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REVIEW **DERLEME**

USE OF NOAC IN CLINICAL PRACTICE OF STROKE:

EXPERT OPINION OF THE TURKISH SOCIETY OF CEREBROVASCULAR DISEASES

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ABSTRACT

It is clear that nonvitamin K oral anticoagulants (NOACs) have been used successfully for more than ten years to prevent stroke in atrial fibrillation. In addition to the fact that they cause significantly less bleeding compared to warfarin and can prevent stroke equally or more, their easy-to-use features stand out in reducing stroke due to atrial fibrillation in primary prophylaxis. These also mean a decrease in the overall prevalence of stroke. For sure, prevention of AF-induced stroke should be perceived as a contemporary requirement for public health. Turkish Society of Cerebrovascular Diseases has prepared this expert opinion for neurologists who strive for this purpose together with cardiologists in the clinical practice of stroke. The article contains frequently encountered problems in the use of NOACs and current solutions for these problems.
Keywords: Cerebral embolism, embolism, stroke, cardioembolism, paroxysmal, atrial fibrillation, prevention.

İNME KLİNİK PRATİĞİNDE NOAK KULLANIMI:

TÜRK BEYİN DAMAR HASTALIKLARI DERNEĞİ UZMAN GÖRÜŞÜ

ÖZ

Non-vitamin K oral antikoagülanların (NOAK) atrial fibrilasyonda inmenin önlenmesi amacıyla on yılı aşan bir süredir başarı ile kullanıldığı açıktır. Varfarine göre belirgin derecede az kanamaya yol açmaları ve inmeyi de eşit veya daha fazla oranda önleyebilmeleri yanı sıra kolay kullanım özellikleri primer proflakside atrial fibrilasyona bağlı inmeyi azaltma konusunda öne çıkmaktadır. Bunlar aynı zamanda genel inme prevalansının azalması anlamına gelmektedir. Yani AF nedenli inmenin engellenmesi toplum sağlığı için çağdaş bir gereklilik olarak algılanmalıdır. İnme klinik pratiğinde kardiyoloji uzmanları ile birlikte bu bağlamda çaba sarf eden nöroloji uzmanları için Türk Beyin Damar Hastalıkları Derneği bu uzman görüşünü hazırladı. Görüşler NOAK grubu ilaçların kullanımında sıkça karşılaşılan sorunlar ve bu problemler için güncel çözüm önerilerini içermektedir.
Anahtar Sözcükler: Serebral embolizm, emboli, inme, kardiyoemboli, paroksismal, atrial fibrilasyon, korunma.

1. Overview of Non-Vitamin K Oral Anticoagulants, Brief Introduction and Pharmacology of Drugs

Anticoagulant drugs are used in the prevention and treatment of venous and arterial thromboembolic diseases. Anticoagulants include various agents that inhibit one or more steps in the coagulation cascade. The history of anticoagulants begins with the discovery of unfractionated heparins. Later, vitamin K antagonist oral anticoagulants (OAC), low molecular weight heparins (LMWH), parenteral direct thrombin inhibitors, and indirect factor Xa (FXa) inhibitor fondaparinux were found, respectively. In recent years, there has been a significant improvement in oral anticoagulant drug options with the introduction of direct-acting oral anticoagulants called non-vitamin K oral anticoagulants (NOAC) (1). NOAC include direct thrombin inhibitors (DTI) and direct FXa inhibitors. DTI suppresses fibrin formation from fibrinogen which is the last step of the coagulation cascade, by blocking free and fibrin-bound thrombin (factor II). The only oral DTI available for clinical use is Dabigatran etexilate. Direct FXa inhibitors prevent the formation of thrombin from prothrombin and are active against both free FXa and FXa bound to the prothrombinase complex (2). Oral direct FXa inhibitors; apixaban, betrixaban, edoxaban and rivaroxaban. The effect of anticoagulant drugs including NOACs on the coagulation cascade is shown in Figure 1.

Apixaban, dabigatran, edoxaban, and rivaroxaban are used for prevention of stroke and venous thromboembolism in patients with nonvalvular AF (NVAF). Betrixaban, on the other hand, has the longest half-life with 19-27 hours and is the newest oral direct FXa inhibitor that was put into use in 2017. It is an anticoagulant approved for long-term venous thromboembolism prophylaxis in patients at risk of thromboembolic complications but is not indicated in patients with NVAF (3).

The fact that it can be applied at a fixed dose and does not require a routine laboratory follow-up in terms of pharmacokinetics and

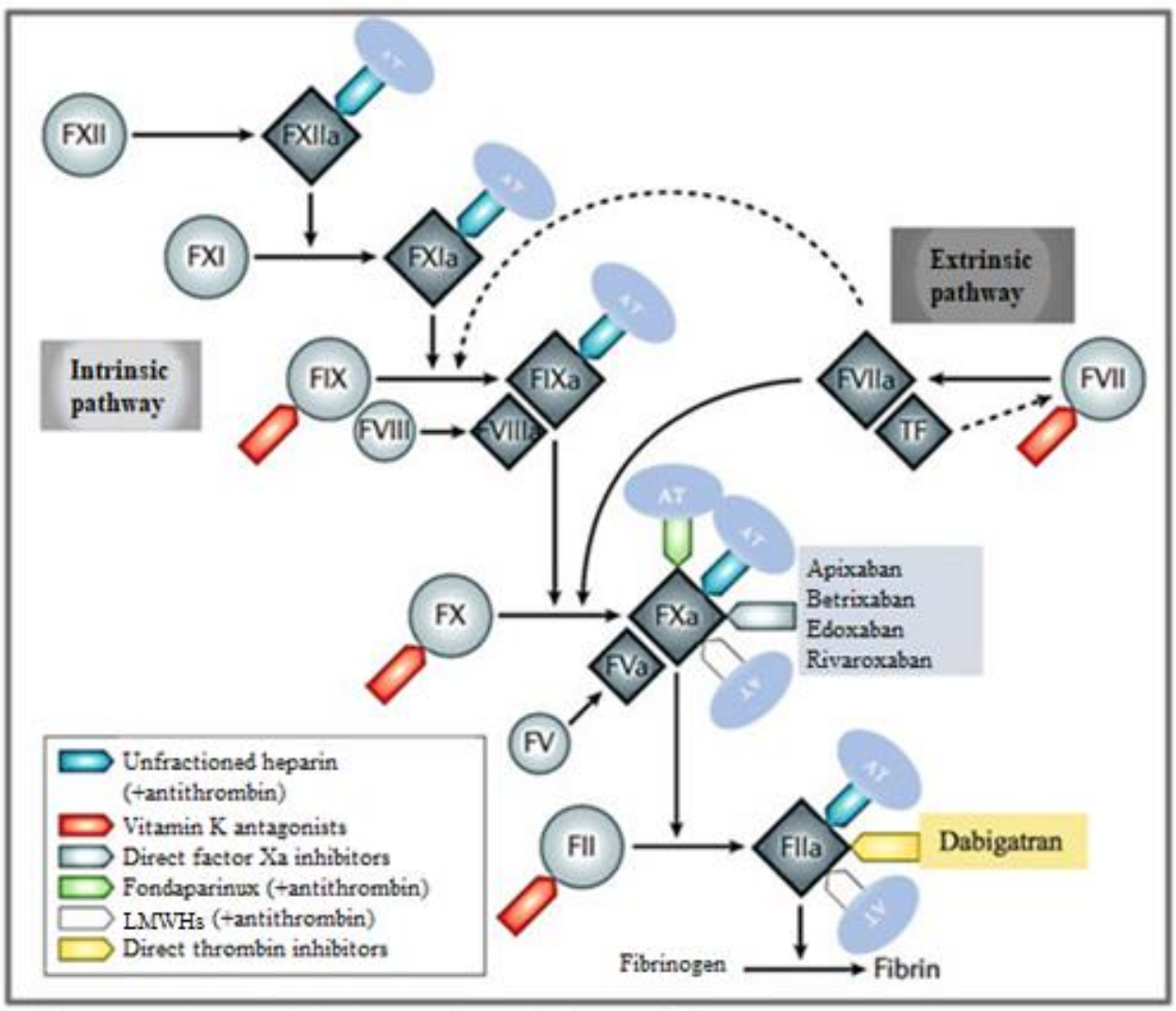

Figure 1. Coagulation cascade and the effects of anticoagulants*.
*Adapted from Perzborn E, Roehrig S, Straub A, et al. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Nat Rev Drug Discov. 2011;101:61-75. Abbreviations: AT: Anti-thrombin, LMWH: Low molecular weight heparins, TF: Tissue factor.

pharmacodynamics is considered as the advantage of NOACs in use. Clinical studies have shown that there is a clear correlation between plasma concentrations of NOACs and their pharmacokinetic anticoagulant effects and that they have predictable pharmacokinetic properties. However, under NOAC treatment, the risk of thromboembolism and bleeding can vary from person to person and is affected by factors such as patient demographics, comedication and kidney function. Unpredictable anticoagulant effects may occur as the same dose causes varying plasma concentrations in different patients (2). For an effective treatment, the NOAC plasma concentration should be in the therapeutic range above 70%. Therefore, a personalized treatment approach should be taken with the consideration of the pharmacokinetic and pharmacodynamic properties of NOACs. NOAC plasma levels increase when patients are over 75-80 years old, weigh less than 60 kg, and develop renal failure (4). NOAC absorption may be altered in patients whose gastrointestinal system anatomy has changed due to obesity surgery or other reasons. Obesity is not an exclusion criterion for NOAC treatment, but in cases with a body mass index over 40 kg / m^2, treatment failure due to low serum levels with dabigatran, for example, has been reported in case

reports (4).

Another important mechanism of interaction for all NOACs is that they undergo a significant gastrointestinal secretion via a P-glycoprotein (P-gp) transporter after absorption in the intestines. Competitive inhibition of this pathway results in increased NOAC plasma levels. Conversely, potent inducers of P-gp significantly reduce NOAC plasma levels. In addition, CYP3A4-type cytochrome P450-dependent elimination plays a role in hepatic clearance of rivaroxaban and apixaban. Potent CYP3A4 inhibition or induction may affect the plasma concentrations of these two drugs. Apart from pharmacokinetic interactions, co-administration of other anticoagulants, platelet inhibitors (e.g. aspirin, clopidogrel, ticlopidine, prasugrel, ticagrelor, and others) and nonsteroidal anti-inflammatory drugs increases the risk of bleeding due to pharmacodynamic interactions (4).

Absorption and metabolism properties of NOACs are presented in Table 1.

NOACs are not indicated in patients with mechanical prosthetic valve, moderate and severe mitral stenosis, pregnancy, active bleeding, advanced stage renal failure and dialysis, severe liver failure and antiphospholipid syndrome (3).

In NVAF patients, apixaban is used at a dose of 2x5 mg and 2x2.5 mg if two of the following three conditions (weight <60 kg, age> 80 and serum creatinine> 1.5 mg / dL).

The recommended dose of dabigatran is 2x150 mg. A dose of 2x110 mg is preferred for patients over 80 years of age, concomitant use of verapamil and increased risk of gastrointestinal bleeding. Its use is not recommended in patients with creatinine clearance <30 ml / min.

The standard dose of edoxaban is 1x60 mg. It should be used as 1x30mg in therapy together with potent P-gp inhibitor, weight <60 kg, creatinine clearance between 15-49 ml/min. Due to the increased clearance of the drug in patients with creatinine clearance of >95 ml/min, caution should be exercised in its use.

The standard dose of rivaroxaban is 1x20 mg. It should be used at 1x15 mg in patients with a creatinine clearance between 15-49 ml / min. The use of apixaban, edoxaban, and rivaroxaban is not recommended in patients with creatinine clearance of <15 ml / min (4).

However, in patients with a creatinine clearance of <15 ml / min or in patients under dialysis, apixaban is recommended in the AHA / ACC / HRS guidelines with a low degree of evidence (5). [See 5.1 for NOAC usage guidelines in renal dysfunction.]

Table 1. Absorption and metabolism properties of NOACs (4).

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Effect mechanism	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability	50%	3-7%	62%	15/20 mg: 66% before meals, 80%-100 with food
Pre-medication	No	Yes	No	Yes
Renal clearance of absorbed dose	27%	80%	50%	35%
Binding to plasma proteins	87%	35%	55%	95%
Dialysis ability	14% (partially dialysable)	50-60% (partially dialysable)	Not applicable	Not applicable
P-gp substrate	Yes	Yes	Yes	Yes
Liver metabolism: including CYP3A4	Yes (~25%)	No	Minimum (<4%)	Yes (~18%)
Absorption with food	No effect	No effect	Minimum effect (6-22% increase)	39% increase
Absorption by H2 receptor blockers and proton pump inhibitors	No effect	12-30% decrease (clinically not significant)	No effect	No effect
Asian ethnicity	No effect	25% increase	No effect	No effect
Elimination half-life	12 hours	12-17 hours	10-14 hours	5-9 hours (young) 11-13 hours (old)
Other		Dyspepsia (5-10%)		Must be taken with food

2. Major Non-vitamin K Oral Anticoagulant Studies in Preventing Stroke in Atrial Fibrillation

Anticoagulant therapy is very important in preventing thromboembolic complications, especially stroke, in patients with AF. As a result of clinical studies comparing NOAC group drugs with warfarin in the recent past, it is seen that it has been used as an additional treatment option. Although the effectiveness of warfarin in preventing cerebral ischemic events in patients with AF is known, new treatments have been sought and NOACs have been developed due to its serious side effects and difficulties in usage. While dabigatran, one of the NOAC group agents, is a direct thrombin inhibitor, Rivaroxaban, apixaban and edoxaban act as direct factor Xa inhibitors.

2.1. RELY Study (Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy): The benefits of dabigatran in preventing stroke in patients with AF have been demonstrated in a prospective and randomized RELY study (6). Patients with a $CHADS_2$ (Table 2) score greater than 1 were included in the study. Warfarin and dabigatran were given twice a day at a dose of 110 mg or 150 mg to approximately 18000 patients with AF. The warfarin dose was targeted to be between INR 2-3. While the effect of 110 mg dabigatran twice a day in preventing stroke and systemic embolism was similar to warfarin, dabigatran high dose was found to be superior to warfarin. Again, in both doses, the risk of intracranial bleeding was found to be lower than warfarin. In this study, the most common side effect of dabigatran was determined as dyspepsia. There was more gastrointestinal bleeding at the 150 mg dose of dabigatran compared to warfarin, but no increase was observed with the low dose.

Table 2. $CHADS_2$ score.

	Score	Score	Annual stroke risk, %
Heart failure	1	0	1.9
Hypertension	1	1	2.8
Age>75	1	2	4
Diabetes	1	3	5.9
Stroke/TIA	2	4	8.5
		5	12.7
		6	18.2

Dabigatran is the first molecule in the NOAC group to be approved by the FDA ("US Food and Drug Administration"). A dose of 2x150 mg of dabigatran for the prevention of stroke in patients with AF was approved by the FDA in 2010, and the use of 2x75 mg is recommended in patients with creatinine clearance of 15-30 mL/min. In ESC ("European Society of Cardiology") guidelines, the HASBLED score (Table 3) is 0-2, a dose of 2x150 mg/day is recommended if the bleeding risk is low, and a dose of 2x110 mg of dabigatran is recommended if the bleeding risk is high, that is, if the HASBLED score is higher than 3 (7).

Table 3: HASBLED Score.

	Score	Score	Annual major bleeding risk	Annual bleeding risk in every 100 patients	Risk Category
Hypertension [Systolic blood pressure of ≥160 mmHg]	1	0	0.9	1.13	
Abnormal renal/hepatic function [Dialysis, creatinine ≥2,3; bil≥2, AST/ALT≥3, cirrhosis]	1+1	1	3.4	1.02	Relatively low
Stroke	1	2	4.1	1.88	Moderate
Bleeding [anemia, major predisposition]	1	3	5.8	3.72	High
Labil INR [TTR<60%]	1	4	8.9	8.7	
Advanced age [Age≥65]	1	5	9.1	12.7	
Drug [Anti-platelet and nonsteroid anti-inflammatory agents Alcohol consumption (≥8/week)]	1+1	6-9	10	12.7	Very high

2.2. ROCKET-AF Study (Rivaroxaban Once Daily Oral Direct FactorXa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation): The efficacy and safety of warfarin and rivaroxaban were compared in 14,264 patients with NVAF. In the double blind, randomized multicenter planned ROCKET-AF study (8); Warfarin with an INR of 2-3 was recommended with 20 mg rivaroxaban (15 mg dose in patients with creatinine clearance of 30–49 ml / min). At the same time, both groups were given a placebo tablet. Patients with a $CHADS_2$ score above 2 (mean CHADS2 score of 3.5) with

moderate and high risk of embolism were included in the study and were monitored for 590 days. As a result of the study, it was determined that rivaroxaban was at least as effective as warfarin in preventing ischemic stroke and systemic embolism (1.7% annually with rivaroxaban; 2.2% annually with warfarin). When major bleeding was evaluated as a side effect, rivaroxaban was similar to warfarin and intracranial bleeding and fatal bleeding rates were found to be lower in the rivaroxaban group compared to the warfarin group.

Rivaroxaban, a direct selective factor Xa inhibitor, is the second drug approved by the FDA in 2011 to prevent ischemic stroke in patients with AF.

2.3. ARISTOTLE Study (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): The efficacy of another agent, Apixaban, which is a direct factor Xa inhibitor, was investigated in a randomized, double-blind ARISTOTLE study (9). In this study, 18,201 patients with nonvalvular AF, with an average $CHADS_2$ score of 2.1, were included in the study. One group received two doses of 5 mg apixaban daily, and the other group received warfarin with an INR between 2-3. Patients were monitored for an average of 1.8 years. As a result of the study, it was observed that 5 mg apixaban twice a day was superior to warfarin in preventing ischemic stroke and systemic embolism (1.27% versus 1.60% annually). Bleeding rates were also found to be lower in patients in the apixaban group (2.13% annually in the apixaban group; 3.09% in the warfarin group). In addition, intracranial bleeding and mortality were found to be less in the apixaban group. If the creatinine clearance is between 15 and 29 ml / min, the dose of apixaban should be adjusted to 2.5 mg twice a day. In addition, if the patient is above the age of 80, serum creatinine is more than 1.5 mg / dL, body weight is less than 60 kg and two of these three criteria are present in the patient, the dose should be reduced. [See 5.1 for the guidelines for use of NOAC in kidney dysfunction.]

Apixaban was approved by the FDA in 2012 for the prevention of ischemic stroke in patients with AF.

2.4. ENGAGE AF-TIMI 48 Study (Edoxaban Once Daily to Prevent Stroke or Systemic Embolism): The efficacy and safety of warfarin and edoxaban in patients with AF were compared in a double-blind, randomized multicenter ENGAGE AF-TIMI 48 study (10). 21.105 patients with a mean $CHADS_2$ score of 2.8 were included in the study, and the patients were monitored for an average of 2.8 years. In a group of patients, edoxaban was given 30 mg once a day or as high dose of 60 mg, and warfarin was given to the other group to keep the INR between 2-3. As a result of the study, it was emphasized that both 30 mg and 60 mg edoxaban doses (1.18% and 1.61% per year) were similar to warfarin (1.5% per year) in preventing ischemic stroke and systemic embolism. When the rates of intracranial bleeding and major bleeding were compared, both doses of edoxaban groups were lower than warfarin. GIS bleeding was higher in the 60 mg edoxaban group compared to the warfarin group. It was similar in the 30 mg edoxaban group and the warfarin group.

The use of edoxaban in the prevention of ischemic stroke in patients with AF was approved by the FDA in 2016.

When all these randomized clinical trials are interpreted, in conclusion, it was emphasized that NOACs are at least as effective as warfarin, and dabigatran at a dose of 2x150 mg and apixaban is superior to warfarin in preventing ischemic stroke and thromboembolism. In general, NOACs caused a significant decrease in the risk of hemorrhagic stroke but did not cause a significant increase in the risk of major bleeding compared to warfarin (11).

3. Selection of Oral Anticoagulant Therapy for Stroke Prevention in Atrial Fibrillation

Anticoagulant treatment is of great importance in the management of patients with AF and in preventing embolic complications, especially stroke. In the prevention of AF-associated recurrent stroke in a secondary prevention perspective, all stroke patients are candidates for anticoagulant therapy unless there is an obstacle to treatment. In terms of primary prevention, it is recommended that the decision of anticoagulant therapy in patients with AF should be made in the light of the CHA_2DS_2VASc score (12) (Table 4) (Figure 2).

