD) and AF compared with other AF patients. NOACs all undergo some renal elimination, although at varying rates. 80% of dabigatran, which is eliminated most, and approximately 25% of apixaban, which is the least eliminated, are excreted through the kidneys.

Renal functions should be evaluated at least once a year in patients receiving NOAC therapy, and more frequently in those with renal dysfunction. In patients who develop acute renal failure, NOACs should be discontinued and parenteral anticoagulation should be started (18).

The effectiveness and safety of all four NOAC types in patients with creatinine clearance (CC) above 30 mL/min have been demonstrated in subgroup analyses of phase-III studies of these drugs (19-23). The use of appropriate NOAC doses has great importance in the treatment of patients with CKD. In studies of apixaban, edoxaban, and rivaroxaban, dose reductions were made according to renal functions. In the RELY study, two different patient groups were created, 110 and 150 mg, regardless of renal functions. It is recommended for dabigatran to use 110 mg in patients with CC below 50 mL/min. The dose adjustment of NOACs according to CC is shown in Figure 3 (16).

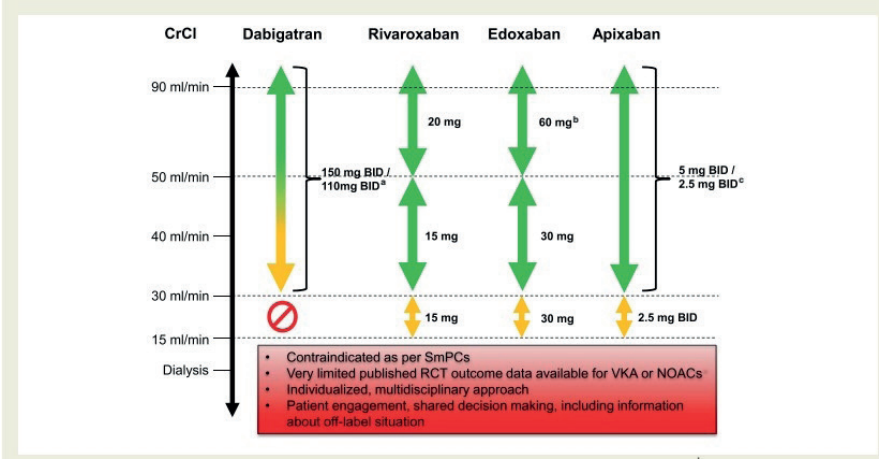

Figure 3. Use of NOACs according to renal functions.

The effectiveness and safety of NOACs in patients with CC below 15 mL/min or in patients undergoing renal replacement treatment are uncertain. In a study, significantly more hospitalizations and deaths due to bleeding occurred with off-label dabigatran and rivaroxaban in patients receiving renal replacement treatment compared to VKAs (24). Although plasma apixaban levels are higher than the therapeutic level in stable dialysis-dependent patients, apixaban treatment of 5 mg twice a day has been approved by the FDA in the USA (25). Besides that, the 2020 ESC guidelines recommend the use of factor Xa inhibitors with caution and at reduced doses for patients with 15-29 mL/min (2).

There are no data regarding the use of NOAC in renal transplant patients. In these patients, dosage adjustments should be made according to renal functions and drug-drug interactions with the immunosuppressive agents used should be taken into consideration.

The use of prophylactic anticoagulants in nephrotic syndrome patients is still a controversial issue today. There is no data in the literature regarding the use of NOAC for thromboprophylaxis in patients with nephrotic syndrome. When deciding which of NOACs or VKAs to prefer in a patient, the pathology causing the nephrotic syndrome, renal functions, serum protein levels, thromboembolism, and bleeding risks should be taken into consideration (26). It should be kept in mind that NOAC may be an alternative for these patients who cannot comply with VKA treatment.

4.2. NOACs in patients with advanced liver disease

Advanced liver disease, like kidney disease, creates a predisposition to both thrombosis and bleeding. In addition, hepatic elimination of drugs, drug metabolism, effectiveness, and drug-induced liver damage differ in liver disease (27). Practical considerations for the use of NOACs in liver disease are presented and summarized in Figure 4 (16).