For many years, the range of drugs in anticoagulant treatment with vitamin K antagonists (VKA) has expanded with the use of NOACs as a result of multi-center studies detailed in the previous section. Today, EMA ("European Medicines Agency") and FDA have approved only for NVAF diagnosis for apixaban, dabigatran, edoxaban and rivaroxaban.

Although the basis of this approval is that patients with mechanical prosthetic valve and moderate-to-severe rheumatic mitral stenosis were not included in these studies, the concept of valvular and non-valvular caused confusion in clinical practice in the selection phase of vitamin K antagonist or NOAC treatment.

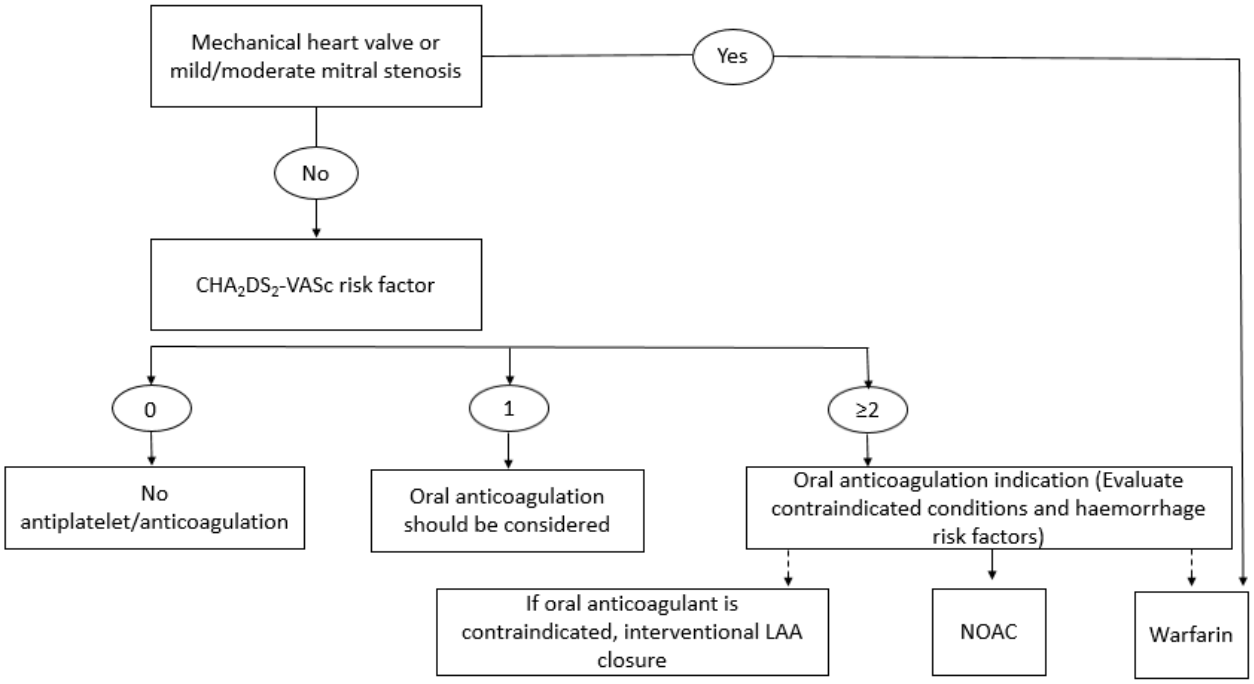

Figure 2. Clinical approaches to anti-coagulant treatment*
*Adapted from Kirchhof P et al., 2016, in the light of the recommendations from the 2016 ESC guidelines.

Table 4. CHA_2DS_2VASc Score.

Criterion	Score	Score	Annual Stroke Risk	Stroke Recurrence
Heart Failure	1	0	0-0.2	0 : Low risk
Hypertension	1	1	0.9-1.3	1-2 : Moderate risk
Age>75	2	2	2.2-2.9	
Diabetes	1	3	3.2-4.6	≥3 : High riski
Stroke	2	4	4.8-6.7	
Vascular disease	1	5	6.7-10	
Age range of 65-74	1	6	9.8-13.6	
Female	1	7	9.6-15.7	
		8	6.7-15.2	
		9	15.2-17.4	

3.1. Valvular and Non-valvular AF Definition: Heart valve disease, in broadest terms, is the damage or defect in one or more of the four heart valves. In NOAC studies evaluating the prevention of AF-associated embolic complications, the presence of only mechanical prosthetic valve and moderate to severe rheumatic mitral stenosis as valvular heart disease was a common exclusion criterion. On the other hand, in the light of different patient recruitment criteria of the studies, it was present in a considerable proportion of patients with various valvular heart diseases (13-26%) (13). Approximately 60% of AF patients have an accompanying valvular heart disease in clinical practice (14).

Valvular and nonvalvular AF are included in various guidelines with different definitions and these definitions have changed over the years. In the 2001 ACC ("American College of Cardiology") / AHA ("American Heart Association") / ESC guidelines, NVAF is defined as a rhythm disorder without rheumatic mitral or prosthetic valvular heart disease (15). In the 2006 update, AF developing without mitral valve repair was also included in this definition. In the 2014 ACC / AHA / HRS ("Heart Rhythm Society") guidelines, NVAF is described as AF detected without rheumatic mitral stenosis, mechanical or bioprosthetic heart valve replacement or mitral valve repair (16).

ESC defined valvular AF as AF that develops in the presence of rheumatic valvular disease (with mitral stenosis in the foreground) or prosthetic valve, and then due to the confusion created by the concept of valvular, they started to use valvular heart disease terminology by referring to the specific pathology in its guidelines since 2016 (7,12). ACCP used the concepts of non-rheumatic AF and NVAF synonymously (17). In order to distinguish NVAF from valvular AF, the definition of "mechanical and rheumatic mitral valvular AF" (MARM-AF) has been included in the literature as a terminological suggestion (18).

With the use of NOAC treatment based on AF, specifically in the NVAF patient subgroup, the need for a clearer and globally accepted definition for the distinction between valvular and non-valvular AF has emerged. In this context, under the leadership of EHRA (European Heart Rhythm Association), a consensus document was published in 2017 and a functional classification was made in which the type of anticoagulant to be used was emphasized (Table 5) (13).

As emphasized in this classification, all AF patients, except for the AF patients with a mechanical prosthetic heart valve and moderate-severe rheumatic mitral stenosis (Table 6), can receive NOAC treatment within the appropriate indications (19).

Table 5. EHRA Classification of AF.

EHRA type 1; Patients with valvular AF requiring vitamin K antagonist therapy
• Mitral stenosis (moderate-severe, rheumatic origin)
• Mechanical prosthetic valve replacement
EHRA type 2; Patients with valvular AF (in light of CHA_2DS_2VASc score criteria) requiring a vitamin K antagonist or NOAC treatment
• Mitral regurgitation
• Mitral valve repair
• Aortic stenosis
• Aortic regurgitation
• Tricuspid regurgitation
• Tricuspid stenosis
• Pulmonary regurgitation
• Pulmonary stenosis
• Bioprosthetic valve replacement
• Trans-aortic valve intervention (TAVI)

Table 6. Mitral stenosis severity grading.

	Mean gradient (mmHg)	Pulmonary artery systolic pressure (mmHg)	Valve area (cm^2)
Mild	<5	<30	>1.5
Moderate	5-10	30-50	1-1.5
Severe	>10	>50	<1.0

3.2. How Does Valvular Heart Disease Accompanying AF Affect Thrombogenesis? There is a hypothesis that thrombus formation in patients with NVAF may be different from those with accompanying valvular heart disease. Blood flow changes in Virchow triad, endocardial damage and exchange of blood elements play a role in the mechanism of thrombogenesis in patients with AF. However, presence of mechanical heart valve, mitral stenosis and left atrial dilatation increases the occurrence of thromboembolism in patients with AF. Typically, thrombus develops in the left atrial appendix in patients with AF. In patients with mechanical prosthetic heart valves, thrombus usually develops on the prosthesis or as a result of the non-physiological blood flow pattern in the left atrium (20). In addition, the fact that the heart valve, which can be considered as a foreign body, activates thrombogenesis by using the intrinsic pathway can also be thought as an additional mechanism. Patients with bioprosthetic heart valves have a lower risk of thrombosis, but this risk is never zero. Thrombosis risk increases with accompanying AF or mitral stenosis in these patients. Those with porcine heart valves have a higher risk of thrombosis than pericardial valve (21). Although the exact mechanism is unclear, the presence of mitral stenosis also increases the risk of thrombosis. The possible factor here is thought to be impaired blood flow in the left atrium (22).

3.3. NOAC Use in Mechanical and Bioprosthetic Valve Replacement: Patients who underwent mechanical heart valve replacement were excluded in all phase III clinical trials of NOAC use. However, in preclinical studies of both apixaban and dabigatran in pigs, it has been shown that they reduced the thrombus size significantly in bileaflet mechanical aortic valve implantation and that the development of bleeding was less than warfarin (23,24). In the RE-ALIGN ("Randomized Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement") study based on these data, dabigatran and warfarin were compared in patients who underwent mechanical bileaflet mitral or aortic valve. The study had to be terminated early with negative data on the protective efficacy and safety of dabigatran treatment. In the light of these data, warfarin remains to be the only oral anticoagulant treatment option in patients with AF with a mechanical heart valve (25).

Despite this negative experience with a mechanical valve, NOAC treatment offers more promising results in the presence of a bioprosthetic valve. DAWA ("Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively") which is one of the NOAC studies specific to patients with bioprosthetic caps, was stopped due to insufficient participation. On the other hand, ARISTOTLE and ENGAGE AF-TIMI-48 studies did not consider the presence of bioprosthetic valve as an exclusion criterion and offered the opportunity to perform subgroup analyses for these patients. 104 bioprosthetic valve patients in ARISTOTLE study and 191 bioprosthetic valve patients in ENGAGE AF-TIMI 48 were randomized to the NOAC and warfarin groups, and in these limited analyses, where the number of stroke and systemic embolism was low, no significant difference was found between warfarin and NOAC in terms of efficacy and safety (13,26). In a meta-analysis comparing antiplatelet therapy and anticoagulation (warfarin and NOAC) treatments among those who had recently undergone bioprosthetic aortic valve replacement, no difference was found between treatments in terms of stroke, thromboembolism, or mortality (27). In the light of this information, EHRA, which classifies patients with AF accompanied by the presence of bioprosthetic valve as EHRA-2 group AF, recommends NOAC treatment as an alternative treatment to warfarin if the bioprosthetic valve has not been performed due to rheumatic mitral valve disease at least 3 after surgery (4). Again, in the light of the information obtained from patients with a history of valve repair in apixaban, edoxaban and rivaroxaban studies, although in a small number, this patient group stands out as another patient group considered suitable for NOAC treatment.

3.4. NOAC Use in AF Patients with Valvular Heart Disease: If we put aside patients with moderate to severe mitral stenosis who have not been subject to any randomized studies, all NOAC studies compared AF patients with certain proportions of accompanying valvular heart disease in the context of NOAC and warfarin treatment. The most common group of patients included for valvular heart disease were patients with moderate or severe mitral insufficiency (13);

which was followed by patients with aortic insufficiency, aortic stenosis, and mild mitral stenosis, respectively.

In the subgroup analyses of ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48 and ROCKET AF studies for individuals with valvular heart disease, NOAC efficacy and reliability were similar when compared with those without valvular heart disease (18,28-30). In these four studies, it is seen that patients with AF and valvular heart disease are more often women, and individuals with persistent AF with a history of heart failure, myocardial infarction or coronary artery disease. When compared with individuals without valvular disease, the presence of stroke or systemic embolism, mortality, major cardiovascular events, and major bleeding draws attention with higher rates. However, these differences were observed similarly in the NOAC or warfarin treatment groups and did not reveal a difference in the main study results in terms of efficacy/reliability. In the light of all this information, in these valvular pathologies considered within the scope of EHRA-2 group AF, NOAC treatment comes to the fore as an alternative in the presence of AF.

Recently, Kim et al. evaluated the effectiveness of NOACs in mitral stenosis patients retrospectively in 2230 patients with AF (31). The annual thromboembolic event rate in mitral stenosis patients using NOAC off-label was 2.2%, while this rate was 4.2% in warfarin (HR 0.28, 95% CI; 0.18-0.45). Although there are serious limitations due to not evaluating the degree of stenosis and its retrospective design, this study draws attention to the need for a randomized study for the efficacy and reliability of NOAC treatment in patients with mitral stenosis in the presence of natural valve.

In conclusion, the current European and American treatment guidelines recommend NOAC treatment as the first-choice anticoagulant treatment method in patients in whom anticoagulant therapy can be performed with either NOAC or warfarin, except for patients with mechanical prosthetic valve and moderate-to-severe mitral stenosis ("Class I, Evidence) level A") (5,12). Warfarin stands out as the only anticoagulant option in patients with mechanical valve and moderate to severe mitral stenosis ("Class I, Level of Evidence B"). NOAC therapy is not recommended in these patients. The European guidelines for the mechanical valve recommend "Class III, Evidence Level B" for all NOACs, and the American guidelines recommend "Class III, Evidence Level B-R" for dabigatran only. The recommendation for moderate-to-severe mitral stenosis is found only in the European guidelines ("Class III, Level of Evidence C").

4. Use of NOAC in Atrial Fibrillation other than Stroke Prophylaxis

4.1. Use of NOAC in Cerebral Venous Thrombosis: While the AHA 2011 guidelines recommend the use of anticoagulants in the treatment of cerebral vein thrombosis (CVT), it does not support the use of NOAC (32). The European Stroke Organization guidelines, updated in 2017, do not recommend the use of NOAC in SVT due to the lack of sufficient data (33,34).

The RE-SPECT CVT study compared the efficacy and reliability of dabigatran and warfarin in CVT. In this study of 120 cases, it was reported that venous thrombotic events did not recur in both groups and that a small number of major bleeding was encountered in both groups (35). In a meta-analysis published by Lee et al., 151 patients taking NOAC (dabigatran, rivaroxaban, apixaban) 261 patients taking VKA were monitored for 3-11 months. While it was determined that NOACs show similar efficiency with VKA in terms of partial / full recanalization; bleeding rates were found to be lower in patients using NOAC although there was no statistically significant difference. Although these results suggest that NOACs are an effective and safe alternative to VKA in the treatment of CVT, it was stated that it would be appropriate to wait for the results of randomized controlled studies (36).

4.2. NOAC Use in Cervical Artery Dissections: The effectiveness of NOACs in preventing ischemic strokes due to cervical artery dissection was compared with standard antithrombotic treatments in two studies. In the first study, it was reported that NOACs cause similar ischemic but less hemorrhagic complications with standard antithrombotic treatments. However, one study showed a higher rate of radiological deterioration than conventional antiplatelet or anticoagulant therapies (37). The second study found that there were no statistically significant differences between NOAC and VKA in terms of ischemic stroke severity and recanalization rates (38).

Although it is thought that NOACs can be an alternative in strokes that develop due to cervical artery dissection, the data regarding the use of NOAC in these patients should be interpreted carefully because of insufficient clinical experience, low number of patients enrolled in studies, and non-randomized treatment approaches (39,40).

4.3. Use of NOAC in Antiphospholipid Syndrome: There is limited information about the efficacy and reliability of using NOAC in antiphospholipid syndromes (APS). In a review that included 728 patients, it was reported that the annual risk of thrombosis in patients using NOAC is around 11%. The RAPS study compared the efficacy of rivaroxaban 20 mg once daily with warfarin (INR: 2.0-3.0) following a single or recurrent venous thromboembolic (VTE) event in 116 patients who were not anticoagulated or were sub-therapeutically anticoagulated, and no thrombotic events or bleeding in either group during the 7-month monitoring period was seen (41). In 3 randomized controlled studies in patients with APS, no difference was found between dabigatran and warfarin in terms of efficacy. EULAR ("European League Against Rheumatism") 2019 guidelines require that rivaroxaban should not be used in adult APS patients with high risk of recurrence due to triple antiphospholipid antibody positivity and recommend that NOACs should only be preferred in patients who cannot reach target INR values despite effective treatment compliance or for whom VKA use is contraindicated. EULAR guidelines also recommend not to switch from VKA to NOACs due to poor compliance with VKA treatment or problems in INR monitoring (42).

It is stated that there is a need for studies in which the clinical heterogeneity of APS as well as the antiphospholipid antibody laboratory phenotype are taken into consideration and the optimal NOAC dose is determined according to the thrombosis type. The Phase 2/3 RISAPS study aims to determine the effectiveness of treatment in stroke patients with a target INR of around 3.5 with 15 mg rivaroxaban twice a day (43).

4.4. NOAC Use in Cancer Patients: Cancer-related stroke is an uncommon condition, and in some patients, cerebral infarction develops before cancer is diagnosed. It is also known that the use of NOAC in cancer patients is not recommended and patients with AF who are diagnosed with cancer are not included in clinical studies (44). In a study conducted with 672 cancer patients in Taiwan, it was reported that the rates of ischemic stroke / systemic embolism and major bleeding were significantly lower in patients using NOAC compared to warfarin, and that intracerebral bleeding did not develop in any patient within a year. It was stated that there was no difference between the two groups in terms of gastrointestinal bleeding, acute myocardial infarction, and death from any cause within 6-12 months (45).

4.5. NOAC Use in Pregnancy: In a study in which a total of 357 pregnant women were examined, it was observed that 48.9% of those using NOAC had live birth, 22.6% had miscarriage and 28.5% had elective pregnancy termination. It was stated that fetal abnormality was encountered at a rate of 5% and 2% of it was defined as embryonopathy. Due to the low number of cases and insufficient data, it is stated that it is not known whether NOACs carry a high risk of embryonopathy during pregnancy and whether the use of NOAC is considered an indication for termination of pregnancy. Due to the lack of sufficient efficiency and reliability data, NOACs are not recommended to be used during pregnancy and breastfeeding (46).

4.6. Use of NOAC in Embolic Strokes of Undetermined Source: The concept of embolic stroke of unknown source ("ESUS") has been defined as non-lacunar cryptogenic strokes that are thought to be embolic, but the source of cardiac embolism could not be determined in etiological studies, and without intracranial and/or cervical lumen stenosis of 50% or more in the vessels feeding the infarct area (47-49).

The protection of NOACs in ESUS was compared with aspirin in two randomized studies. In the NAVIGATE ESUS study, the efficacy and reliability of rivaroxaban (15mg / day) and aspirin (100mg / day) were compared in ESUS. The study was terminated early due to high bleeding rates and hemorrhagic stroke in the rivaroxaban group in the 11th month (50). In the RESPECT-ESUS study, the efficacy and reliability of dabigatran (110-150 mg twice a day) and aspirin (100 mg / day) in ESUS were compared. The annual stroke rate was 4.1% in the dabigatran group and 4.8% in the aspirin group, but this difference was not statistically significant. No significant difference was observed between major bleeding rates and

hemorrhagic stroke rates, and the superiority of dabigatran over aspirin in ESUS patients could not be demonstrated (51). It is thought that ATTICUS and ARCADIA, two ongoing randomized controlled studies comparing apixaban and aspirin, may provide new approaches to the efficacy of NOACs in ESUS (52,53).

5. Laboratory Prior to Starting NOAC

The dose of NOAC group drugs should be determined by considering the patient's age, body weight, kidney functions, other drugs used and conditions that create bleeding risk. Therefore, a complete blood count, kidney and liver function tests and a coagulation panel should be requested for the patient before starting NOAC treatment. (4,5,54,55). In addition, it is important to have thyroid function tests and electrolytes in the blood in terms of evaluating the conditions that may cause AF. Treatment should be delayed in patients with a complete blood count showing thrombocytopenia (<50x103 / mm^3) and severe anemia. A multidisciplinary decision should be made to use NOAC in patients with a platelet count of <100x103 / mm^3.

The first clinical follow-up of patients in whom NOAC is initiated should be done one month later. Subsequent follow-ups should be performed regularly by considering the individual characteristics of the patient, at intervals of 1-6 months (Figure 3).4 If the patient does not have a condition that requires more frequent follow-ups, kidney and liver functions and complete blood count should be observed at least once a year. At every visit, the patient should be questioned whether they use the NOAC drug regularly, the history of thromboembolic and hemorrhagic events, drug side effects, other drugs used, and the patient's bleeding risk should be re-evaluated. The follow-up of the patients should be personalized. Monitoring coagulation tests such as prothrombin time and INR in patients receiving NOAC is unnecessary and may be misleading (56,57).