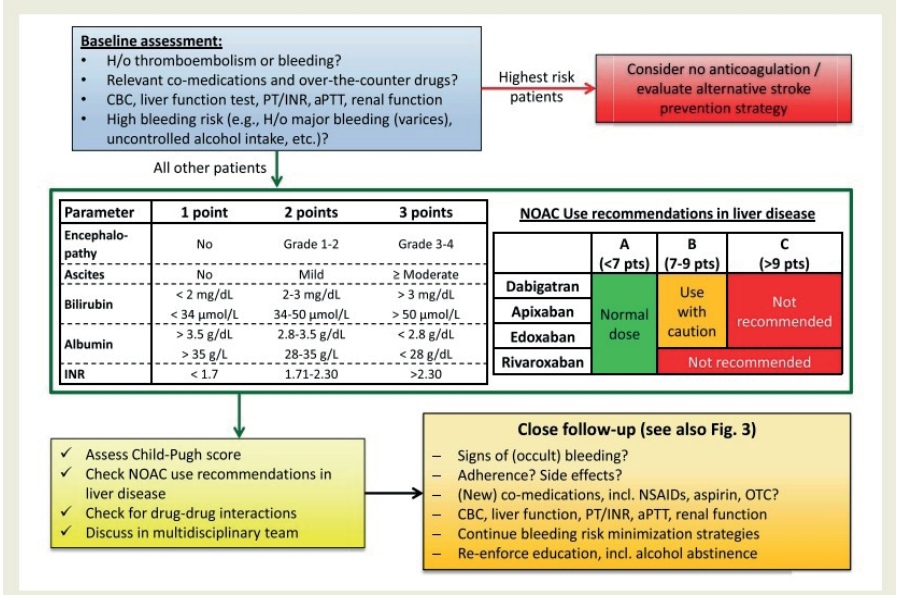

Figure 4. NOACs in patients with liver disease.

4.3. NOAC treatments in cancer patients

The risk of thrombosis is increased in patients with cancer compared with patients without it. There is an increased risk of both arterial and venous thromboembolism in patients with malignancy. At the same time, the risk of bleeding in patients with malignancies raises concerns about the use of anticoagulant drugs. Especially in patients undergoing chemotherapy, it is an approached adopted in current practice to switch to low molecular weight heparins and continue the chemotherapy process with heparin treatment, due to the difficulty in maintaining the therapeutic window and the fact that these patients do not infrequently require diagnostic and treatment interventions during the cancer therapy process. On the other hand, many studies excluded patients with active malignancies, and the remaining studies included small numbers of cancer patients. In the ARISTOTLE study, apixaban was more effective and safer than VKA in patients with active malignancy or a history of malignancy (28).

A published prescription registry analysis showed that bleeding and thrombotic risks were similar in patients with and without malignancy and that NOACs used at standard doses were more effective in both bleeding thromboembolism risks in both groups (29). Another important point to consider is that the interaction of chemotherapeutic drugs and NOACs is not yet fully known, and NOACs should be used more carefully in patients receiving chemotherapy (18). It is important to use proton pump inhibitors along with NOACs in patients with malignancy to reduce the bleeding risk.

5. Cardioversion and NOACs

Current guidelines recommend anticoagulation at least 3 weeks before cardioversion and 4 weeks afterward, regardless of the type of cardioversion (30). Three different studies have been published comparing the use of apixaban, edoxaban, and rivaroxaban with the use of VKAs in patients undergoing cardioversion (31-33). Data regarding dabigatran and cardioversion were presented in a post-hoc analysis of the RELY study (34). As a result of these studies, both thromboembolic events and bleeding rates were observed to be lower with each of the four NOACs compared to warfarin, but none of these studies had the statistical power to evaluate superiority or non-inferiority.

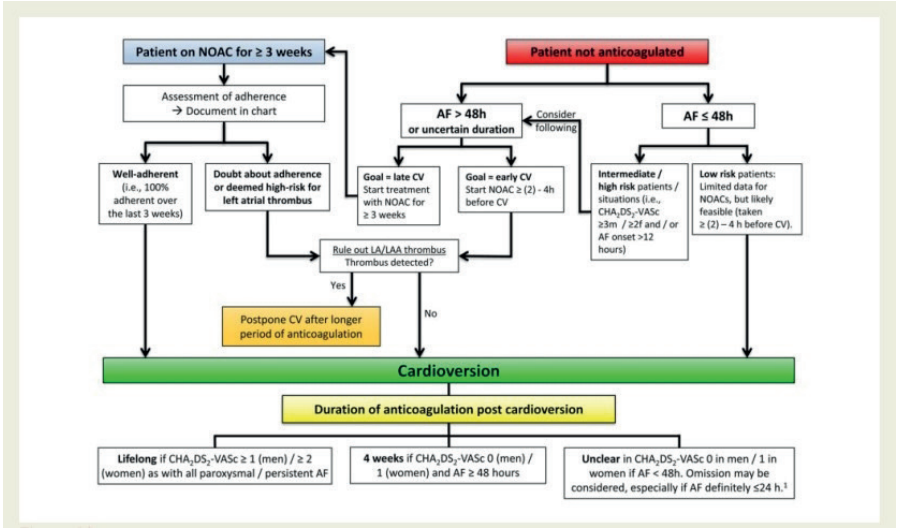

Figure 5. Practical management of patients that cardioverted with or without NOAC therapy (16).

6. NOAC treatment in venous thromboembolism and pulmonary embolism

In RCTs regarding the use of NOACs in the treatment of venous thromboembolism (VTE) and pulmonary embolism (PE), patients using dabigatran and edoxaban received parenteral heparin therapy for at least 5 days before starting oral therapy. Dabigatran 150 mg twice daily and edoxaban 60 mg once daily have been used. In studies of apixaban and rivaroxaban, parenteral anticoagulant treatment was not given beforehand and anticoagulation was started directly with NOAC. The results of these studies showed that NOAC treatment was non-inferiority and safer than standard heparin and VKA treatment (35). As a result of these RCTs and meta-analysis, NOAC treatment was included in the PE guideline with a Class-1 indication (36). In a meta-analysis, 5 RCTs involving a total of 7897 were examined and similar results were obtained with NOAC treatment compared to standard VKA treatment in deep vein thrombosis, PE, recurrent PE, recurrent VTE, all-cause of death and major bleeding (37).

7. AF patients presenting with acute stroke while on NOACs

Ischemic stroke occurs in 1-2% of patients receiving anticoagulant therapy each year. When encountering such patients, medication compliance should be questioned first. If there is an opportunity to optimize treatment

in secondary prevention, drug levels can be measured at admission to the hospital (38). Thrombolytic therapy within 4.5 hours after stroke is an important treatment in suitable patients. Fibrinolytic therapy cannot be used in patients receiving anticoagulant therapy. Thrombolytic therapy should not be administered to patients receiving NOAC until 24 hours after the last dose. Alternatively, anticoagulant therapy with idarucizumab can be rapidly reversed in patients receiving dabigatran. Published case series have reported that intravenous thrombolytic therapy is possible and safe after the reversal of dabigatran effect (39, 40). In addition, fibrinolytic treatment can be applied by measuring the plasma level Factor Xa inhibitors, but the use of rapid tests measuring plasma levels is not yet widespread worldwide. If measurable, fibrinolytic treatment can be safely applied at levels below 30 ng/mL. (41).

There is no RCT on which NOAC treatment should be chosen or drug switching in patients with ischemic stroke under NOAC treatment.

When to restart NOAC treatment after stroke should be determined according to the patient's risk of re-ischemic stroke and hemorrhagic transformation secondary to stroke. In patients who have a transient ischemic attack and are shown to have no bleeding by CT or MRI, anticoagulation should be restarted after 1 day. In patients with mild neurological deficits (National Institutes of Health Stroke Scale score, NIHSS, below 8), it is recommended to restart anticoagulation treatment 3 days after onset of the event. In patients with moderate neurological deficits (NIHSS between 8 and 15) the presence of bleeding should be evaluated with CT or MRI on day 6. If there is no bleeding, restarting anticoagulant treatment should be considered. In patients with the severe neurological deficit (NIHSS over 16), anticoagulant treatment should be started on 12th day and bleeding status should be evaluated with imaging methods (1, 18).