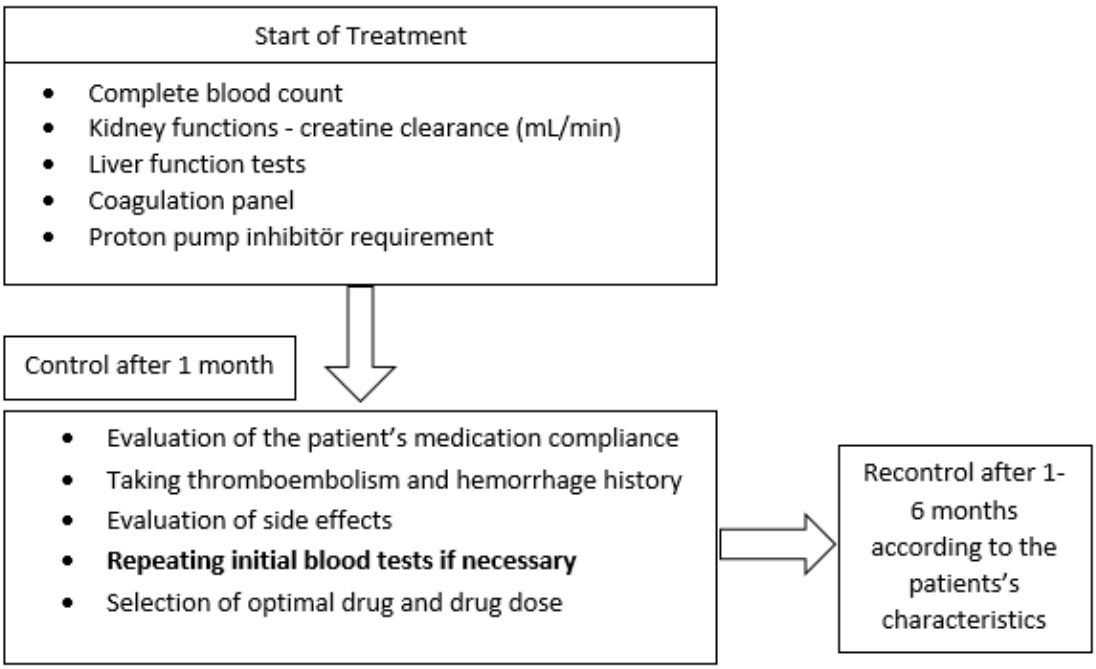

Figure 3. The first follow-up evaluation and follow-up visits of a patient taking NOAC

5.1. NOAC Use in Patients with Renal Failure: Although at different rates, all NOACs are excreted from the kidneys (Dabigatran 80%, edoxaban 50%, rivaroxaban 35% and apixaban 27%).58 In patients with impaired renal function or with impaired renal function during monitoring, drug selection or dose may need to be changed to reduce the risk of bleeding. Renal functions may deteriorate rapidly, especially in elderly patients, due to insufficient fluid intake, use of diuretics and drug interactions. In addition, it is known that kidney functions are more frequently impaired in

patients with AF. In this respect, considering the risk profile of patients using NOAC, kidney functions should be evaluated at least once a year and more frequently if necessary.4 In patients ≥75 years of age, who are sensitive or taking dabigatran, the first kidney function control should be done after 6 months at the latest. In patients with creatinine clearance (CrCl) of ≤60 mL / min, the follow-up time can be planned by dividing the CrCl level into 10 (4). For example, blood tests in a patient with CrCl of 30 mL / min should be done at least every 3 months.

It is recommended to use creatinine clearance (CrCl, mL / min) calculated by the Cockcroft-Gault formula to determine the renal function (59). In randomized studies comparing NOACs with warfarin, patients with CrCl <30 mL / min and in comparative studies with apixaban, patients with CrCl <25 mL / min were excluded from the studies. Therefore, data on the use of NOAC in patients with advanced and end-stage renal failure (CrCl <25-30 mL / min) are also limited (6,8-10). There are results indicating that edoxaban blood level and efficiency decreases with CrCl increase (CrCl> 95 mL / min), and that a different NOAC may be preferred in these patients (10). The efficacy and safety of NOACs in patients with moderately impaired renal function (CrCl 30-50 mL / min) are similar to those in patients with CrCl> 50 mL / min.60 There is not enough clinical data regarding the use of NOAC in patients with advanced and end-stage renal failure (CrCl <25-30 mL/min) or patients undergoing hemodialysis (6.8-10). There are retrospective research findings showing that apixaban has the same efficacy as warfarin but causes less bleeding in hemodialysis patients, but results from randomized studies on this subject should be expected (60,61). Although the use of 2x5 mg of apixaban in hemodialysis patients in the United States has been licensed, the use of NOAC in patients with CrCl ≤15 mL/min or undergoing hemodialysis in Europe is not approved. Although there is not enough evidence in patients with kidney transplantation, the use and the dose of NOAC should be decided by calculating the CrCl of the transplanted kidney and the interaction with the drugs used in these patients should be considered.

In conclusion, when determining the NOAC selection and drug dosage, patients' CrCl levels and comorbid status must be taken into consideration (Table 7).

Table 7. Recommended NOAC doses based on creatinine clearance.

NOAC	CrCl (>50 mL/min)	CrCl (30-50 mL/min)	CrCl (15-29 mL/min)	CrCl (<15 mL/min)
Dabigatran	2x150 mg	2x110 mg / 2x150 mg*	Insufficient data	Insufficient data
Rivaroxaban	20 mg	15 mg	15 mg	Insufficient data
Apixaban	2x5 mg**	2x5 mg **	2x5mg**	Insufficient data
Edoxaban	60 mg*	30 mg	30 mg	Insufficient data

* Dabigatran dosage should be determined by evaluating the patient's thromboembolism and bleeding risk individually.
** If there are two of the criteria (patient age ≥80, body weight ≤60 kg, creatinine ≥1.5 mg / dl), it should be switched to 2x2.5 mg.
* 30 mg should be used for those who weigh <60 kg or who use phosphorylated glycoprotein inhibitors.

5.2. NOAC Use in Patients with Liver Failure: Liver disease is associated with an increased risk of bleeding, as well as an increased susceptibility to thrombotic events. Liver function tests should be requested at least once a year in patients using NOAC (4). Patients with significant active liver disease such as cirrhosis, liver enzyme levels twice or higher than normal and bilirubin levels 1.5 times normal or above were excluded from NOAC studies (6,8-10). Therefore, our knowledge of treatment side effects in these patients is limited. All NOACs are contraindicated in patients with coagulopathy associated with liver disease or cirrhosis of level C (10-15 points) according to the Child-Pugh classification and patients at risk of bleeding (Table 8) (4). NOACs should not be initiated in patients with a platelet count of <70x103. Rivaroxaban should not be used in patients with Child B cirrhosis (7-9 points), other NOACs should be used with caution (62,63). It is most appropriate to initiate and continue NOACs consulting with a multidisciplinary team (including hepatologist and hematologist) in patients with liver dysfunction.

6. Use of NOAC in Patients Receiving Tube Feeding

Patients who receive tube feeding in neurology services and/or neurology intensive care units also take their medicines in this way. It is very important that solid oral formulations of drugs can be administered via a nasogastric (NG) tube after being crushed and dissolved in food or water (64). If NOACs are administered by tube,

Table 8. Child-Pugh Classification (A:1-6 points, B:7-9, C:10-15).

	1 point	2 points	3 points
Encephalopathy	-	Stage 1-2 (recovery with treatment)	Stage 3-4 (resistant)
Ascites	-	Mild (diuretic responsive)	Moderate-Severe (diuretic unresponsive)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
INR	<1.7	1.71–2.30	>2.30

their pharmacokinetic properties may be affected (65). Bioavailability is a concrete measure that shows how much the body "benefits" from a drug given to have a systemic effect. If NOAs are administered by tube, their pharmacokinetic properties may be affected (65). Bioavailability is a concrete measure that shows how much the body "benefits" from a drug given to have a systemic effect. Three parameters are considered in terms of pharmacokinetics and bioavailability. These are C_{max} (highest drug concentration in the systemic circulation), t_{max} (time from drug administration to peak concentration in the systemic circulation) and EAA = AUC (area under the plasma concentration-time curve) (66).

6.1. Dabigatran: The drug in the capsule contains granules coated with tartaric acid. With tartaric acid, an acidic microenvironment is created and the absorption and dissolution of the drug increases. While the oral bioavailability of dabigatran is between 3% and 7% when swallowed in its unopened capsule form, this bioavailability increases to 75% when the capsule is opened.

The increase in bioavailability as a result of opening the capsule may cause bleeding (67). In summary, capsules should be taken orally. The capsule should not be opened or crushed. It should not be administered through the enteral feeding tube (Table 9) (68).

Table 9. Characteristics of NOACs and their applications with enteral feeding tubes (64,70,78).

Drug	Formulation	Effect Mechanism	Administration with NG/G after crushing	Usage	Notes
Dabigatran (Pradaxa®)	Capsules filled with pellets 75, 110, 150 mg	Direct thrombin inhibitor	***No***	The capsule should be swallowed as a whole without opening.	Bioavailability increases by 75% when the capsule is opened
Rivaroxaban (Xarelto®)	Film coated tablet 10, 15, 20 mg	Factor Xa inhibition	Yes	Stable in 50 mL of sterile water or apple puree.	Bioavailability increases when taken with food Postpyloric application is not recommended.
Apixaban (Eliquis®)	Film coated tablet 2.5, 5 mg	Factor Xa inhibition	Yes	It should be suspended in 60 mL of 5% dextrose.	Bioavailability decreases when crushed or taken with food
Edoxaban (Lixiana®)	Film coated tablet 30, 60 mg	Factor Xa inhibition	Yes	Factor Xa inhibition	Bioavailability decreases when crushed or taken with food

NG, nasogastric feeding tube; G, gastric feeding tube, NOAC, Non-vitamin K oral anti-coagulant.

6.2. Rivaroxaban: Since they are film-coated tablets, they can be crushed. The absolute bioavailability of rivaroxaban is dose dependent in terms of pharmacokinetics. For example, for 2.5 and 10 mg, it has 80% -100% bioavailability that is not affected by food. Absolute bioavailability is 66% for 20 mg taken after fasting. The bioavailability of 20 mg rivaroxaban taken with food increases. That is, AUC and Cmax values increase by 39% and 76%, respectively. It is recommended to take 15 and 20 mg doses of rivaroxaban with food. Rivaroxaban 15mg-20mg is crushed and suspended in 50 mL of water, followed by rapid enteral feeding. However, enteral nutrition is not required to increase the bioavailability of 2.5 mg and 10 mg tablets. The crushed tablets remain intact for 4 hours in water or apple puree. Crushed tablets will not stick to polyvinyl chloride or silicone NG tubes (69). Application of rivaroxaban to the distal of the stomach should be avoided. In this case, rivaroxaban should be taken only with an NG tube or gastric tube. In summary, taking rivaroxaban with food increases its bioavailability. Provided that the feeding tube is in the stomach, it can be crushed.

6.3. Apixaban: They are film-coated tablets with a bioavailability of 50%. When Apixaban tablet is crushed and taken, there is no change in its bioavailability compared to oral intake. However, when crushed and given with 30 grams of apple puree, Cmax and AUC values decrease by

20% and 16%, respectively, in its bioavailability compared to oral intake. The manufacturer recommends that the crushed drug be suspended in 60 mL of 5% dextrose solution and administered through an NG tube (70). The crushed tablets remain intact for 4 hours in water or apple puree. In summary, if it will be administered through an NG, it should be given by suspending with 5% dextrose. When given with nutritional supplements, a decrease is seen in its bioavailability.

6.4. Edoxaban: Bioavailability of film-coated tablets is 62%. NG can be crushed through the tube. The bioavailability of edoxaban when crushed with food is similar to that of oral administration. Even if the tablet is crushed, it is in the range of 80% -125%, which is a suitable range for bioequivalence. In other words, Cmax and AUC values are in the effective range. Edoxaban does not stick to the polyvinyl chloride NG tube. In summary, edoxaban can be crushed and administered through an NG tube. It does not interact with food (64).

Consequently, it is not recommended to administer dabigatran among the four NOACs by tube. Rivaroxaban, apixaban, and edoxaban can be given with an NG tube. It should be taken into account that the bioavailability of rivaroxaban and apixaban changes with food in tube feeding. As the absorption of rivaroxaban is acid-dependent, use of the drug should be avoided if post-pyloric nutrition is used. There are no restrictive studies on post-pyloric nutrition for apixaban and edoxaban.

7. Periprocedural and Perioperative Management of Patients using NOAC

Approximately 10% of those who use oral anticoagulant drugs require a surgical procedure for any reason every year, and oral anticoagulant drugs used should be stopped before certain surgical procedures (71). In patients undergoing surgical or invasive procedures, suspending anticoagulant therapy may temporarily increase the risk of thromboembolism while continuing treatment may increase the risk of operational bleeding (72). Balancing these two conditions presents difficulties in managing anticoagulant therapy. Before surgery, an anticoagulant with a long half-life such as warfarin should be stopped for a longer period (approximately 5 days). Since the effects of NOACs start rapidly, their half-life is short and their elimination from the body is fast, it is sufficient to suspend taking the drug for a shorter time than warfarin. The fact that NOACs have FDA-approved antidotes enables rapid treatment when encountered possible bleeding risk or quick elimination of the effect of the anticoagulant regimen in patients who will be taken into emergency operation. Idarucizumab reverses the effects of dabigatran, and andexanate alpha reverses the effects of both apixaban and rivaroxaban (73,74). It should be kept in mind that antidote drugs may increase the risk of thromboembolism.

First of all, it is necessary to answer the following questions and make the necessary planning before the procedure.

1- Is the surgical procedure to be done elective? Is it urgent?
2- Is it necessary to suspend anticoagulant therapy depending on the type of surgical procedure?
3- If the drug use will be stopped, how many days before the procedure should oral anticoagulant drugs be stopped?
4- Is bridging treatment needed or not during this process?
5- When should anticoagulant therapy be started again?

The risk of thromboembolism that may occur with the discontinuation of oral anticoagulant therapy is divided into low/medium/high risk (Table 10), while the same classification is categorized as minimal (insignificant bleeding)/low and high-risk bleeding according to the risk of bleeding in the surgical procedure (Table 11).

7.1. Calculation of Thromboembolism Risk: It is calculated according to age and comorbid conditions in people with AF, where the CHA_2DS_2-VAs score is used. However, if the patient has a recent history of stroke or pulmonary embolism, it is recommended to delay the surgical procedure (Table 10).

7.2. Determining the Risk of Bleeding: The type of surgical procedure and the invasive procedure to be performed are important here. Comorbid conditions in the patient (age, renal failure) and the use of drugs that affect hemostasis should also be considered. In cases with high risk of bleeding, anticoagulation should be stopped for a longer period (Table 11).

Table 10. Risk classification for perioperative thromboembolism.

Risk Classification	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
Low <4% / year arterial thromboembolism or <2%/month venous thromboembolism	Bicuspid aortic heart valve without major risk factors (AF, stroke, transient ischemic attack, HT, DM, CHF,> 75 years of age) for stroke	$CHADS_2$ score of 0-2 CHA_2DS_2-VASc score of 0-1 no history of stroke or transient ischemic attack	Venous thromboembolism that was over 12 months ago
Medium <4-10% / year arterial thromboembolism or <4-10% / month venous thromboembolism	Major risk factor for stroke and bicuspid aortic heart valve	$CHADS_2$ score of 3-4 CHA_2DS_2-VASc score of 2-4	Active cancer Thrombophilia that is not severe Recurrent venous thromboembolism Venous thromboembolism over 3-12 months ago
High <10% / year arterial thromboembolism or <10% / month venous thromboembolism	History of stroke or transient ischemic attack within the last 6 months Mechanical heart valve	$CHADS_2$ score of 5-6 CHA_2DS_2-VASc score of >4 Stroke or transient ischemic attack in the last 3 months Rheumatic valve disease	Venous thromboembolism in the last 3 months Protein C, S and antithrombin 3 deficiency Antiphospholipid antibody syndrome Multiple thrombophilia

Table 11. Bleeding risk classification by operation type.

Minimum	Low	High
Dental operations - Tooth extraction of up to two teeth - Gum biopsy - Peridontal procedures - Root canal treatment	Laparoscopic cholecystectomy Laparoscopic inguinal hernia repair	Intracranial or spinal surgeries By-pass, heart valve replacement
Skin biopsy Superficial mass excisions Cataract Endoscopic procedures performed without biopsy Inserting a pacemaker	Other dermatological procedures Other eye operations Coronary angiography Other intra-abdominal, intrathoracic, orthopedic, vascular procedures	Major surgeries (aortic aneurysm repair, aortafemoral bypass) Major urological surgeries (mass resection, prostatectomy) Major orthopedic procedures Biopsies taken from organs Lung resection

7.3. Determining the Suspension Time for Anti-coagulant Therapy: It differs according to the anticoagulant agent used by the patient. Warfarin requires a longer break than the surgical procedure compared to NOACs. Although NOACs have short half-lives, their half-lives may be prolonged (at different creatinine clearance values) in case of renal failure and the discontinuation time of the drug may change before an invasive procedure (Table 12a).

7.4. Determining Whether Bridging Therapy is Needed: Patients at high risk for thromboembolism benefit from bridging therapy with unfractionated heparin or LMWH when anticoagulant therapy is stopped. Current guidelines (2019 ACC / AHA) recommend bridging therapy in high-risk (mechanical heart valve replacement, pulmonary embolism) patients (5), but these recommendations are based on observational studies and expert opinion. However, depending on the patient's risk of thromboembolism and operational bleeding risk (such as non-clinical bleeding, low and moderate bleeding risk), sometimes not interrupting anticoagulant therapy, or not implementing bridging therapy at all constitutes a more appropriate approach. In a meta-analysis of 12 cohorts and 6 randomized studies, groups that received and did not receive bridging therapy were compared. While the risk of thromboembolic stroke between the two groups remained the same, the risk of bleeding was greater in the bridging group. The situation was the same in patients using NOAC (75). Observational studies and large randomized studies show that when bridging therapy is implemented, the rate of perioperative and periprocedural bleeding increases without a reduction in

Table 12a. Discontinuation times of non-vitamin K oral anticoagulant drug according to bleeding risk before elective operations.

	Creatinine Clearance (mL/min)	Drug suspension time and amount of skipping doses in operations with low risk of bleeding		Drug suspension time and amount of skipping doses in operations with high risk of bleeding	
Dabigatran	>80	28-42 hours	2 dose	56-70 hours	5-6 doses
(Daily use 2	50-79	34-51 hours	3-4 doses	68-85 hours	6-7 doses
doses)	30-49	38-57 hours	4-5 doses	76-95 hours	7-8 doses
	15-29	56-84 hours	5-7 doses	112-140 hours	9-12 doses
Renal excretion %80	< 15	If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.		If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.	
Antidote idarizumab					
Apixaban	>50	14-24 hours	2 doses	28-40 hours	4 doses
(Daily use 2	15-49	34-54 hours	3-4 doses	68-90 hours	6-7 doses
doses)	< 15	If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.		If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.	
Renal excretion %27					
Antidote andexenat alfa					
Rivaroxaban	>80	16-24 hours	1 dose	40 hours	2 doses
(Daily use 2	30-79	18-27 hours	1 dose	36-45 hours	2 doses
doses)	15-29	20-30 hours	1-2 doses	40-50 hours	2-3 doses
	< 15	If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.		If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.	
Renal excretion %33					
Antidote andexenat alfa					
Edoxaban	>50	16-27 hours	1 dose	32-45 hours	2 doses
(Daily use single	30-49	18-30 hours	1 dose	36-50 hours	2 doses
dose)	15-29	34-51 hours	2 doses	68-85 hours	3-4 doses
	< 15	If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.		If it's acute renal failure, can be delayed until recovery or switching to warfarin or low molecular weight heparin may be considered.	
Renal excretion %50					
Antidote andexenat alfa					

thromboembolism. This bleeding also increases morbidity and mortality. With these analyses, the authors showed that bridging therapy increased the risk of bleeding approximately 3 times (76,77). In another study, the rate of bleeding and thromboembolism was examined in the group that received and did not receive bridging treatment, and while this ratio was 1:13 in the group who received bridging treatment, it was 1: 5 in the group who did not receive the treatment. Thromboembolic events are less common in the periprocedural period, and bridging therapy increases the risk of bleeding. This practice seems to be harmful without any benefit. Bridging therapy has no clearly demonstrated effect, except for the high thromboembolism risk group.

ACC reports that NOACs should be stopped for a period of 2 half-lives before low bleeding risk, and a period of 5 half-life before moderate / high / uncertain bleeding risk, and NOACs should not be stopped in cases of insignificant bleeding risk (76). (Figure 4). Information on stopping and resuming of warfarin treatment before the procedure is visualized in Figure 5.

7.5. Time to Start Anticoagulant Therapy again: The time to re-start depends on the person's renal functions and the bleeding risk of the surgical procedure. Considering that the effects of NOACs start quickly in the post-op period, it is appropriate to start approximately 24 hours after the operation (in those with low bleeding risk) and 48 - 72 hours after the operation for those with

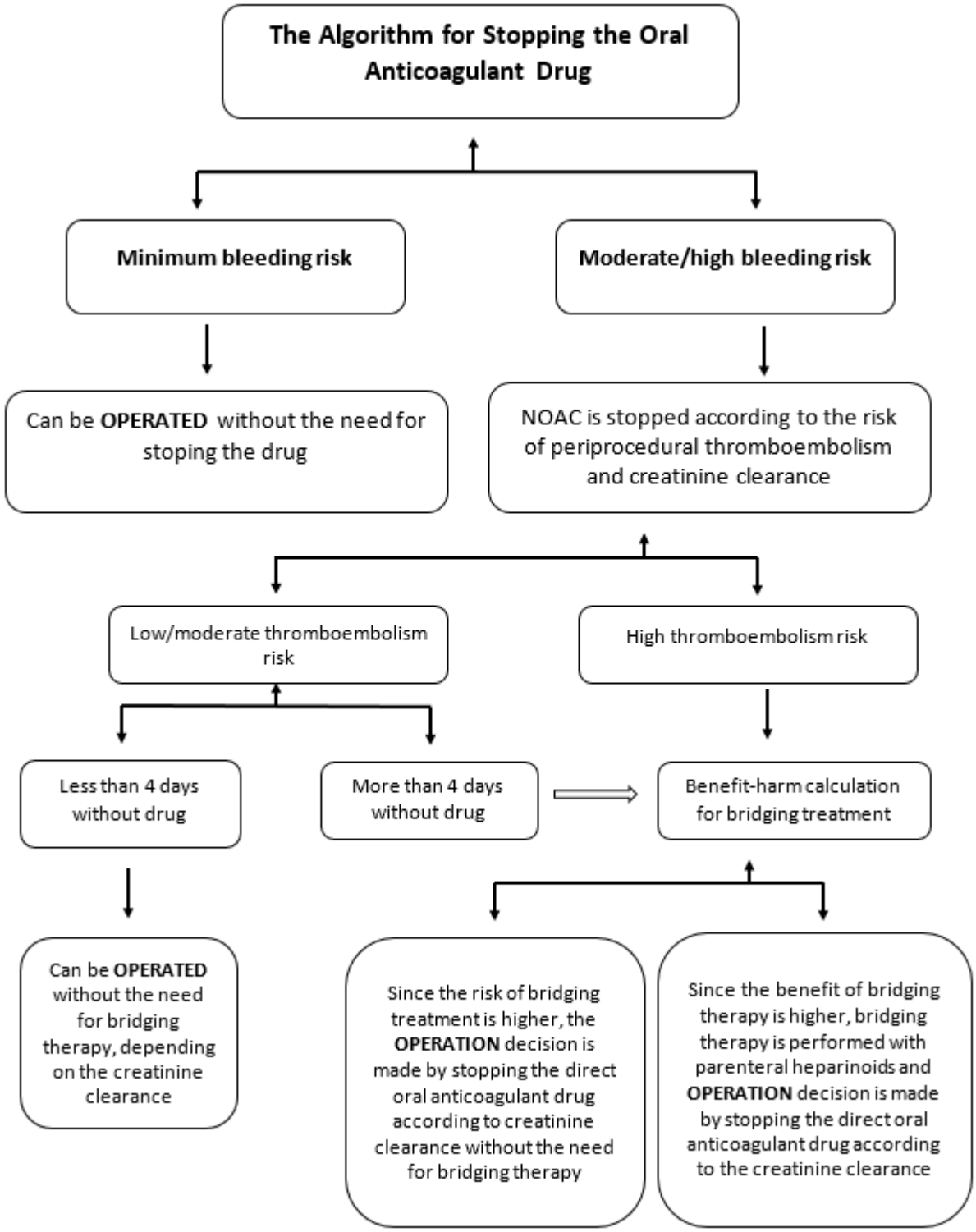

Figure 4. The algorithm for stopping the oral anticoagulant drug.

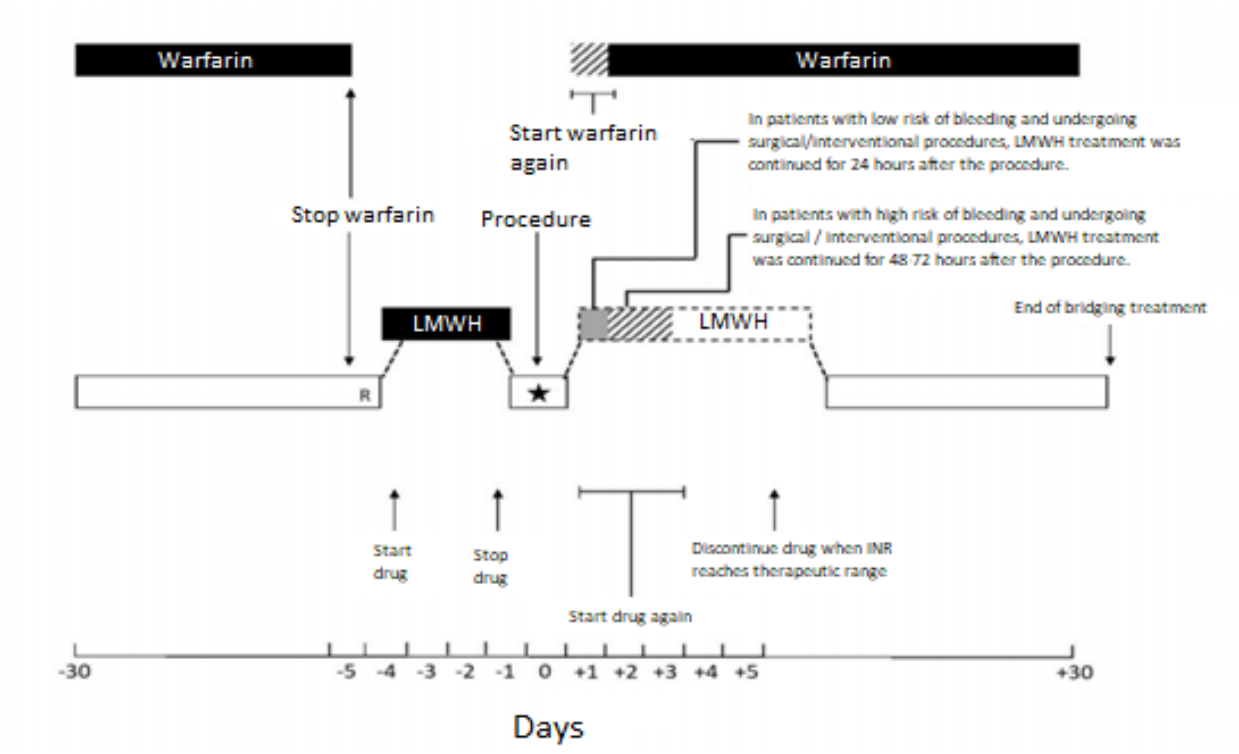

Figure 5. Preprocedural stopping and resuming of warfarin.

high bleeding risk (Table 12b). A similar application is valid for warfarin as shown in Figure 5.

In conclusion, NOACs should not be stopped in surgical procedures with minimal bleeding risk. In cases with low risk of thromboembolism and low risk of bleeding (such as tooth extraction, endoscopy without biopsy or bronchoscopy, laparoscopic cholecystectomy), stopping NOAC 1 day in prior causes 1 or 2 doses to be skipped, where there is no need for bridging treatment. In cases with high risk of bleeding and high thromboembolism risk, anticoagulant therapy should be stopped, and bridging therapy should be implemented (It is necessary to stop warfarin 5 days in advance and NOACs 48-72 hours before). It should be started 24 hours after the operation in patients with low bleeding risk and 48-72 hours after the operation in patients with moderate-high bleeding risk.

Table 12b: Time of initiation of NOAC by bleeding risk.

Medication initiation time in operations with low bleeding risk	Medication initiation time in operations with high bleeding risk
24 hours after the operation	48-72 hours after the operation

8. NOAC and Drug Interactions

One of the important conditions affecting the treatment strategy in primary and secondary stroke prophylaxis is the fact that patients are generally of advanced age and receive various treatments due to other chronic diseases and risk factors. In this situation where multiple drug use is quite common, drug interactions should be considered in the selection of new oral anticoagulants and dose adjustment. The NOAC group, which includes dabigatran, apixaban, rivaroxaban and edoxaban, has significant therapeutic advantages compared to a vitamin K antagonist, such as warfarin, due to its faster and predictable anticoagulant effects, less frequent laboratory monitoring, and less drug-nutrient and drug-drug interactions. When the results of the ROCKET - AF and ARISTOTLE studies were

examined, it was revealed that 2/3 of the patients who used NOAC used more than 5 drugs together with NOAC, and the clinical importance of NOAC and drug-drug interactions has increased (78).

Since the correct NOAC dose is associated with both increased thrombotic and bleeding complication risk, drug-drug interactions should be well known in the adjustment of the correct NOAC dose. The most common NOAC drug-drug interaction occurs through the cytochrome P450 (CYP450) enzyme system and / or the transporter permeability glycoprotein (P-gp). Some drugs may cause changes in NOAC doses by inducing or inhibiting one or both enzyme systems and / or transport proteins. In the use of NOAC with a drug that inhibits the cytochrome P450 enzyme system and / or P-gp transport protein, it should be kept in mind that the serum concentration of NOAC generally increases, and serum NOAC concentrations may decrease with the use of this enzyme system and a drug that induces its transport protein. CYP3A4 enzyme system is an important metabolizer for apixaban (20-25%) and rivaroxaban (50%) while P-gp transport protein is an important mediator for dabigatran, apixaban, and rivaroxaban (79).

The interactions of some drugs frequently used in combination with non-vitamin K oral anticoagulants are given below and their plasma levels are summarized in Table 13.

Table 13. The effects of drugs on non-vitamin K oral anticoagulant plasma levels (4).

Drugs	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Amiodaron	12%-60 increase	Minor effect	Minor effect	%40 increase
Digoxin	No effect	No effect	No effect	No effect
Diltiazem	No effect	%40 artma	No effect	Insufficient data
Dronedarone	70%-100 increase	Insufficient data	Moderate effect	%85 increase
Quinidine	53% increase	Insufficient data	Insufficient data	%77 increase
Verapamil	12%-180 increase	Insufficient data	No effect	%53 increase
Atorvastatin	No effect	No effect	No effect	No effect
Ticagrelor	25% increase	Insufficient data	Insufficient data	Insufficient data
Clarithromycin	15%-20 increase	60% increase	54% increase	%90 increase
Erythromycin	15%-20 increase	60% increase	34% increase	%90 increase
Rifampicin	66% decrease	54% decrease	50% decrease	%35 decrease
Flukonazol	Insufficient data	Insufficient data	42% increase	Insufficient data
Ketoconazole	140%-150 increase	100% increase	160% increase	%87-95 increase
Naproxen	Insufficient data	55% artma	Insufficient data	No effect
Proton pump inhibitors	12%-30 decrease	No effect	No effect	No effect

8.1. Anti- arrhythmics: Amiodarone is an anti-arrhythmic drug with moderate CYP3A4 and mild-to-moderate P-gp inhibitory effects, which may cause drug interactions even weeks after discontinuation due to its long half-life. There is no need to reduce the dose of NOAC when amiodarone is used with NOACs. Similarly, it is not necessary to reduce the NOAC dose in the use of digoxin, which are P-gp substrates, diltiazem and quinidine, which are moderate CYP3A4 and P-gp inhibitors while it should not be forgotten that it is necessary to be careful in terms of bleeding risk in patients over the age of 75, with a creatinine clearance of 30-50ml/min and patients weighing below 50 kg. While the use of dronedarone, which is a moderate CYP3A4 and strong P-gp inhibitor, with dabigatran is contraindicated, its use with rivaroxaban should be avoided, and the dose of edoxaban should be reduced to 30 mg / day. In the use of dabigatran with verapamil, the dose of dabigatran is reduced to 110 mg twice a day, while for other NOACs, it is not necessary to reduce the döşe (80).

8.2. Antibiotics: In the use of clarithromycin which is an inhibitor of potent CYP3A4 and moderate P-gp, it is not necessary to reduce the NOAC dose, while the dose of erythromycin with similar characteristics should be reduced to 30 mg

/ day. When using rifampicin, which is a potent CYP3A4 and P-gp inducer, together with NOACs, it should be avoided to use with NOACs due to their reduced anticoagulant effect. It should be kept in mind that the risk of NVAF-induced stroke, systemic embolism and the recurrence risk of deep vein thrombosis or pulmonary embolism will increase with the use of rifampicin (81,82).

8.3. Anti-epileptics: It is reported that using phenytoin, carbamazepine, and phenobarbital which are potent CYP3A4 and P-gp inducers, should not be used with dabigatran, apixaban, and rivaroxaban, and that it requires extreme caution when used with edoxaban due to reduced anticoagulant effect (83).

8.4. Anti-depressants: Care should be taken in terms of bleeding risk due to the increased anticoagulant effects of drugs such as SSRI / SNRI (escitalopram, sertraline, venlafaxine) when used with NOACs.

8.5. Anti-inflammatory Drugs: Caution should be exercised in the use of nonsteroidal anti-inflammatory drugs together with NOACs due to the increased risk of bleeding and it should be kept in mind that the risk of bleeding may increase in patients with creatinine clearance of 30-50 mL / min and body weight below 50 kg, especially in patients over 75 years of age (84).

8.6. Anti-platelet Drugs: When using aspirin or clopidogrel together with NOACs, caution should be exercised due to the increased risk of bleeding and patients should be monitored closely for signs of bleeding. For dual treatments after acute coronary syndrome, the recommendation of a cardiologist should be taken and given with a high risk of bleeding. Although experience with prasugrel and ticagrelor is limited, it should be avoided due to the high risk of bleeding or used with extreme caution only on cardiologist-neurologist recommendation (85).

8.7. Anti-fungal Drugs: While the use of itraconazole and ketoconazole, which are potent CYP3A4 and P-gp inhibitors, together with dabigatran is contraindicated, the use of voriconazole and posaconazole with all NOACs is not recommended. Although there are insufficient data on fluconazole, which is a moderate CYP3A4 inhibitor, it is stated that it does not cause a clinically significant interaction and can be used without changing the dose of NOAC.

8.8. Anti-virals: It is not recommended to use HIV protease inhibitors (ritonavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir), which are potent CYP3A4 inhibitors and P-gp inhibitors / inductors, together with NOACs.

8.9. Anti-acids: Although proton pump inhibitors and H2 receptor blockers have slightly reduced the bioavailability of dabigatran, they do not cause a significant change in its clinical efficacy. It has been demonstrated that there is no clinically significant interaction in the use of anti-acids together with NOACs, and there is no need to change the dose of NOAC when used together.

8.10. Immunosuppressants: Cyclosporine is a moderate CYP3A4 and potent P-gp inhibitor and its concomitant use with dabigatran is contraindicated. It should not be forgotten that rivaroxaban and apixaban increase the effect of bleeding, and the dose of edoxaban should be reduced to 30 mg / day. While it is not recommended to use tacrolimus with dabigatran, its interaction with other NOACs is not fully known.

8.11. Anti-lipidemic Drugs: It has been shown that there is no clinically significant interaction in the use of atorvastatin, which is a CYP3A4 inhibitor, with all NOACs (4,86,87).

As a result, although NOACs, whose use is increasing day by day, have less drug interactions than vitamin K antagonists, it should be kept in mind by physicians that there may be changes in their pharmacokinetics in patients with some comorbidities, who use multiple drugs, and the need for dose adjustments according to plasma levels.

9. Transition between Warfarin, Heparin, Low Molecular Weight Heparin and NOACs

NOACs are widely used to prevent embolism in AF. In recent years, a significant portion of newly diagnosed AF patients have been treated with NOACs (88). Real-life data show that one third of the patients in whom NOAC was initiated switched from vitamin K antagonist treatment to NOAC, and one fifth discontinued NOAC treatment during the first year. More rarely, a switch from NOAC to vitamin K antagonist oral anticoagulants has also been observed (89-91).

Transition between anticoagulant therapies can be in the form of transition from warfarin and parenteral anticoagulants (heparin and low molecular weight heparin) to NOAC or vice versa. In all scenarios, in switching between drugs the pharmacodynamic (INR for warfarin, aPTT for unfractionated heparin) and pharmacokinetic

(half-life) profile of each drug should be taken into consideration and renal functions should be monitored closely. The aim in the management of the transition period between anticoagulant treatments is to minimize the risk of hemorrhagic complications while preventing the development of thromboembolic events by keeping the time that the patient is not under therapeutic anticoagulation effect as short as possible.

Patients using anticoagulant medications may need to change their medications for medical (fluctuating INR levels, insufficient time spent in the therapeutic interval, development of renal or hepatic failure, increased risk of bleeding, development of thrombotic and hemorrhagic complications) or social (inability to have an INR follow-up, cost, patient preference) reasons (92,93).

In this section, recommendations for the management of the transition process between anticoagulant drugs will be presented. These recommendations are presented in line with current data, and clinical decisions should be made by considering the risk of thromboembolism and bleeding individually for each patient (Table 14).

9.1. Transition from Warfarin to NOAC: In bidirectional transition between warfarin and NOAC, INR measurements and the half-life of warfarin should be considered. When INR is ≤2 after warfarin is discontinued, NOAC can be started immediately. When the INR is in the range of 2-2.5, NOAC can be started on the same day (preferably the next day). If the INR is in the range of 2.5-3, the test should be repeated within 1-3 days and it should be decided whether to start NOAC according to the test result. When INR is> 2.5, the time when it will fall below 2.5 depends on the current INR level and the half-life of the vitamin K antagonist (36-48 hours for Warfarin). It is stated that rivaroxaban can be started when the INR is ≤3, edoxaban when INR is ≤2.5, and apixaban and dabigatran when INR is ≤2 (4). When INR is ≥3, the initiation of NOAC should be delayed. It should be noted that NOAC, especially anti-factor-Xa inhibitors, can increase INR.

9.2. Transition from NOAC to Warfarin: As the effect of warfarin starts late, it may take 5-10 days for the INR to reach the therapeutic range. Therefore, NOAC and warfarin should be used together until the INR reaches the therapeutic range. Warfarin loading dose is not recommended. Since NOACs, especially anti-factor-Xa inhibitors, can cause an increase in INR, it is recommended to measure INR just before the NOAC dose and 24 hours after the last dose of NOAC. If INR is ≤2, the measurement should be repeated 1-3 days later, when it is > 2, NOAC should be discontinued. While NOAC is discontinued and treatment is continued with warfarin, the INR should be closely monitored during the first month (until the result of three consecutive INR tests is in the range of 2-3).

When switching from edoxaban to warfarin in the ENGAGE-AF trial, patients received half-dose edoxaban for 14 days until the INR was within the therapeutic range, during which intensive INR testing was performed (94). With this strategy, the risk of stroke and bleeding is minimized. However, the efficacy and safety of the half-dose regimen in switching from other NOACs to warfarin has not been demonstrated. The duration of use of dabigatran and warfarin together in the transition from dabigatran to warfarin should be determined by CrCl. Dabigatran and warfarin should be used together for three days when CrCl is ≥50 ml/min, for two days when it is 30-49 ml/min, and for one day when 15-29 ml/min.

In cases where it is not appropriate to use NOAC simultaneously while starting warfarin, LMWH should be started with warfarin. LMWH should be given when the next dose of NOAC is due, and treatment should continue with warfarin only once the INR is within the therapeutic range.4

Inappropriate continuation of the transition from NOAC to warfarin is associated with an increased risk of stroke (95,96).

9.3. Transition from NOAC to Parenteral Anti-coagulants: When the next NOAC dose is due, parenteral anticoagulants (IV unfractionated heparin and subcutaneous LMWH) can be started (4). Caution should be exercised in renal dysfunction.

9.4. Transition from Parenteral Anti-coagulants to NOAC: NOAC can be started 2-4 hours after stopping IV unfractionated heparin (half-life of 2 hours). After LMWH is discontinued, NOAC can be started when the next dose is due. Caution should be exercised in patients with renal impairment as LMWH elimination may be prolonged (4).

9.5. Transition from NOAC to NOAC: When the next NOAC dose is due, the new NOAC treatment can be started. It should be kept in mind that the plasma concentrations of drugs in patients

Table 14. Recommendations for transition between anti-coagulant therapies.