It has been shown that the prognosis of patients receiving NOAC therapy and developing intracranial bleeding is similar to that of patients experiencing bleeding under VKA (42). In these patients, NOACs should be discontinued immediately and the coagulation status should be corrected. Idarucizumab should be used in patients receiving dabigatran therapy. Andexanet alfa can be used in patients who develop bleeding under Factor Xa inhibitors.

The decision and timing of restarting anticoagulant treatment after intracranial bleeding is evaluated together with the degree of regression of intracranial bleeding, the risk of recurrence, and the patient's risk of ischemic stroke. An individualized decision should be made based on the benefit/loss ratio on a patient basis.

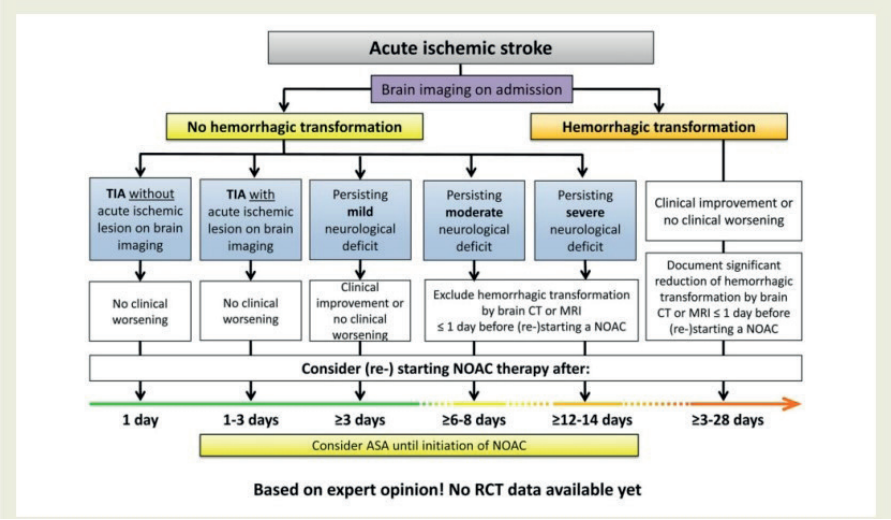

Figure 6. Re-initiation of anticoagulation after TIA/stroke. Without proven evidence/ RCT data available, based on expert opinion (16).

7. AF patients presenting with bleeding on NOACs

Studies have shown that NOACs cause less intracranial and life-threatening bleeding than VKAs. In addition, more positive results were obtained in patients receiving NOAC, especially intracranial bleeding, compared to warfarin (43-45). In patients with bleeding, treatment methods are determined according to the severity of the bleeding. The first thing to do is to increase the diuresis of the drug the wear off. Other options are the use of specific (antidotes) and nonspecific agents (prothrombin complexes). Fresh frozen plasma, protamine and vitamin K are ineffective in bleeding with NOAC (46). Local hemostatic methods should be used in minor bleeding that occurs under NOAC treatment. If recurrent bleeding occurs despite precautions, it is necessary to switch to a NOAC with a different bleeding profile or dose adjustment should be made.

In case of major bleeding that is not life-threatening, adequate diuresis, especially in dabigatran, should be provided. If idarucizumab cannot be reached in case of severe bleeding with dabigatran, dialysis may be considered in patients with renal failure (18). Dialysis is ineffective in bleeding due to the factor Xa inhibitors because they are highly bound to the plasma proteins. Tranexamic acid or desmopressin may be considered, especially in patients with coagulopathy. Studies are showing the benefits of using tranexamic acid, especially in patients with bleeding due to trauma (47).

In case of major bleeding that is life-threatening idarucizumab and andexanet alfa should be used. Idarucizumab is administered as two bolus doses of 2.5 g and its effect begins within minutes. In clinically appropriate patients, dabigatran can be restarted 24 hours after treatment. Andexanet alfa should be used in different doses depending on the NOAC type and the last time the drug was taken. In cases where antidotes are not available, the use of prothrombin or activated prothrombin coagulation complexes should be considered. Which of these two complexes is preferred should be based on the center's experience (18).