Current Drug	Drug to be Transitioned to	Recommendation
Warfarin	NOAC	• Stop warfarin • If INR is ≤2, start NOAC immediately • IF INR is 2-2.5, start NOAC the same day or preferably the next day • If INR is 2.5-3, repeat INR in 1-3 days • When INR is> 2.5, when the INR will be <2.5 depends on the current INR level and the half-life of the vitamin K antagonist (36-48 hours for Warfarin) • If INR is ≥3, postpone the start of NOAC • Since NOAC can increase INR, INR measurement should be done before and after NOAC starts.
Warfarin	LMWH	• Stop warfarin and start LMWH when INR is <2
Dabigatran	Warfarin	• CrCl ≥50 ml/min; start warfarin and stop dabigatran 3 days later • CrC l30-49 ml/min; start warfarin and stop dabigatran 2 days later • CrCl 15-29 ml/min; start warfarin and stop dabigatran 1 day later • CrCl<15 ml/min; not recommended • If INR is ≤2, INR measurement 1-3 days later • If INR is >2, INR measurement 1 day after stopping NOAC • Frequent measurement of INR for 1 month
Rivaroxaban Apixaban	Warfarin	• Start warfarin and stop NOAC 3 days later • If INR≤2, measurement of INR after 1-3 days • If INR> 2, INR measurement 1 day after NOAC is discontinued • Frequent measurement of INR OR continuous anticoagulation for 1 month: • Stop NOAC, start LMWH and warfarin when the next dose is due, stop LMWH when INR is in the therapeutic range.
Edoxaban	Warfarin	• Patients taking 60 mg: Reduce edoxaban to 30mg and start warfarin simultaneously. Stop edoxaban when INR is ≥2 • Patients taking 30 mg: Reduce edoxaban to 15mg and start warfarin simultaneously. Stop the edoxaban when INR is ≥2 • If INR is ≤2, measurement of INR after 1-3 days • If INR is > 2, INR measurement 1 day after NOAC is discontinued • Frequent measurement of INR OR continuous anticoagulation for 1 month: • Stop NOAC, start LMWH and warfarin when the next dose is due, stop LMWH when INR is within the therapeutic range.
NOAC	NOAC	• Stop the current NOAC and start new NOAC when it's time for next dose • Caution in patients with renal dysfunction
NOAC	Parenteral anticoagulant	• Stop NOAC, start parenteral anticoagulant when the next dose is due. • Check renal function for LMWH
Parenteral anticoagulant	NOAC	• Intravenous: start NOAC 2-4 hours after stopping UFH • Subcutaneous: When the next dose of LMWH is due, start NOAC instead of LMWH.
LMWH	Warfarin	• Start warfarin and give it with LMWH for 5 days or until INR is ≥2, then stop LMWH
LMWH	NOAC	• Stop LMWH and start NOAC when the next dose is due.

NOAC: Non-vitamin K antagonist oral anticoagulant, INR: "International normalized ratio", LMWH: Low molecular weight heparin, CrCL: Creatinine clearance, UFH: Unfractionated heparin.

with renal dysfunction may be high (4).

10. NOAC Dose: In Which Patients should a Low Dose be Used?

When starting the NOAC treatment, dose adjustment should be made on a patient basis, and low dose therapy should be given in selected patients.4 In patients with high risk of bleeding and/or in cases where serum drug levels may increase, dose reduction may be required in clinical practice.4 Before starting NOAC and periodically, kidney function tests, liver function tests, complete blood count should be requested, other medications and comorbidities that the patient is using should be questioned, and anticoagulant needs and treatment preferences should be evaluated.4,16 When the NOAC dose is reduced, the serum drug level is not recommended routinely as its beneficial effects have not been proven clinically.4 Guideline recommendations for stroke prevention in patients with AF is shown in Table 15.

Patients with a low-dose NOAC indication have been shown to have a higher risk of thromboembolic and hemorrhagic complications compared to patients eligible for the standard döşe (97). When starting NOAC treatment, it is

Table 15. Guideline recommendations for NOAC doses in the scope of stroke prevention in AF patients.

NOAC	Standard Dose	Dose Reduction
Apixaban	2x5mg	2x2,5mg if two out of three criteria are present Age ≥80 Body weight ≤60kg, Creatinine ≥1,5mg/dL (or CrCl 15-29 mL/min)
Dabigatran	2x150mg or 2x110mg	No predetermined dose reduction criteria
Edoxaban	1x60mg	1x30mg if body weight is ≤60kg, potent P-Gp inhibitor use or CrCl≤50mL/min
Rivaroxaban	1x20mg	1x15mg If CrCl≤50mL/min

necessary to balance the risk of bleeding and stroke (97). When low-dose NOAC was used in accordance with indications, recommendations and product information, there was no difference in the standard dose NOAC in terms of efficacy and safety (98). The use of anticoagulants in renal dysfunction is discussed in detail in section 5.1 of this article. To review briefly in the context of dosage, we should note that AF and renal failure are mutually affecting conditions, kidney disorder increases the risk of new onset AF, while AF increases the risk of developing kidney disease, and at the same time, kidney disorder is a risk factor for bleeding (4,99-102). Dabigatran has the highest (80%) renal excretion, edoxaban has 50%, rivaroxaban 35% and apixaban 27% (103). The relationship between NOACs, AF, and renal function requires dose reduction for each NOAC in kidney disease (103). When compared with warfarin in mild-moderate chronic kidney disease (CKD) and in subgroup analysis compared to patients without CKD, all four NOACs show consistent efficacy and safety (4,99,101,104,105). Dose adjustment according to creatinine clearance is recommended as shown in Table 7 (4,103).

In randomized controlled studies, there are insufficient data regarding the use of NOAC in patients with severe renal failure who received renal replacement therapy. Considering each NOAC pharmacokinetics, dose reduction criteria and study data, apixaban or edoxaban may be preferred in patients with a CrCl of 15-30 mL/min (4). In severe renal failure (CrCl <15 mL/min) and dialysis patients, routine use of NOAC should be avoided in these patients as there is no sufficient or definitive results regarding the use of NOAC (4,16).

Compared to warfarin, clinically important drug-drug interaction is significantly less for NOACs. However, in some combinations it may be necessary to adjust the dose of NOAC. Since all NOACs interact with P-gp in post-absorption re-secretion, an inhibition in this pathway results in increased plasma levels (4,16). Most of the antiarrhythmic drugs commonly used in AF patients (verapamil, dronedarone, amiodarone, quinidine, etc.) are P-gp inhibitors (4,51,106). Therefore, the dose of dabigatran and edoxaban should be reduced while using verapamil. However, verapamil and rivaroxaban can be used as a full dose. When using dronedarone, dabigatran is contraindicated, rivaroxaban should be avoided and the dose of edoxaban should be reduced (1x30mg). When using amiodarone, reducing the dose of NOAC should be considered by taking other factors into account (4,51,106).

Antiepileptic drugs affect anticoagulation by a variety of potential mechanisms, but these relationships have not yet been clearly elucidated (4). Wang et al. examined the effects of antiepileptic use on bleeding in patients using NOAC in their study and showed that the combination of NOAC and valproic acid, phenytoin, or levetiracetam cause more major bleeding compared to NOAC alone (107). In the 2018 EHRA guidelines, it was recommended that valproic acid and levetiracetam should not be used together with NOAC, that carbamazepine, phenobarbital and phenytoin should not be used with dabigatran and rivaroxaban, and that the use of apixaban and edoxaban should be avoided or their use should be cautiously and with expert opinion, and reported that there is not enough data on other antiepileptic drugs (4). However, it should be noted that

especially levetriacetam does not create a significant Pgp induction, that there is no human study that can enable us to make suggestions for its use with NOACs, and that there is no significant risk with the available information (108).

Coexistence of AF and coronary disease is a common condition. When acute coronary syndrome develops in patients with AF or when percutaneous coronary intervention is performed, treatment adjustment should be made by calculating the risks of cardioembolic ischemia, coronary ischemia, and treatment-related bleeding and establishing a balance (4,109).

The use of dual antiaggregant is called dual antiplatelet therapy (DAPT). DAPT is recommended to prevent stent thrombosis, but it is not sufficient to prevent embolic events in AF. When an oral anticoagulant is added to the use of DAPT in patients with AF, it is called "triple antithrombotic therapy", the use of single antiplatelet and oral anticoagulant together is called "dual antithrombotic therapy" (4,109). Adding aspirin and / or $P2Y_{12}$ inhibitor (often clopidogrel) to oral anticoagulant therapy increases the risk of bleeding, and when NOAC is preferred, this increase in bleeding risk is less common than warfarin (4,109). In three large studies conducted with these patients, it has been shown that double or triple therapies containing NOAC have similar rates of ischemic events and mortality compared with those containing warfarin, while the incidence of bleeding is lower. 109 When triple antithrombotic therapy and dual antithrombotic therapy were compared, it was shown that triple therapy prevents stent thrombosis better but leads to more bleeding (109). In the light of randomized controlled studies, meta-analyses and guidelines recommend the use of dabigatran (2x150mg) or apixaban (2x5mg) or low-dose rivaroxaban (1x15mg) together with antiaggregant therapy when acute coronary syndrome develops, or percutaneous coronary intervention is performed in patients with AF (4,109). When neuro-endovascular intervention is required in patients with AF, although there is not enough data in the literature, approaches can be planned according to the clinical and endovascular evaluation based on the coronary intervention strategy.

When compared to warfarin, the use of dabigatran 2x150mg, edoxaban 1x60mg and rivaroxaban has been shown to increase the risk of GIS bleeding (110). When using dabigatran and edoxaban, the risk of GIS bleeding is dose dependent (9). The use of apicaban or dabigatran of 2x110mg may be considered in patients at high risk for GIS bleeding or with GIS bleeding while using warfarin (103,110).

11. Measurement of the Effects of NOACs: Hematological Tests

Vitamin K antagonist anticoagulant drugs are difficult to use and poorly compatible drugs for physicians and patients due to reasons such as their pharmacological interactions, the need for dose interval monitoring and not being used in a fixed dose. The pharmacodynamic and pharmacokinetic profiles of NOACs are much more predictable than vitamin K antagonist oral anticoagulants, and it is accepted that there is a correlation between plasma concentrations and anticoagulant activity. It can be used in a fixed dose. Therefore, it is not necessary to monitor the drug level or anticoagulation level during routine use (2). However, it has been reported that the possibility of thromboembolism and bleeding under NOAC treatment may differ individually, especially depending on the use of multiple drugs, demographic characteristics, and kidney functions. As the use of these drugs becomes more widespread, the need for pharmacodynamic and pharmacokinetic drug monitoring may become evident in clinical practice (2,111). In some special cases, it is necessary to measure anticoagulant activity (Table 16) (111-113).

Table 16. Conditions requiring laboratory testing in patients using non-vitamin K oral anti-coagulants.

1. Conditions where drug accumulation may occur
   - I. Acute renal failure
   - II. Liver failure
   - III. High dose drug intake
2. Bleeding
3. Thrombosis
4. Deciding when emergency surgery or intervention is needed
5. Special patient groups
   - I. Obesity
   - II. Gastrointestinal malabsorption
6. Thrombolytic therapy indication in acute ischemic stroke
7. NOAC antidote use

11.1. PT, TT, aPTT: NOACs act as anti-coagulants by inhibiting activated serine proteases, particularly thrombin and FXa, and therefore, they may interfere with commonly used global clotting assays. The effects of NOACs on prothrombin time (PT) and activated partial thromboplastin time (aPTT) vary greatly depending on the reagent and test platforms used for the test and do not provide standard results. It is not recommended for monitoring the anticoagulant effects of NOACs. Therefore, different measurements and tests were needed to provide pharmacokinetic and pharmacokinetic monitoring of NOACs when necessary (Table 17) (112,113).

Dabigatran etexilate prolongs the clotting times of tests based on thrombin production and conversion of fibrinogen to fibrin. The peak plasma concentration and maximum anticoagulant effect of dabigatran is achieved within 3 hours after oral intake. Activated partial thromboplastin time can provide a qualitative assessment of dabigatran activity, but the sensitivity may vary depending on the type and model of the coagulometer and the reagent used (114). Most patients treated with dabigatran have prolonged aPTT. If the dabigatran effect rises above the therapeutic level, aPTT is unlikely to be normal, but aPTT may be normal even if dabigatran has achieved the desired anticoagulant effect (115). A normal thrombin time (TT) indicates no anticoagulant effect of dabigatran with a high negative predictive value. TT is very sensitive to dabigatran, and TT may be prolonged even when used at ineffective doses (116).

Prothrombin time, aPTT, and coagulation time are not specific for factor Xa inhibitors and are not sensitive enough to indicate the level of anticoagulation provided by factor Xa inhibitors (117). The maximum efficacy of apixaban and rivaroxaban occurs 3 hours after the drug intake and 2 hours after for edoxaban (118,119). Among the factor X inhibitors, rivaroxaban has the most effect on prothrombin time (PT), followed by edoxaban and apixaban, respectively. Rivaroxaban prolongs PT in a concentration-dependent manner. Test sensitivity depends largely on the reagent used (120). If the anticoagulant effect of rivaroxaban is above the therapeutic level, PT cannot be normal, but PT may be normal even when the desired level of anticoagulant activity is present (113). For apixaban, depending on the reagent used, PT may be found to be normal even if the effective anticoagulant activity is reached. Therefore, PT is not recommended for estimating plasma drug concentrations of apixaban or evaluating its efficacy (119). PT is prolonged at very high doses of edoxaban (118).

Table 17. Recommended laboratory tests for non-vitamin K oral anticoagulants and reliability.

	Direct thrombin inhibitors (Dabigatran)		**Factor Xa inhibitors (Apixaban, rivaroxaban, edoxaban)**	
Test	**Sensitivity**	**Usability**	**Sensitivity**	**Usability**
Prothrombin time (PT)	Low	Not suitable at therapeutic concentrations, may show effect at subtherapeutic doses	Low	Shows efficacy
Activated partial thromboplastin time (aPTT)	Low, Better than PT	Helpful, but normal test result does not rule out efficacy	Low	Not significant
Thrombin time (TT)	High sensitivity (hypersensitive)	Shows efficacy	Not significant	Not significant
Chromogenic anti-factorXa level	Not significant	Shows efficacy	High	Quantitative result
Ekarin coagulation time (ECT)	Sensitive	Quantitative result	Not significant	Not significant
Diluted thrombin time (dTT)	Sensitive	Quantitative result	Not significant	Not significant
HepTest	Sensitive	Quantitative result	Sensitive	Quantitative result
Plasma drug level	Sensitive	Quantitative result	Sensitive	Quantitative result
Prothrombinase mediated coagulation time (PiCT)	Low	Not determined yet	Sensitive except for low doses	Not determined yet

11.2. dTT: The concentration of dabigatran in blood can be monitored using calibrated functional tests that measure the effects of ecarin or thrombin formation on coagulation (2). Diluted thrombin time (dTT) may be preferred as it gives analytically more sensitive results at different dabigatran blood concentrations. Normal human plasma, previously pooled, is used to dilute the patient's plasma during dTT measurement. Thrombin time is measured in citrated plasma by adding a large amount of bovine or human plasma. The time in seconds for fibrin clot formation at 37°C is recorded. Recalcification of the plasma is not required. dTT reflects the conversion rate of fibrinogen to fibrin and is affected by the presence in plasma of direct thrombin inhibitors such as heparin and dabigatran (2,121).

11.3. ECT: Another platform that shows inhibition of thrombin formation is ecarin coagulation time (ECT) (122). Ecarin, a snake venom, is an enzyme that converts prothrombin to meizothrombin. The resulting meizothrombin activates fibrinogen and initiates an artificial in vitro coagulation. Since the coagulation-inducing effect of ecarin is weaker than thrombin, the presence of dabigatran, a direct thrombin inhibitor, in the environment extends the test time, so ECT is more sensitive for direct thrombin inhibitors (2). Chromogenic substrates are used instead of coagulation time in the latest generation devices that measure ecarin and dTT (Ecarin Chromogenic Assay - ECA) (113).

Clot formation is followed by coagulometry in HemosIL test (Instrumentation Laboratory, Bedford, MA), DG-Clot DTI test (Grifols, Barcelona, Spain), Hyphen Hemoclot test (Hyphen Biomed, Neuville-sur-Oise, France) and Technoclot DTI (Technoclone GmbH, Vienna, Austria). Biophen DTI test (Hyphen Biomed, Neuvillesur-Oise, France) and Innovance DTI (Siemens Healthineers, Marburg, Germany) tests, which are chromogenic methods, are based on the principle of scavenging a specific chromogenic substrate that can be followed photometrically from the test environment by FIIa. The STA-ECA II test (Stago, Asnières sur Seine, France) is a chromogenic ecarin test that can be used to measure dabigatran concentrations. A meta-analysis comparing these methods showed that all tests yield acceptable significant results, but different results may occur with different tests depending on the dabigatran concentration. It should be noted that in order to achieve low and high concentrations, at least two calibration curves must be obtained. While 67 ng/mL is used for DVT prophylaxis in dTT measurements, dabigatran levels above 200 ng/mL carry an increased risk of bleeding when used for stroke prophylaxis (2,113).

The pharmacodynamic effects of factor Xa inhibitors are more difficult to demonstrate. Diluted thrombin time and ecarin-induced clotting time tests are not affected by factor Xa inhibitors.

11.4. Anti-Factor Xa Tests: Functional anti-factor Xa tests are used to measure the concentrations of factor Xa inhibitors rivaroxaban, apixaban, edoxaban and betrixaban. These tests measure Factor Xa activity, based on the principle that a chromogenic synthetic substrate is scavenged by factor Xa. Scavenging of the fluorescent chromogenic substance will not occur or will be delayed when factor Xa inhibitors are present in the test environment. These tests were first developed to show the effects of low molecular weight heparin. The inhibition level of factor Xa activity is determined by comparing the serum of patients using the drug with the serum of healthy individuals. In these tests, Factor Xa activity at the peak at different drug doses, the time to peak of Factor Xa activity inhibition and the area under the curve of Factor Xa activity are measured to obtain data about anticoagulant activity (BIOPHEN DiXal, BIOPHEN Heparin LRT, STA Liquid Anti-Xa, Technochrom anti-Xa, HemosIL liquid anti-Xa, DG Chrom anti-Xa) (2).

HepTest measures the inhibition of exogenous factor Xa in the test environment based on the level of heparin catalyzing the inactivation of factor Xa. It can be used for rivaroxaban and apixaban, but clinical validation studies are needed (111).

11.5. LC-MS/MS: Another method that can be used to show the concentrations of factor Xa inhibitors is liquid chromatography-mass spectrometry / mass spectrometry (Liquid Chromatography-Mass Spectrometry / Mass Spectrometry, LC-MS / MS). LC-MS / MS is an analytical chemistry technique that combines the physical separation and mass analysis capabilities of liquid chromatography and mass spectrometry. This method is very sensitive to the drug molecule, and thus it is not affected by the coagulation procedure. Mass spectrometry and anti-Xa chromogenic assays are considered as the most specific and sensitive tests for factor Xa inhibitors.

However, these tests are very expensive and require specially trained personnel, and it does not seem possible to access them under emergency conditions throughout the country.

11.6. Other Tests: Another alternative test that can quantitatively demonstrate the effectiveness of NOACs is thrombin generation tests. Thrombin generation tests have been used for nearly a century to show both hemostasis and anticoagulant activity. It is more sensitive than PT and aPTT in showing hemostasis in vivo, and it is not affected by natural anticoagulants such as protein C, protein S, antithrombin. In recent years, automatic tests using fluorogenic substrates and recording the turbidity level have been developed, and calibrated automated thrombograms (Calibrated Automated Thrombogram - CAT, Asniers, Seine, Cedex, France; Technothrombin TGA, Technoclone, Vienna, Austria) are used frequently. In this test, patient plasma is mixed with tissue factor, phospholipids, calcium chloride to form clots. Thrombin formation and dissolution is monitored over time. Quantitative analysis is performed by measuring the total thrombin amount which is calculated by the time until thrombin formation starts, the time until thrombin formation reaches the peak, the peak height, the area under the curve. Studies conducted with dabigatran, rivaroxaban, apixaban, and edoxaban have shown that this test shows anticoagulant activity regardless of the drug level in blood. However, new clinical studies are needed to demonstrate the correlation of test results with thrombosis and bleeding in order for its use in patients receiving NOAC (113).

The sensitivity of viscoelastic tests such as thromboelastography and rotational thromboelastometry for NOACs has been reported very differently in different studies. It is considered non-sensitive at low or even at therapeutic concentrations (117). Microfluidic based factor II-X inhibitor tests are used to detect NOACs in blood. Surgery can be performed at levels below 30 ng/mL. Antidote administration can be terminated when the drug level falls below 50 ng/mL (117).

An acceptable correlation has been demonstrated between NOAC concentrations and the Dilute Russell viper venom time (DRVVT) test (123,124). Prothrombinase-induced clotting time (PiCT; Pentapharm, Basel, Switzerland), fibrinogen level measurement by the Claus method, thromboelastography (ROTEM, Tem Innovations, Munich, Germany; TEG, Haemonetics, Braintree, MA) are other candidate tests whose use is on the agenda to test NOAC effectiveness (125).

12. Ischemic Stroke While Using NOAC: What Should be Done?

The risk of recurrent stroke is highest during the first 90 days after the first stroke. Early relapse is associated with serious consequences such as longer hospital stays and increased neurological disability and death. Therefore, it is of great importance to rearrange the treatment in patients with stroke under anti-thrombotic therapy. NOACs, which have been used in recent years, have started a new treatment period in the prevention of primary and secondary stroke in patients with NVAF. Compared to traditional agents such as VKA, NOACs have advantages in terms of effectiveness, reliability (risk of intracerebral bleeding) and ease of use (126,127). While the use of NOACs, which have been shown to be at least as effective and safe as warfarin in preventing stroke in patients with NVAF, is increasingly widespread, the discussions about the approach to patients who develop stroke while taking NOAC are increasingly continuing. The development of both ischemic and hemorrhagic stroke is lower in patients using NOAC than warfarin, but it occurs at a clinically questionable rate (annual ischemic stroke risk 1-2%, hemorrhagic stroke risk 0.5%) (128).

It is of great importance to rapidly evaluate the coagulation disorder in terms of initiating intravenous thrombolytic therapy in patients presenting with acute ischemic stroke. There is no practical test for NOACs that quantitatively evaluates the anticoagulant effect (see Chapter 11). aPTT test can be performed for dabigatran while anti-factor Xa tests can be performed for rivaroxaban, edoxaban, and apixaban (103). Coagulation tests used routinely do not reliably document the effective plasma concentration of NOACs. The last recommendation of the AHA is that IV tPA should not be used unless at least 48 hours have passed since the NOAC intake and appropriate laboratory tests (such as aPTT, INR, platelet count, ecarin clotting time, thrombin time or anti-factor Xa activity) are not normal (129). There are also data in the literature that show reasonable use of IV tPA in patients with ischemic stroke while using NOAC. GWTG-Stroke ("American Heart Association Get with the

Guidelines-Stroke Registry") database is one of them. According to an analysis of this database in 2018, IV tPA was given to 42,887 patients with acute ischemic stroke in the first 4.5 hours, of which 251 were NOAC (dabigatran 87, rivaroxaban 129, apixaban 35) and one thousand and five hundred subtherapeutic (INR <1.7) were taking VKA. The percentage of symptomatic post-tPA intracranial hemorrhage was 4.8 in the NOAC group, 4.9 in those receiving warfarin, 3.9 in those not using OAC, and the difference was not statistically significant. No significant difference was found between the three groups in terms of parameters such as severe hemorrhagic life threatening, in-hospital mortality, functional status at discharge (130).

In a meta-analysis investigating the efficacy and reliability of IV thrombolysis in patients using NOAC and had ischemic stroke, in 492 cases compiled from 55 studies (dabigatran 181, rivaroxaban 215, apixaban 40, unknown NOAC 56 patients) who underwent IV tPA while taking NOACs, it was found that the median time between the latest NOAC intake and onset of symptoms was 8 hours. Most patients received the last dose of NOAC within 24 hours prior to stroke (55% patients within 12 hours, 34% patients within 13-24 hours). With the introduction of idarucizumab in 2015, andexanet alfa in 2018, and the reversal of anticoagulation, the risk of bleeding was reduced. The data supporting the use of IV rtPA after correcting coagulopathy with these agents in patients who had acute ischemic stroke while using NOAC is increasing. If possible, IV rt-PA can be administered in the early period after using these agents (131).

According to current data, thrombectomy appears to be safer than IV tPA in patients who had an ischemic stroke while using NOAC. In a study addressing this issue, no significant difference was found in intracerebral bleeding, recanalization success, and long-term prognosis in patients taking OAC who underwent only mechanical thrombectomy (23 VKA, 9 rivaroxaban, 3 apixaban, 1 dabigatran) compared to those who did not take OAC (132).

While subtherapeutic anticoagulation is the most common cause of treatment failure for patients receiving warfarin, missed doses are one of the most common causes for patients receiving NOAC. In one study, the risk of recurrent ischemic stroke was found to be 1.9% at the appropriate NOAC dose, and 20% at a low NOAC dose. There was no significant difference between intracerebral bleeding rates in the appropriate and low dose groups. In other words, standard dose NOAC reduces the recurrence of ischemic stroke without increasing the risk of intracerebral bleeding (133). In another study comparing 713 patients with AF using NOAC, multivariate analyses showed that ischemic cerebrovascular events are associated with insufficient NOAC dose, atrial dilatation, hyperlipidemia and high CHA2DS2-VASc score (134). In the ORBIT-AF study ("Outcome Registry for Better Informed Treatment of Atrial Fibrillation"), it was reported that 1 in 7 patients treated with NOAC were prescribed with low dose NOAC (135). So low dose may be a frequent and important reason for recurrence.

Another important issue is the time of restarting OAC treatment in patients who had an ischemic stroke while using NOAC. In the Basel study, a total of 204 consecutive NVAF patients who were admitted with an acute ischemic stroke or TIA and started NOAC or VKA as a secondary prophylaxis were monitored for at least 3 months, and the good functional prognosis in patients who started early (in the first 7 days after the stroke) was higher than those who started NOAC late (38% vs. 13%) while there was no increase in mortality and no symptomatic intracranial bleeding was observed (136). However, studies on this subject are not sufficient. Since it is known that the risk of intracerebral bleeding with NOACs is lower than VKA, and if NOAC is to be started again, it seems safe to start it after waiting at least as long as (possibly earlier) the time of restarting warfarin to prevent recurrent stroke after acute ischemic stroke. Although it varies according to the size of the infarct, it is safe to start in the first 7 days. In necessary cases, especially in large infarcts, the OAC onset time algorithm, which is recommended mostly for warfarin, can also be applied to NOACs (86). Considering the literature, it may be safe to start treatment within the first 7 days after stroke, especially in patients with high risk of recurrent stroke and small ischemic lesions. In order to prevent recurrence of stroke, it is of great importance whether the patient takes the NOAC drug regularly, skips the dose, and takes the appropriate dose. When using a low-dose NOAC, if the patient had ischemic stroke, the same molecule can be increased to the effective dose or another

NOAC can be started. If a standard effective dose of NOAC is used, it can be replaced with another NOAC which is thought to be more effective in preventing ischemic stroke recurrence.

If the patient is on NOAC with high efficacy and at an appropriate dose, then a transition to VKA can be made, provided that it is closely monitored within the therapeutic range. In addition, the NOAC indication should be reviewed again, and the need for VKA should be evaluated once more. Closure of the atrial appendix may be considered. All patients with a stroke when on NOAC should be re-examined as if they had a stroke for the first time, and it should be kept in mind that there may be another cause of stroke (such as small vessel disease) and should be investigated. All risk factors should be reassessed (134). The results of studies such as "ARAMIS", which are planned to determine the strategy to be followed in the development of acute stroke in patients using NOAC, will shed light on our approach to these patients (136). Until these studies are concluded and more precise data are obtained, decisions on the treatment should be made by considering the benefit-harm ratio on a patient-specific basis.

13. Antiaggregant NOAC Combination

Coronary artery disease and AF are more common with advanced age. AF is observed in approximately 5-8% of patients with percutaneous coronary intervention (PCI). As a result of randomized controlled studies, OACs are the most effective treatment options in protecting patients with AF from embolic stroke and systemic embolism, and in the current guidelines, OAC use is recommended in patients with a CHA2DS2-VASc score ≥ 2 (male) ≥ 3 (female) at the Class I evidence level and in male patients with a score of 1 and female patients with a score of 2 at the class IIa evidence (12). Dual antiplatelet therapy is also recommended to protect patients from stent thrombosis after stent applications. However, in patients with AF and recommended PCI, Acetylsalicylic acid (ASA) + OAC + Clopidogrel alone increased the risk of bleeding 3-4 times compared to OAC only (137). In many studies, it has been observed that the addition of NOACs to dual antiaggregant treatment does not provide any clinical benefits and that it increases the rates of major bleeding. In the ATLAS-ACS2TIMI 51 study, when rivaroxaban was given 2 × 2.5 mg/day or 2 × 5 mg / day in combination with dual antiaggregant, ischemic events were less common, but major bleeding increased (138). In the APRAISE-2 study, the study was terminated prematurely due to the increased major bleeding seen in the combination of full-dose apixaban and dual antiaggregant (139).

Early discontinuation of ASA in patients using OAC and $P2Y_{12}$ inhibitors or its use only in the periprocedural period has been investigated in many studies. In the randomized WOEST study, which is the first of these studies, VKA + ASA + clopidogrel and VKA + clopidogrel arms were compared. This triple therapy paradigm has changed since this study showed that the combination of VKA and clopidogrel decreased bleeding complications without increasing thrombotic and embolic events in comparison with the conventional triple therapy (140). The contents of the 4 studies conducted following this study are summarized in Table 18 (141-144).

Table 18. Characteristics of studies on anticoagulant and antiaggregant combination after PCI.

	Triple antithrombotic therapy	Dual antithrombotic therapy	Accompanying arm	Patients (n)	Mean age (yıl)	Mean gender n (%)	Post stroke n (%)	CHA_2-DS_2VASc	HAS-BLED
Pioneer AF[142]	VKA-INR 2-3 $P2Y_{12}$ inhibitor+ASA	Rivaroxaban 1x15mg + $P2Y_{12}$ inhibitor	Rivaroxaban 2X2,5mg+ ASA+ $P2Y_{12}$ inhibitor	2124	70	1582 (74%)	0(0%)	3,7+/-1,6	3,0+/-0,9
RE-Dual PCI[141]	VKA-INR 2-3 $P2Y_{12}$ inhibitor + ASA	Dabigatran 2x150mg+ $P2Y_{12}$ inhibitor	Dabigatran 2x150mg+ $P2Y_{12}$ inhibitor	2725	69/72*	2070(76%)	226 (8,3%)	3,7+/-1,5	2.7+/-0.7
Augustus[143]	VKA-INR 2-3 $P2Y_{12}$ inhibitörü	Apixaban 2x 5 mg+ $P2Y_{12}$	Secondary randomization +/- ASA	4614	71	3277(71%)	633 (13,8%)	3,9+/- 1.6	2.9+/-0.9
Entrust AF (144)	VKA-INR 2-3 $P2Y_{12}$ inhibitor+ASA	Edoxaban 1x60mg + $P2Y_{12}$	_	1506	70	1120 (74%)	189 (12,5%)	4.0 (3.0-5.0)	3.0 (2.0-3.0)

Low-dose rivaroxaban was used in the PIONEER AF-PCI study, which was not previously recommended for stroke prophylaxis. Ischemic stroke has been observed more frequently in moderately high-risk patients. Therefore, it does not seem to be a sufficient alternative to VKA-based triple therapy in preventing stroke in moderate-high risk patients. In the RE-DUAL PCI study, lower bleeding rates were observed with similar ischemic risks in the use of high-dose dabigatran. There is an increased ischemic risk at low doses. The use of high doses in young patients may be an appropriate indication (142).

In the AUGUSTUS study, the ischemic and embolic events were similar in both anticoagulant arms, and it was observed that major bleeding rates increased with the addition of ASA, although there was no reduction in ischemic and embolic events. The addition of ASA in the first 30 days caused an increase in bleeding while causing a decrease in ischemic and embolic events. However, in its use for more than 30 days, it does not decrease ischemic events and additionally causes an increase in severe bleedings. In summary, it was observed in this study that the doses used in stroke prophylaxis were safe. No significant increase was observed with apixaban-based dual and triple therapies (143).

In the ENTRUST-AF PCI study, less bleeding was observed when used with $P2Y_{12}$ inhibitors at approved doses in stroke prophylaxis compared to VKA-based triple therapy. However, the increased incidence of ischemic events observed in the first week raised the question of whether ASA should be given for a few more days in the early period (144).

13.1. Dual Therapies in the Elderly: Fewer side effects are expected with NOACs compared to VKA in elderly patients. There are insufficient data in the studies mentioned above on major hemorrhages and ischemic events. However, in summary, it may be appropriate to administer periprocedural ASA and NOAC with clopidogrel when PCI is required in elderly patients with AF.

13.2. Benefit-Harm Assessment: In NOAC-based dual therapies, there is an absolute increase of 0.4% in the risk of major cardiovascular events compared to VKA-based triple therapies, a 1.1% absolute reduction in major bleeding, and an absolute benefit of 0.7% in favor of NOAC-based dual strategies in terms of benefit and harm (145). The sub-analysis of the AUGUSTUS study showed that triple therapy was advantageous in the first month for major cardiovascular events, but this benefit was not sustained after 30 days (146).

13.3. ASA Treatment Duration and Risk of Stent Thrombosis: Early termination of ASA brings to mind the risk of stent thrombosis. However, the risk of stent thrombosis was found to be low in all studies. In the AUGUSTUS study, it was necessary to add ASA to 250 patients to prevent stent thrombosis, while major bleeding was detected in one of the 55 patients in whom ASA was added. Therefore, it is concluded that ASA does not need to be used together with OAK+$P2Y_{12}$ inhibitors after 30 days. In the first month, a decision can be made by evaluating the risk of bleeding and ischemia on patient basis.

13.4. Approach in patients with carotid stenosis: Dual antiplatelet therapy is recommended in carotid stent patients to reduce the risk of periprocedural ischemic events (147). Hawkins et al. observed that temporary discontinuation of anticoagulant therapy and switching to dual antiplatelet therapy resulted in an increased risk of ischemic stroke (148). In order to minimize the risk of hemorrhagic complications, if possible, transition to NOAC in NVAF patients receiving VKA therapy may be preferred (149). The recommendations of the 2020 guidelines of the European Society of Cardiology (150) regarding treatment strategies and the duration of use for patients who need oral anticoagulant and antiaggregant treatments are summarized in Table 19.

The common conclusion from all studies is that bleeding increases with intensive antithrombotic therapy. It is recommended to use recommended doses in stroke prophylaxis to prevent stroke and coronary ischemia in patients with AF who underwent PCI. NOAC-based strategies should be preferred over VKA-based strategies because of the low risk of bleeding. There are no data to support the use of triple therapies administered with the addition of ASA after 30 days. Due to the risk of stent thrombosis in the first month, the benefit-harm rates should be evaluated in this patient group and the decision of optimal antithrombotic treatment should be made on a patient basis. Dose reduction should be avoided in elderly patients who are at high risk of stroke.

Table 19. Recommendations of the European Society of Cardiology 2020 guidelines.

Recommendations for AF patients with acute coronary syndrome (ACS)	Class	Level
In AF patients with ACS undergoing uncomplicated PCI, if the risk of stent thrombosis is low and the concerns about the risk of bleeding preclude concerns about the risk of stent thrombosis, early discontinuation of aspirin (<1 week) and dual therapy with an OAC and a P2Y12 inhibitor (preferably clopidogrel) is recommended to continue up to 12 months	I	B
Triple therapy with Aspirin, clopidogrel and OAC for more than 1 week after ACS can only be recommended for a maximum of 1 month when there is concern about stent thrombosis more than the risk of bleeding. The treatment plan should be clearly stated upon discharge from the hospital.	IIa	C
General recommendations and concurrent antiplatelet therapy indication for patients with AF	**Class**	**Level**
It is recommended to use NOAC instead of VKA when antiplatelet combination is required in patients with AF suitable for NOAC.	I	A
In patients with high bleeding risk (HAS-BLED> 3), Rivaroxaban 15 mg should be preferred instead of Rivaroxaban 20 mg alone or during DAPT to reduce the risk of bleeding.	IIa	B
In patients with a high risk of bleeding (HAS-BLED> 3), Dabigatran 110 mg should be preferred instead of Dabigatran 150 mg alone or during DAPT to reduce the risk of bleeding.	IIa	B
In patients with VKA indication, when antiplatelet combination is required, it should be carefully adjusted so that the TTR is 70% and INR is between 2-2.5.	IIa	B
Recommendations in chronic coronary syndrome patients with AF who received PCI	**Class**	**Level**
After an uncomplicated PCI, early discontinuation of aspirin (<1 week) and continuation of dual therapy with OAC for up to 6 months is recommended if the risk of stent thrombosis is low, regardless of the type of stent used, or if concerns about the risk of bleeding preclude concerns about the risk of stent thrombosis.	I	B
When the risk of stent thrombosis is high, triple therapy with aspirin, clopidogrel, and OAC for more than 1 week should only be considered for a maximum of 1 month when there is more concern about stent thrombosis than the risk of bleeding. The treatment plan should be clearly stated upon discharge from the hospital.	IIa	C

14. Hemorrhagic Stroke in a Patient Using NOAC

In patients receiving anticoagulant therapy, intracranial hemorrhages associated with this therapy can occur at intracerebral, intraventricular, subarachnoid, subdural, and epidural distances. These bleedings can sometimes lead to mild and temporary consequences that do not cause deficits, and sometimes severe enough to be life-threatening. Discontinuation and reversal of anticoagulation is a medical emergency in patients with anticoagulant-associated intracranial bleeding due to hematoma enlargement, neurological deterioration, major risk of disability, and death.

Minor bleeding such as nosebleeds, skin bruising, slow gastrointestinal bleeding can usually be managed conservatively with local hemostatic measures. However, patients with severe major bleeding should be treated in an intensive care setting with appropriate hemodynamic support. Options for bleeding management include drug removal with activated charcoal or hemodialysis, antifibrinolytic agent, clotting factor products (PCC: "Prothrombin Complex Concentrate", aPCC: "activated Prothrombin Complex Concentrate"), specific antidotes and/or surgical interventions (Table 20).

14.1. Basic Treatment Strategies for all Patients with Major Bleeding

All anticoagulant and antiplatelet therapy should be discontinued immediately.

Rapid and continuous hemodynamic evaluation should be done.

Care should be taken to have an effective airway and a large-diameter venous access.

Body temperature, blood pH and electrolyte balance, including calcium, should be optimized.

In line with the guideline recommendations in acute intracerebral hemorrhage, it is suggested that decreasing a systolic blood pressure of 150-220 mmHg to the threshold of 140 mmHg and a systolic blood pressure of 220 mmHg and above to the limits of 140-160 mmHg is a reasonable goal (151).

Platelet transfusion is suitable for an individual with a platelet count of <100,000 / microL or a known platelet function defect.

The hemoglobin level can be useful both to assess the severity of bleeding and to determine the need for erythrocyte transfusion.

Considering the renal dependence of NOACs,

Table 20. Post-bleeding treatment strategies associated with NOAC.

Type of Bleeding	Agent	Potential Interventions
Major bleeding ▪ Intracranial ▪ Retroperitoneal ▪ Compartment syndrome ▪ Massive gastrointestinal	Dabigatran (Pradaxa®)	▪ Idarucizumab ▪ aPCC (FEIBA®) * ▪ Antifibrinolytic agent ▪ Stopping anticoagulants ▪ Oral activated charcoal ▪ Hemodialysis ▪ Erythrocyte suspension if necessary for anemia ▪ Platelet suspension for thrombocytopenia ▪ Surgical
	Rivaroxaban (Xarelto®) Apixaban (Eliquis®) Edoxaban (Lixiana®) Betrixaban (Bevyxxa®)	▪ Andexanet alfa (AndexXa®) ▪ PCC (Kcentra®) ▪ Antifibrinolytic agent ▪ Stopping anticoagulants ▪ Oral activated charcoal ▪ Hemodialysis ▪ Erythrocyte suspension if necessary for anemia ▪ Platelet suspension for thrombocytopenia ▪ Surgical
Minor Bleeding ▪ Epistaxis ▪ Bruising ▪ Slow gastrointestinal	Dabigatran (Pradaxa®)	▪ Local hemostatic measures ▪ Stopping anticoagulants ▪ Half-life ▪ Antifibrinolytic agent
	Rivaroxaban (Xarelto®) Apixaban (Eliquis®) Edoxaban (Lixiana®) Betrixaban (Bevyxxa®)	▪ Local hemostatic measures ▪ Stopping anticoagulants ▪ Half-life ▪ Antifibrinolytic agent

aPCC: activated Prothrombin Complex Concentrate
* aPCC is recommended only if Idarucizumab cannot be used and / or if continued bleeding is likely to be fatal within hours
¶ As the kidney function deteriorates, the half-life of Dabigatran will increase. The half-life of Rivaroxaban, Apixaban, Edoxaban and Betrixaban will be prolonged in severe liver failure.

creatinine and creatinine clearance can be measured in patients with significant bleeding. Also, uremia can further reduce hemostasis by impairing platelet function.