8. NOACs for patients undergoing surgical or percutaneous intervention

When to stop NOAC before surgery and when to start again after surgery should be determined according to the characteristics of the patients such as age, bleeding history, kidney functions, and the type of surgical operation. In dental procedures, cataract and glaucoma operations, superficial surgeries, and endoscopies that do not require biopsy, the operation should be performed without discontinuing anticoagulant treatment, even if bleeding can be easily stopped and the risk of bleeding is very low. Such operations can be performed 12-24 hours after the last NOAC dose. The appropriate approach is to start the anticoagulant agent again 6 hours after the procedure. It is recommended to perform the procedure 24 hours after the last NOAC dose in patients with normal kidney functions and low bleeding risk (endoscopic procedure, prostate or bladder biopsy, electrophysiological studies and ablations, pacemaker implantation or non-coronary angiographic interventions).

In patients receiving dabigatran, if the CC is 30-50 mL/min, the last 4 doses should not be given, if it is between 50-80 mL/min, the last 3 doses, and if it is over 80 mL/min, the last 2 doses should not be given and the procedure should be performed. In patients receiving Factor Xa inhibitors and whose CC is between 15-29 mL/min, the last dose should be taken at least 36 hours before the procedure and not continued afterward.

In a big meta-analysis including 9 RCTs, the effectiveness and safety of NOACs (other than edoxaban) and VKA were compared in patients undergoing surgical procedures (48). The majority of patients underwent surgical interventions with a low or very low risk of bleeding. The frequency of embolic events observed in patients receiving NOAC and VKA therapy was similar, but the frequency varied according to the type of surgery performed. Perioperative major bleeding rates were similar in both groups.

Additionally, in the analysis, bleeding occurred more with dabigatran than with warfarin, and with the other two NOACs at rates similar to warfarin. There was no change in bleeding rates according to surgery type.

It is recommended that NOAC should be discontinued 48 hours or earlier in operations such as polypectomy with high-risk bleeding, complex endoscopic procedures, thoracic and abdominal surgeries, epidural, spinal anesthesia, liver, and kidney biopsy. In patients receiving dabigatran, treatment should be stopped gradually according to CC. It should be kept in mind that bridging with LMWH is not recommended before any operations. The bridging therapy causes an increase in the risk of bleeding (49).

If postoperative bleeding control is fully achieved, NOAC can be restarted 6-8 hours after the operation. In types of operations where the risk of bleeding continues for 48-72 hours, thromboprophylaxis should be started 6-8 hours after the operation and NOAC should be postponed during this period. There is no data regarding the use of low-dose NOAC after surgery.

NOACs should be discontinued in patients undergoing emergency surgery. If there is an opportunity for emergency surgeries that need to be performed within minutes, idarucizumab should be used for dabigatran, andexanet alfa should be used for Factor Xa inhibitors (50). If antidotes cannot be obtained, routine coagulation tests should be performed, non-specific bleeding precautions should be taken, and general anesthesia should be preferred for the operation (49). In operations should be performed within hours, the intervention should be postponed at least 12 hours, ideally 24 hours, after the last dose received (18).

9. Conclusion

NOACs are drugs used as an alternative to VKAs in the treatment of AF and venous thromboembolism. In studies, similar or better results were obtained with the use of NOACs than VKAs in terms of effectiveness and reliability. Each NOAC preparation has different metabolic properties. It is expected that the use of NOACs in patients with high bleeding risk will increase with the introduction of two antidotes (idaricuzimab and andexanet alfa) that have recently been approved for use in bleeding. Their use will become safer with ongoing and upcoming new RCTs.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al, 2016 ESC guidelines for the management of atrial fibrillation developedin collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO). Eur Heart. 2016;J37:2893-962.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498.
3. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019;140:e125-51.
4. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm 2017;33:345-67.
5. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
6. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. Eur Heart J 2011;32:1968-76.
7. Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB et al.; ESC Scientific Document Group. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace 2017;19:1757-8.
8. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.

9. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ et al.; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013;369:1206-14.

10. Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, Travassos KSO, Pereira LV, Filho JAL, et al. Rivaroxaban Versus Warfarin in Patients with Mechanical Heart Valves: Open-Label, Proof-of-Concept trial-The RIWA study. Am J Cardiovasc Drugs. 2021;21(3):363-71.

11. Guimaraes HP, Lopes RD, de Barros E, Liporace IL, Sampaio RO, Tarasoutchi F et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med 2020;383:2117-26.

12. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. JACC Cardiovasc Interv 2017;10:66-74.

13. Kawashima H, Watanabe Y, Hioki H, Kozuma K, Kataoka A, Nakashima M et al.; OCEAN-TAVI Investigator. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation after TAVR. JACC Cardiovasc Interv 2020;13:2587-97.

14. Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol 2020;7:e18-27.

15. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood 2018;132:1365-71.

16. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021;23(10):1612-676.

17. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467–507.

18. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal. 2018;00:1-64.

19. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-104.

20. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin

in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014;129:961-70.

21. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012;33:2821-30.
22. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE Randomized Clinical Trial. JAMA Cardiol. 2016;1:451-60.
23. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, et al. Ontreatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from ROCKET AF. Circulation. 2016;134:37-47.
24. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 2015;131:972-9.
25. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017;28:2241-8.
26. Sexton DJ, Freitas DG, Little MA, McHugh T, Magee C, Conlon PJ, et al. Direct-Acting Oral Anticoagulants as Prophylaxis Against Thromboembolism in the Nephrotic Syndrome. Kidney Int Rep. 2018;3(4):784-93.
27. Lauschke VM, Ingelman-Sundberg M. The importance of patient-specific factors for hepatic drug response and toxicity. Int J Mol Sci. 2016;17:1714
28. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
29. Ording AG, Horvath-Puho E, Adelborg K, Pedersen L, Prandoni P, Sørensen HT. Thromboembolic and bleeding complications during oral anticoagulation therapy in cancer patients with atrial fibrillation: a Danish nationwide population-based cohort study. Cancer Med. 2017;6:1165-72.
30. Corrigendum to: 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Feb 1;42(5):546-47.
31. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J. 2014;35:3346-55.

32. Ezekowitz MD, Pollack CV, Sanders P, Halperin JL, Spahr J, Cater N, et al. Apixaban compared with parenteral heparin and/or vitamin K antagonist in patients with nonvalvular atrial fibrillation undergoing cardioversion: rationale and design of the EMANATE trial. AmHeart J. 2016;179:59-68.

33. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. Lancet. 2016;388:1995-2003.

34. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011;123:131-6.

35. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320-8.

36. Konstantinides SV, Torbicki A, Giancarlo A, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal. 2014;35:3033-80.

37. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database of Systematic Reviews. 2015, Issue 12. Art. No.: CD010957. DOI:10.1002/14651858.CD010957.pub2.

38. Purrucker JC, Haas K, Rizos T, Khan S, Poli S, Kraft P, et al. Coagulation Testing in acute ischemic stroke patients taking non-vitamin K antagonist oral anticoagulants. Stroke. 2017;48:152-8.

39. Tse DM, Young L, Ranta A, Barber PA. Intravenous alteplase and endovascular clot retrieval following reversal of dabigatran with idarucizumab. J Neurol Neurosurg Psychiatry. 2017.

40. Kermer P, Eschenfelder CC, Diener HC, Grond M, Abdalla Y, Althaus K, et al. Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany-a national case collection. Int J Stroke. 2017;12:383-91.

41. Drouet L, Bal Dit Sollier C, Steiner T, Purrucker J. Measuring non-vitamin K antagonist oral anticoagulant levels: when is it appropriate and which methods should be used? Int J Stroke. 2016;11:748-58.

42. Wilson D, Seiffge DJ, Traenka C, Basir G, Purrucker JC, Rizos T, et al. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. Neurology. 2017;88:1693-700.

43. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. J Am Coll Cardiol. 2014;63:2141-7.

44. Piccini JP, Garg J, Patel MR, Lokhnygina Y, Goodman SG, Becker RC, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. Eur Heart J. 2014;35:1873-80.

45. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation. 2013;128:2325-32.

46. Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:3042-67.

47. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23-32.

48. He H, Ke B, Li Y, Han F, Li X, Zeng Y. Novel oral anticoagulants in the preoperative period: a meta-analysis. J Thromb Thrombolysis. 2018;45(3):386-96.

49. Beyer-Westendorf J, Gelbricht V, Forster K, Ebertz F, Kohler C, Werth S, et al. Peri- interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014;35:1888-96.

50. Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375: 1131-41.