Evaluating liver function can contribute to increase reduced hemostasis.

14.2. Treatment strategies to reverse the effects of the anticoagulant agent: The specific antidote for dabigatran is Idarucizumab (Praxbind®), while the antidote for direct factor Xa inhibitors is Andexanet alfa (AndexXa®).

Non-specific agents such as coagulation factor products (PCC and aPCC)

Antifibrinolytic agents

Desmopressin (DDAVP®)

Removal of the drug from the circulation or the gastrointestinal tract; oral administration of activated charcoal can keep anticoagulants that have not yet been absorbed from the gastrointestinal system and remove them from the system.

Hemodialysis

These strategies are based on clinical experience and data from case series. The aim is to try to balance the risk of life-threatening bleeding with the increased risk of thrombosis. However, caution should be exercised in patients with minor bleeding as PCC and some antidotes have the potential to cause thrombosis. In other words, the use of these products should not be considered as routine or "standard care". The clinician should be aware of the possible thrombosis.

14.2.1. Idarucizumab (Praxbind®): Dabigatran (direct thrombin inhibitor) was the first antidote to be used to reverse anticoagulation and received FDA approval in 2015 (74). The method of use is as two consecutive infusions (2x2.5 g vials). Idarucizumab should not be used in patients with normal TT.

14.2.2.Andexanet alfa (AndexXa®): It is an antidote approved by the FDA in 2018 to reverse the bleeding caused by Rivaroxaban and Apixaban.

Low dose - 400 mg bolus at 30 mg / min followed by 480 mg infusion for 2 hours (Rivaroxaban ≤ 10 mg, Apixaban ≤ 5 mg or if ≥ 8 hours have passed since the last dose of factor Xa inhibitor). High dose - 30 mg / min, 800 mg bolus followed by 960 mg infusion for 2 hours (Rivaroxaban> 10 mg, Apixaban> 5 mg or if ≤8 hours have passed since the last dose of factor Xa inhibitor). In one study, good hemostatic efficacy was observed after the use of Andexanet alfa in patients with acute major bleeding associated with factor Xa inhibitor use (73).

14.2.3. Coagulation Factor Products: This group includes non-activated PCC and activated PCC. They contain high levels of three or four clotting factors (II, VII, IX and X) along with PCC, protein C and protein S purified from plasma. It is recommended to be administered intravenously at a rate of 2 ml per minute. It has been shown that fixed dosing is easier to apply in terms of efficacy (152). The second dose is not recommended because the risk-benefit ratio cannot be predicted. aPCC are PCCs that contain at least one factor in active form. FEIBA® is the only aPCC available in the United States. It is also available under different names in other countries. The recommended dosage range for FEIBA® is 50 - 100 units / kg.

Andexanet and PCC products are not recommended to be used together.

14.2.4. rFVIIa (Recombinant Activated Factor VII): Although rFVIIa has been shown to provide coagulation in vitro, animal bleeding models did not suggest that rFVIIa would be beneficial in bleeding associated with direct oral anticoagulants.

14.2.5. Plasma Products: The use of fresh frozen plasma (FFP) may be appropriate as part of a massive transfusion protocol in patients with severe bleeding who have developed diluted coagulopathy. However, since these plasma products carry various potential risks such as volumetric overload and infection transmission, their use in bleeding directly related to oral anticoagulants is not recommended.

14.2.6. Antifibrinolytic agents: Antifibrinolytic agents such as Tranexamic acid and epsilon aminocaproic acid can be used for severe bleeding. Both have oral and intravenous forms. However, intravenous administration is preferred for major and life-threatening bleeding.

14.2.7. Desmopressin (DDAVP®): Considering the low risk of thrombosis, low cost, and widespread availability, it may be appropriate to use in patients with major and life-threatening bleeding associated with direct oral anticoagulants. It can be used subcutaneously or intravenously. The dose is 0.3 mcg / kg.

14.2.8. Oral Activated Charcoal: If the oral anticoagulant dose has been taken within the last two hours, oral activated charcoal administration may be recommended. The dose is 50-100 g.

14.2.9. Hemodialysis: If drug removal potential is high in selected patients, hemodialysis can be used (Dabigatran). Direct factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban) cannot be removed by hemodialysis.

The decision to initiate NOAC after intracranial hemorrhage is difficult. A patient-based personalized decision should be made by taking into consideration the balance between the patient's thromboembolism risk and hemorrhagic complications. It should be kept in mind that the left atrial appendix closure method in such patients may be an alternative treatment to NOAC.

15. NOAC in Atrial Fibrillation at High Risk of Hemorrhagic Stroke

AF is a complex medical condition that increases the risk of ischemic stroke by five times (153). It has been reported that anticoagulant therapy reduces the risk of ischemic stroke in two-thirds of patients with AF through a minimal increase in extracranial hemorrhage (154,155). There is an inherent risk of bleeding in any anticoagulation decision, however, one of the severe complications that is difficult to predict is intracranial hemorrhage which are relatively rare and have a more fatal course and is associated with severe disability in survivors (156,157).

Rivaroxaban, apixaban and edoxaban, which show their effects with through factor-Xa inhibition, and dabigatran etexilate, which is a direct thrombin inhibitor, are generally named as NOAC and they have important advantages such as early on-set of effects, not requiring drug efficacy monitoring, rare food interactions and less side effects when compared to vitamin K antagonist drugs (158). In addition to all these positive features, there are serious disadvantages such as the lack of standard laboratory tests and coagulation markers that can evaluate their efficacy in risky situations, and that well-defined

antidotes are not widely used in case of bleeding complications (159). For this reason, determining the benefit-harm balance with ischemic-hemorrhagic stroke risk analysis is more important in anticoagulation with NOACs before treatment.

15.1. NOACs and the Risk of Hemorrhagic Stroke: In the RE-LY study, the annual hemorrhagic stroke rates were 0.38% in the warfarin group, 0.12% (p <0.001) in the 110 mg dabigatran group and 0.10% (p <0.001) in the 150 mg dabigatran group. Intracranial bleeding rates were higher in the warfarin group (0.74%) compared to both the low dose and high dose dabigatran groups (0.23%, 0.30%, respectively, p <0.05). Compared to the 110 mg dose, the 150 mg dose of dabigatran had an increased risk of major bleeding (p = 0.052), but the net clinical benefit was almost the same for the two doses (6). While there was no statistically significant difference in outcome rates with hemorrhagic stroke in the ROCKET AF study, intracranial bleeding was significantly lower in the rivaroxaban group (0.5%, 0.7% per year, respectively, p=0.02) (8). In the ARISTOTLE study, the rate of hemorrhagic stroke was 49% lower in the apixaban group compared to the warfarin group, and the hemorrhagic transformation rates were lower in those with ischemic stroke compared to the warfarin group. The rate of intracranial bleeding was 0.33% per year in the apixaban group and 0.8% per year in the warfarin group (P <0.001) (9). Lastly, in ENGAGE-AF-TIMI, the annual rate of hemorrhagic stroke was 0.47% with warfarin, 0.26% with high-dose edoxaban, and 0.16% (p<0.001) with low-dose edoxaban. Intracranial bleeding rates were 0.85% in warfarin, 0.39% in high dose edoxaban, and 0.26% in low dose edoxaban (p<0.001). In high dose edoxaban, increased haemorrhagic stroke rates were reduced, ischemic stroke rates balanced, and net clinical benefit remained similar compared to the lower dose. As a result, the incidence of hemorrhagic stroke was significantly lower in both edoxaban doses than warfarin (10).

Following these studies, the efficacy and safety of NOACs were investigated by a meta-analysis of four studies, and patients using high-dose NOAC were evaluated. As a result of this meta-analysis, NOACs reduced stroke and systemic embolic events by 19% compared to warfarin (relative risk 0.81) and furthermore, hemorrhagic stroke (p<0.0001), death from all causes (p=0.0003) and intracranial bleeding (<0.0001) were less in the NOAC group (11).

In a recent population-based cohort study, it was shown that NOACs have similar or better efficacy and safety compared to warfarin, and the advantages of NOAC treatment are most pronounced in patients under 80 years of age with standard doses and with lower doses in patients over 80 years of age (160).

15.2. High Bleeding Risk Assessment: Various factors based on clinical, electrophysiological, biological, radiological, and genetic markers have been shown to play a role in determining the risk of stroke (156). Comorbid conditions affect both the recurrence of stroke and the risk of bleeding in patients with AF, making anticoagulation decision difficult (12). CHA_2DS_2-VASc score is one of the several risk stratification schemes that can help determine the 1-year risk of thromboembolism in a patient with non-valvular AF, and currently, most guidelines recommend the use of the CHA_2DS_2-VASc score (Table 4) at Class 1, Evidence A level to make a decision on anticoagulation therapy (12,161). In this chart, which is also used in the AF management guidelines of the European Society of Cardiology (ESC), oral anticoagulant treatment, primarily NOAC, is recommended for every patient with a score of ≥2, the preference of oral anticoagulant treatment is emphasized in patients with a score of 1, and antithrombotic therapy is not recommended in patients with a score of 0.12 In addition, the HAS-BLED bleeding risk chart (Table 3) is included in this guideline, the high bleeding risk is defined as score ≥3, and careful monitoring of antithrombotic therapy is recommended in this case (12,162,163). Apart from HAS-BLED, other bleeding risk schemes including varying numbers and parameters have been developed in AF patients receiving oral anticoagulant therapy (Table 21) (163,164). However, this situation has led to misunderstandings and improper use due to the complex and variable characteristics of the parameters used (162-164). Therefore, guidelines focus more on modifiable bleeding risk factors rather than emphasizing the use or value of bleeding risk scores (Table 22) (12). However, the risk of bleeding is not limited to modifiable risk factors determined at baseline or outcome only; it is a dynamic process with many variables (165). In a recent study comparing modifiable risk factors

Table 21. Parameters included in various bleeding risk schemes according to their frequency of use (164).

The frequency of use of the parameter in 10 well-known bleeding schemes	Risk Factor Parameters		ABC	ORBIT	ATRIA	HAS-BLED	HEMORRHAGES	Shireman	IMPROVE	Ruiz-Gimenez	Kuijer	OBRI
10/10	Age	≥85							√			
		≥75		√	√		√			√		
		≥70						√				
		≥65				√						√
		≥60									√	
		≥50	√									
8/10	Anemia			√	√		√	√	√	√	√	√
7/10	Past/Distant bleeding		√	√	√	√	√	√				√
6/10	Renal disorder			√	√	√	√			√		√
4/10	Malignancy						√		√	√	√	
3/10	Stroke					√	√					√
3/10	Liver disease					√	√		√			
3/10	Hypertension				√	√	√					
3/10	Excessive alcohol consumption					√	√	√				
3/10	Combined antiplatelet therapy			√		√		√				
2/10	Recent bleeding							√		√		
2/10	Female gender							√			√	
2/10	Diabetes mellitus							√				√
2/10	Decreased platelet count						√		√			
1/10	Myocardial Infarction											√
1/10	Biomarkers		√									
1/10	Labil INR					√						
1/10	Increased risk of falling						√					
1/10	Genetic factors						√					
1/10	Bleeding history 3 months before admission								√			
1/10	Coronary intensive care / coronary care unit								√			
1/10	Central venous catheter								√			
1/10	Rheumatic disease								√			
1/10	Clinically obvious carpulmonaryembolism									√		
	Total Number of Risk Factors		**3**	**5**	**5**	**9**	**12**	**8**	**10**	**6**	**3**	**7**

with other commonly used bleeding risk schemes, the highest c-index was found in the HAS-BLED chart (165). The use of bleeding risk schemes in determining the risk of bleeding in patients with AF is a Class IIa, Evidence B level guideline recommendation.

In a recent study, the initial CHA_2DS_2-VASc and HAS-BLED scores of patients with anticoagulation-associated intracranial hemorrhage were determined, and the risk optimization was evaluated by subtracting them from each other. In the cohort of patients with

anticoagulation-associated intracranial hemorrhage, approximately one-third of whom received NOAC, only 50% of patients were found to have an increased risk of bleeding initially, and the need for biomarkers to predict the risk of hemorrhagic complications more accurately was mentioned (166).

The CROMIS-2 study reported that the presence of cerebral microhemorrhage in patients with AF who were anticoagulated after a recent ischemic stroke or transient ischemic attack was an independent risk factor of symptomatic intracranial bleeding without increasing recurrent ischemic stroke (157).

In order to predict NOAC-associated bleeding, in addition to hepatic and renal function tests that directly affect drug pharmacokinetics and hemostasis regulation and that are included in some bleeding risk schemes as well as classical parameters such as thrombocytopenia and anemia, IL-6, CRP, vWF, high-sensitive troponin, NT-proBNP, cystatin Different biomarkers such as -C, growth differentiation factor-15 (oxidative stress marker) have also been investigated and reported to be effective. However, data on these biomarkers are still limited (156). The use of high-sensitive troponin and natriuretic peptide-like biomarkers in selected cases in the assessment of bleeding risk in patients with AF has taken its place as a guideline recommendation at Class IIb, Evidence B level (12). Risk schemes are simple and useful tools for quick guidance in treatment decisions. However, it should be noted that this benefit is limited due to factors such as limited parameters and their power of influence not being addressed in detail, the heterogeneity caused by individual differences, the potential for the score to change in the dynamic process.

In conclusion, the correct strategy in the treatment of patients with AF with a high risk of hemorrhagic stroke will be to focus not only on anticoagulant therapy but also on measures to reduce the risk of bleeding. Difficult decisions including correction of known modifiable risk factors such as hypertension, drug use, alcohol consumption, closer monitoring of patients, elimination of treatable risks such as intracranial aneurysm, gastrointestinal ulcers in necessary cases, alternative new therapeutic options, use of more optimal risk scoring schemes, and stopping, discontinuing, and resuming of treatment when needed, can be considered as a summary of these treatment strategies that should be decided upon by a multidisciplinary team.

Table 22. Bleeding risk factors according to their ability to be modified (12).

Can be modified
• Hypertension (especially when systolic blood pressure iss >160 mmHg)
• "Labile INR" or "Duration in the therapeutic range <60%" for OAC users
• Use of drugs such as antiplatelet, NSAID that predispose to bleeding
• ≥ 8 alcohol consumption/week
Potentially modifiable bleeding risk factors
• Anemia
• Impaired renal function
• Impaired liver function
• Decreased platelet count or function
Bleeding risk factors that can't be modified
• Age (>65)(≥75)
• Major bleeding history
• Dialysis-dependent kidney damage or renal transplant
• Cirrhosis
• Malignancy
• Genetic factors
Biomarker-based bleeding risk factors
• High-sensitive troponin
• Growth differentiation factor-15
• Serum creatinine / estimated creatinine clearance

16. NOAC-Use Regulations in Turkey: Current Situation and the Factors that Need to be Corrected

The situation of NOAC use in our country should be addressed in two headings that are licensing/therapeutic indications and reimbursement indication/conditions of the Social Security Institution (SSI). For this reason, the subject will be examined in two sections as items that need to be corrected in the light of the examination of the prospectus information of the products licensed in our country and the review of the Health Practice Statement (HPS) and recommendations.

16.1. Therapeutic Indications of Licensed and Used NOACs: There are four drugs in the NOAC category that are licensed and used in our country in the order of licensing dates: dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Lixiana®) The indications for use taken from the package insert information are listed below. The prospectus information was created by companies and their trade names were used because they were taken verbatim.

16.1.1. Paradaxa® Indications: Pradaxa® is indicated for primary prevention of venous thromboembolic (VTE) events in adult patients undergoing elective total hip replacement surgery or total knee replacement surgery. It is indicated for the prevention of stroke and systemic embolism (SPAF) in adult patients with nonvalvular atrial fibrillation with one or more risk factors such as history of stroke or transient ischemic attack, age 75, heart failure (New York Heart Association (NYHA) Class ≥II), diabetes mellitus, and hypertension. It is indicated for the treatment of acute deep vein thrombosis (DVT) and / or pulmonary embolism (PE).

16.1.2. Xarelto® Indications: Xarelto® is indicated in adult patients with non-valvular atrial fibrillation and have one or more risk factors such as congestive heart failure, hypertension, age ≥75, diabetes mellitus, previous stroke, or transient ischemic attack for the prevention of stroke and systemic embolism. Xarelto is indicated for deep vein thrombosis (DVT) and the prevention of recurrent DVT and Pulmonary Embolism (PE) after acute DVT in adult patients. Xarelto® is indicated for the prevention of recurrent PE and DVT with the treatment of Pulmonary Embolism (PE) in adult patients.

16.1.3. Eliquis® Indications: Eliquis® use is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in adult patients with NVAF who have one or more risk factors such as previous stroke or transient ischemic attack (TIA), age 75 and over, hypertension, diabetes, symptomatic heart failure (NYHA Class II and above), and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults.

16.1.4. Lixiana® Indications: Lixiana® is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors such as congestive heart failure, hypertension, age 75 and above, diabetes, previous stroke or transient ischemic attack (TIA), and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of PE with recurrent DVT in adults.

When the treatment indications of the prospectuses are examined, it is seen that they are used in the prevention of stroke from a neurological perspective, and treatment of deep vein thrombosis and pulmonary embolism. They can be used in nonvalvular atrial fibrillation patients with transient ischemic attack or ischemic stroke to prevent stroke. In addition, there are indications to be used for prevention in NVAF patients without TIA or stroke symptoms, in the presence of the additional risks mentioned above. Many acute or chronic neurological diseases can lead to a decrease in the patient's movements and lead to being bedridden. Treatment of DVT and/or PE that may occur in this situation and prevention of its recurrence is also one of the neurological uses (167).

16.2. HPS Criteria for NOAC Reimbursement: HPS should not be considered as a guide in terms of choosing and applying treatment, but as a set of rules in which the conditions for the cost of the available options are covered by the SSI. While planning a treatment, the physician makes a decision together with the patient, sharing the options with the current scientific data and guidelines. The failure of HPS to meet this treatment does not mean that the treatment approach is wrong, and it is constantly

updated according to the developments in the treatments by taking into account the applications of the specialty associations.

"16.06.2020 Amendment Communiqué Processed Updated 2013 HPS" is the recently updated communiqué containing the last change before our article was published. The field related to NOAC in HPS includes sections of "4.2 - Regulations regarding some specific diseases and drug use, 4.2.15 - Principles of use of clopidogrel, cilostazol, ivabradine, prasugrel, dabigatran, rivaroxaban, apixaban, ticagrelor and ranolazine, 4.2.15.D Dabigatran, rivaroxaban, edoxaban and apixaban". Here, the subtitle "D-1" examines the conditions related to the treatment and prevention of stroke and the subtitle "D-2" addresses treatment and prevention conditions of DVT and PE (168).

Accordingly:

4.2.15.D-1- Dabigatran, rivaroxaban, edoxaban ve apixaban;

(1) Provided that it is stated in the medical board report; in patients with moderate to severe mitral stenosis or nonvalvular atrial fibrillation without a mechanical prosthetic valve who have one or more of the conditions of a history of stroke or transient ischemic attack, age ≥ 75 years, heart failure NYHA Class ≥II, diabetes mellitus or hypertension;

a) Warfarin can be discontinued and dabigatran or rivaroxaban or apixaban or edoxaban treatment can be initiated in cases where the target INR value cannot be kept between 2-3 in at least three of the last 5 measurements performed with at least one week intervals after using warfarin for at least 2 months.

b) Those who have a cerebrovascular event while under warfarin treatment can be directly switched to dabigatran or rivaroxaban or apixaban or edoxaban.

(2) It is reimbursed when the situations defined above are specified and if prescribed by specialist physicians, based on a 6-month medical board report by at least three of the specialists of cardiology, internal medicine, chest diseases, cardiovascular surgery and neurology provided that at least one of the physicians is a specialist in cardiology or neurology.

(3) If drugs with active ingredients of dabigatran, rivaroxaban, edoxaban and apixaban are used in combination, they won't be reimbursed by the Institution.

4.2.15.D-2-Rivaroxaban, Dabigatran, Apixaban ve Edoxaban;

(1) In adult patients:

a) Rivaroxaban, dabigatran, edoxaban and apixaban are used to prevent recurrent DVT and Pulmonary Embolism (PE) after acute DVT with Deep Vein Thrombosis (DVT) treatment or to prevent recurrent PE and DVT with Pulmonary Embolism (PE) treatment.

b) In the above cases, warfarin can be discontinued and rivaroxaban or dabigatran or apixaban or edoxaban can be started if the target INR value cannot be kept between 2-3 in at least three of the last 5 measurements performed at least one week apart after warfarin use for at least 2 months prior.

(2) Warfarin use is not required in active cancer patients with recurrent idiopathic pulmonary embolism or homozygous thrombophilia or previous venous thromboembolism (VTE) or immobile patients (provided that the cause is stated in the report).

(3) From specialist physicians of cardiology, internal medicine, chest diseases, cardiovascular surgery in which the above-defined conditions are specified, it is reimbursed if prescribed by these specialist physicians based on the 6-month medical board report prepared by physicians from the same specialty or physicians any three of these specialties.

(4) If it is decided to continue the drug treatment at the end of the report period, the treatment can be continued by issuing a new medical board report stating this situation.

When the relevant parts are examined, it is noteworthy that regulations are made for conditions and some special cases in terms of usage and reporting in NVAF and DVT, which are determined as indications. It has been stated in the HPS that NOACs can be used DVT treatment and prevention of recurrence in patients with NVAF and with at least one of the risk factors described. In both cases, it was stated that after using warfarin for at least 2 months, warfarin could be discontinued in cases where the target INR value could not be kept between 2-3 in at least three of the last 5 measurements made at least one week apart. An exceptional case for NVAF is that it is stated that NOAC can be used directly in those who had a cerebrovascular event while under warfarin treatment. Similarly, for DVT and PE, in active cancer patients with recurrent idiopathic

pulmonary embolism or homozygous thrombophilia, or in immobile patients with venous thromboembolism, NOAC can be initiated without seeking warfarin use.

During the reporting process for NVAF patients, a 6-month medical board report must be issued by including at least three of the specialist physicians of cardiology, internal medicine, chest diseases, cardiovascular surgery, and neurology provided that at least one of the physicians is a cardiologist or neurologist. When reporting for DVT is required, the neurology physician is not authorized and the report should be prepared for a period of 6 months by specialist physicians of cardiology, internal medicine, chest diseases, cardiovascular surgery with three from the same specialty or any three of these specialties. In addition, a report is required for the prescriptions to be reimbursed by SSI in both indication categories.

16.3. Areas that Need to be Improved in the NOACs Usage Regulation: There is no area that needs to be corrected in terms of active ingredient licensing indications of pharmaceutical companies for NOAC use. Fundamental issues can be addressed in relation to HPS and reimbursement. In particular, the requirement to use warfarin prior and allowing the reimbursement of other drugs when the appropriate treatment interval cannot be set with this active ingredient limits the patient and the doctor in terms of treatment choices. Even though warfarin is considered as a more economical choice, frequent INR follow-ups are made in practice and the decision is made accordingly. In this case, the patient and their relatives have to come to the hospital, transportation costs and workforce loss for that day occur. At the same time, it can be accepted that the economic advantage loses its importance in terms of the insurance institution when the outpatient clinic application and the fees arising from it are included. In addition, it may be necessary to provide an ambulance as some of the patients have difficulty in mobilization due to severe neurological deficits. This situation means difficulty for the patient and absence from the workforce in terms of the health organization. HPS states performing measurements every other week which corresponds to 4-5 measurements per month, and it means frequent transfer and admission of patients to the health institution. In addition, some patients live in rural areas far from the centers where the INR value will be measured.

The COVID-19 pandemic is a serious health problem for the whole world, including our country. Not only this disease, but also the fear of contamination causes delay in hospital admissions and patients suffer from other diseases. In addition, it would not be wrong to say that hospital admissions are a risk for patients due to INR monitoring. Low molecular weight heparins used in the treatment of DVT and/or PE are pharmacological agents that are also used in the treatment of COVID-19. Scientific Medical Committee recommends that thrombosis prophylaxis be administered in all COVID-19 patients as long as there is no active bleeding or thrombocytopenia (<25-30.000 / μl) in the study of "anti-cytokine-anti-inflammatory therapies, coagulopathy management". The use of these drugs in COVID-19 patients increases the need for drugs, and it is not a remote possibility to think that the increase in the number of patients may cause difficulties in obtaining the drug.

Considering all of these, the requirement for NOAC fees to be reimbursed in the patient group in which warfarin was used for a certain period of time for both NVAF and DVT, PE and whose treatment interval could not be achieved, should be removed. Cases of DVT and PE are frequently triggered by immobility in patients monitored by neurologists. Neurologists should be able to report and prescribe NOACs in patients with DVT and PE as they can report and prescribe in patients with NVAF. In addition, due to the COVID-19 pandemic, the need for LMWH use is predicted to increase. LMWH is used for DVT, PE prophylaxis in patients with immobility. Using NOAC for DVT, PE prophylaxis may be an alternative and solution to the apparent stock shortage for LMWH.

REFERENCES

1. Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Nat Rev Drug Discov 2011; 10(1): 61-75.
2. Wieland E, Shipkova M. Pharmacokinetic and Pharmacodynamic Drug Monitoring of Direct-Acting Oral Anticoagulants: Where Do We Stand? Ther Drug Monit 2019; 41(2): 180-191.
3. Leung LLK. Direct oral anticoagulants (DOACs) and parenteral direct-acting anticoagulants: Dosing and adverse effects. UpToDate 2020; Waltham, MA(UpToDate Inc).
4. Steffel J, Verhamme P, Potpara TS, 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. Eur Heart J 2018; 39(16): 1330-1393.
5. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74(1): 104-132.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361(12): 1139-1151.
7. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010; 12(10): 1360-1420.
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365(10): 883-891.
9. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365(11): 981-992.
10. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369(22): 2093-2104.
11. Ruff CT, Giugliano RP, Braunwald E, 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(9921): 955-962.
12. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016; 37(38): 2893-2962.
13. Lip GYH, Collet JP, Caterina R, et al. 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(11): 1757-1758.
14. Lip GY, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace 2014; 16(3): 308-319.
15. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to develop guidelines for the management of patients with atrial fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. Eur Heart J 2001; 22(20): 1852-1923.
16. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64(21): e1-76.
17. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e531S-e75S.
18. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. Eur Heart J 2014; 35(47): 3328-3335.
19. American College of Cardiology/American Heart Association Task Force on Practice G, Society of Cardiovascular A, Society for Cardiovascular A, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006; 114(5): e84-231.
20. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017; 135(25): e1159-e95.
21. Hetzer R, Hill JD, Kerth WJ, Wilson AJ, Adappa MG, Gerbode F. Thrombosis and degeneration of Hancock valves: clinical and pathological findings. Ann Thorac Surg 1978; 26(4): 317-322.
22. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Heart J 1962; 24: 349-357.
23. Lester PA, Coleman DM, Diaz JA, et al. Apixaban Versus Warfarin for Mechanical Heart Valve Thromboprophylaxis in a Swine Aortic Heterotopic Valve Model. Arterioscler Thromb Vasc Biol 2017; 37(5): 942-948.
24. McKellar SH, Abel S, Camp CL, Suri RM, Ereth MH, Schaff HV. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. J Thorac Cardiovasc Surg 2011; 141(6): 1410-1416.
25. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369(13): 1206-1214.
26. Guimaraes PO, Pokorney SD, Lopes RD, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: Insights from the ARISTOTLE trial. Clin Cardiol 2019; 42(5): 568-571.
27. An KR, Belley-Cote EP, Um KJ, et al. Antiplatelet Therapy versus Anticoagulation after Surgical Bioprosthetic Aortic Valve Replacement: A Systematic Review and Meta-Analysis. Thromb Haemost 2019; 119(2): 328-339.
28. Avezum A, Lopes RD, Schulte PJ, et al. Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Circulation 2015; 132(8): 624-632.
29. Breithardt G, Baumgartner H, Berkowitz SD, et al. Native

valve disease in patients with non-valvular atrial fibrillation on warfarin or rivaroxaban. Heart 2016; 102(13): 1036-1043.
30. Ezekowitz MD, Nagarakanti R, Noack H, et al. Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation 2016; 134(8): 589-598.
31. Kim JY, Kim SH, Myong JP, et al. Outcomes of Direct Oral Anticoagulants in Patients With Mitral Stenosis. J Am Coll Cardiol 2019; 73(10): 1123-1131.
32. Saposnik G, Barinagarrementeria F, Brown RD, Jr., et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42(4): 1158-1192.
33. Bose G, Graveline J, Yogendrakumar V, Fergusson D, Dowlatshahi D. Direct oral anticoagulants in treatment of cerebral venous thrombosis: a systematic review protocol. Syst Rev 2019; 8(1): 99.
34. Ferro JM, Bousser MG, Canhao P, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis - endorsed by the European Academy of Neurology. Eur J Neurol 2017; 24(10): 1203-1213.
35. Wasay M, Khan M, Rajput HM, et al. New Oral Anticoagulants versus Warfarin for Cerebral Venous Thrombosis: A Multi-Center, Observational Study. J Stroke 2019; 21(2): 220-223.
36. Lee GKH, Chen VH, Tan CH, et al. Comparing the efficacy and safety of direct oral anticoagulants with vitamin K antagonist in cerebral venous thrombosis. J Thromb Thrombolysis 2020.
37. Caprio FZ, Bernstein RA, Alberts MJ, et al. Efficacy and safety of novel oral anticoagulants in patients with cervical artery dissections. Cerebrovasc Dis 2014; 38(4): 247-253.
38. Mustanoja S, Metso TM, Putaala J, et al. Helsinki experience on nonvitamin K oral anticoagulants for treating cervical artery dissection. Brain Behav 2015; 5(8): e00349.
39. Cappellari M, Bovi P. Direct oral anticoagulants in patients with cervical artery dissection and cerebral venous thrombosis. A case series and review of the literature. Int J Cardiol 2017; 244: 282-284.
40. Ince B. Serebral Venöz Sinüs Trombozlarının Tedavisinde Yeni Oral Antikoagülan İlaçlar. Türk Beyin Damar Hast Derg 2016; 22(2): 49-51.
41. Cohen H, Hunt BJ, Efthymiou M, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol 2016; 3(9): e426-36.
42. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019; 78(10): 1296-1304.
43. Cohen H. The use of direct oral anticoagulants in antiphospholipid syndrome. Clin Adv Hematol Oncol 2020; 18(1): 19-23.
44. Hsu JY, Liu AB. Anticoagulants for cancer-associated ischemic stroke. Ci Ji Yi Xue Za Zhi 2019; 31(3): 144-148.
45. Wu VC, Wang CL, Huang YT, et al. Novel Oral Anticoagulant versus Warfarin in Cancer Patients with Atrial Fibrillation: An 8-Year Population-Based Cohort Study. J Cancer 2020; 11(1): 92-99.
46. Beyer-Westendorf J, Michalski F, Tittl L, et al. Pregnancy outcome in patients exposed to direct oral anticoagulants - and the challenge of event reporting. Thromb Haemost 2016; 116(4): 651-658.
47. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. Stroke 2017; 48(4): 867-872.
48. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014; 13(4): 429-438.
49. Perera KS, Vanassche T, Bosch J, et al. Embolic strokes of undetermined source: Prevalence and patient features in the ESUS Global Registry. Int J Stroke 2016; 11(5): 526-533.
50. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med 2018; 378(23): 2191-2201.
51. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med 2019; 380(20): 1906-1917.
52. Geisler T, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. Int J Stroke 2017; 12(9): 985-990.
53. Kamel H, Longstreth WT, Jr., Tirschwell DL, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods. Int J Stroke 2019; 14(2): 207-214.
54. Karamichalakis N, Georgopoulos S, Vlachos K, et al. Efficacy and safety of novel anticoagulants in the elderly. J Geriatr Cardiol 2016; 13(8): 718-723.
55. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018; 154(5): 1121-1201.
56. Eikelboom JW, Quinlan DJ, Hirsh J, Connolly SJ, Weitz JI. Laboratory Monitoring of Non-Vitamin K Antagonist Oral Anticoagulant Use in Patients With Atrial Fibrillation: A Review. JAMA Cardiol 2017; 2(5): 566-574.
57. Salmonson T, Dogne JM, Janssen H, Garcia Burgos J, Blake P. Non-vitamin-K oral anticoagulants and laboratory testing: now and in the future: Views from a workshop at the European Medicines Agency (EMA). Eur Heart J Cardiovasc Pharmacother 2017; 3(1): 42-47.
58. Di Lullo L, Ronco C, Cozzolino M, et al. Nonvitamin K-dependent oral anticoagulants (NOACs) in chronic kidney disease patients with atrial fibrillation. Thromb Res 2017; 155: 38-47.
59. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ, Gracia-Iguacel C, Ortiz A. Creatinine Clearance Is Not Equal to Glomerular Filtration Rate and Cockcroft-Gault Equation Is Not Equal to CKD-EPI Collaboration Equation. Am J Med 2016; 129(12): 1259-1263.
60. Klijn CJ, Paciaroni M, Berge E, et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. Eur Stroke J 2019; 4(3): 198-223.
61. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation 2018; 138(15): 1519-1529.
62. Intagliata NM, Henry ZH, Maitland H, et al. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. Dig Dis Sci 2016; 61(6): 1721-1727.

63. Kubitza D, Roth A, Becka M, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2013; 76(1): 89-98.
64. Duchin K, Duggal A, Atiee GJ, et al. An Open-Label Crossover Study of the Pharmacokinetics of the 60-mg Edoxaban Tablet Crushed and Administered Either by a Nasogastric Tube or in Apple Puree in Healthy Adults. Clin Pharmacokinet 2018; 57(2): 221-228.
65. Kayaalp, S. O. : Akılcıl Tedavi Yönünden Tıbbi Farmakoloji, Gözden Geçirilmiş 13. Baskı, I. Cilt 1603 sayfa, Pelikan Kitabevi, Ankara, 2012.
66. Kayaalp SO. Akılcıl Tedavi Yönünden Tıbbi Farmakoloji, Gözden Geçirilmiş 13. Baskı, I. Cilt Ankara: Pelikan Kitabevi; 2012.
67. Pradaxa-Dabigatran. [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc 2015.
68. Peterson J, Hoehns J. Administration of Direct Oral Anticoagulants Through Enteral Feeding Tubes. Journal of Pharmacy Technology 2016; 32:196-200.(1): 196-200.
69. Xarelto-Rivaroxaban. [Package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2020.
70. Eliquis-Apixaban. [Package insert]. Princeton, NJ: BristolMyers Squibb; 2019.
71. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012; 120(15): 2954-2962.
72. Doukelis JD, Lip, G.H.Y. Perioperative management of patients receiving anticoagulants. UpToDate 2020; Waltham, MA.
73. Connolly SJ, Crowther M, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med 2019; 380(14): 1326-1335.
74. Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med 2017; 377(5): 431-441.
75. Kuo HC, Liu FL, Chen JT, Cherng YG, Tam KW, Tai YH. Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: A systematic review and meta-analysis. Clin Cardiol 2020; 43(5): 441-449.
76. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol 2017; 69(7): 871-898.
77. Tao J, Oprea AD. Updates in periprocedural management of direct oral anticoagulants. Curr Opin Anaesthesiol 2020; 33(3): 423-431.
78. Wiggins BS, Dixon DL, Neyens RR, Page RL, 2nd, Gluckman TJ. Select Drug-Drug Interactions With Direct Oral Anticoagulants: JACC Review Topic of the Week. J Am Coll Cardiol 2020; 75(11): 1341-1350.
79. commission N-Ce. NOAC GUIDELINES. http://wwwcechealthnswgovau/__data/assets/pdf_file/0007/326419/noac_guidelinespdf 2017; (13-9-2020 ulaşıldı).
80. Hartter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa((R))) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol 2013; 75(4): 1053-1562.
81. Delavenne X, Ollier E, Basset T, et al. A semi-mechanistic absorption model to evaluate drug-drug interaction with dabigatran: application with clarithromycin. Br J Clin Pharmacol 2013; 76(1): 107-113.
82. Hartter S, Koenen-Bergmann M, Sharma A, et al. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. Br J Clin Pharmacol 2012; 74(3): 490-500.
83. Bounameaux H, Camm AJ. Edoxaban: an update on the new oral direct factor Xa inhibitor. Drugs 2014; 74(11): 1209-1231.
84. Voukalis C, Lip GY, Shantsila E. Drug-drug interactions of non-vitamin K oral anticoagulants. Expert Opin Drug Metab Toxicol 2016; 12(12): 1445-1461.
85. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013; 127(5): 634-640.
86. Heidbuchel H, Verhamme P, Alings M, 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: Executive summary. Eur Heart J 2017; 38(27): 2137-2149.
87. Linnebur SA, Hanlon JT. Drug Interactions With Non-Vitamin K Oral Anticoagulants. JAMA 2018; 319(8): 828-829.
88. Huisman MV, Rothman KJ, Paquette M, et al. Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II. Am J Med 2015; 128(12): 1306-13 e1.
89. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. Eur J Clin Pharmacol 2016; 72(3): 329-338.
90. Martinez C, Katholing A, Wallenhorst C, Freedman SB. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. Thromb Haemost 2016; 115(1): 31-39.
91. Pottegard A, Poulsen BK, Larsen MD, Hallas J. Dynamics of vitamin K antagonist and new oral anticoagulants use in atrial fibrillation: a Danish drug utilization study. J Thromb Haemost 2014; 12(9): 1413-1418.
92. Beyer-Westendorf J, Gelbricht V, Forster K, et al. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care--results from the Dresden NOAC registry. Br J Clin Pharmacol 2014; 78(4): 908-917.
93. Hellfritzsch M, Grove EL, Husted SE, et al. Clinical events preceding switching and discontinuation of oral anticoagulant treatment in patients with atrial fibrillation. Europace 2017; 19(7): 1091-1095.
94. Ruff CT, Giugliano RP, Braunwald E, et al. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol 2014; 64(6): 576-584.
95. Granger C, Alexander J, Hanna M, Wang J, Mohan P, J L. Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial. Eur Heart J 2012; 33: 685-686.
96. Granger CB, Lopes RD, Hanna M, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J 2015; 169(1): 25-30.
97. Wang KL, Lopes RD, Patel MR, et al. Efficacy and safety of reduced-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. Eur Heart J 2019; 40(19): 1492-1500.

98. Staerk L, Gerds TA, Lip GYH, et al. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med 2018; 283(1): 45-55.
99. Fordyce CB, Hellkamp AS, Lokhnygina Y, et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF. Circulation 2016; 134(1): 37-47.
100. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009; 119(10): 1363-1369.
101. Hijazi Z, Hohnloser SH, Oldgren J, 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(9): 961-970.
102. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2009; 158(4): 629-636.
103. Diener HC, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. Eur Heart J 2017; 38(12): 860-868.
104. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation 2016; 134(1): 24-36.
105. Hijazi Z, Hohnloser SH, Andersson U, 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(4): 451-460.
106. Diener HC, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1. Eur Heart J 2017; 38(12): 852-859.
107. Wang CL, Wu VC, Chang KH, et al. Assessing major bleeding risk in atrial fibrillation patients concurrently taking non-vitamin K antagonist oral anticoagulants and antiepileptic drugs. Eur Heart J Cardiovasc Pharmacother 2020; 6(3): 147-154.
108. Mathy FX, Dohin E, Bonfitto F, Pelgrims B. Drug-drug interaction between levetiracetam and non-vitamin K antagonist anticoagulants. Eur Heart J 2019; 40(19): 1571.
109. Potpara TS, Mujovic N, Proietti M, et al. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. Europace 2020; 22(1): 33-46.
110. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World J Gastroenterol 2017; 23(11): 1954-1563.
111. Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy 2017; 37(2): 236-248.
112. Connors JM. Testing and monitoring direct oral anticoagulants. Blood 2018; 132(19): 2009-15.
113. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. J Thromb Haemost 2018; 16(2): 209-219.
114. Gosselin RC, Adcock DM. The laboratory's 2015 perspective on direct oral anticoagulant testing. J Thromb Haemost 2016; 14(5): 886-893.
115. Douxfils J, Dogne JM, Mullier F, et al. Comparison of calibrated dilute thrombin time and aPTT tests with LC-MS/MS for the therapeutic monitoring of patients treated with dabigatran etexilate. Thromb Haemost 2013; 110(3): 543-549.
116. Lessire S, Douxfils J, Baudar J, et al. Is Thrombin Time useful for the assessment of dabigatran concentrations? An in vitro and ex vivo study. Thromb Res 2015; 136(3): 693-696.
117. Frydman GH, Ellett F, Van Cott EM, et al. A New Test for the Detection of Direct Oral Anticoagulants (Rivaroxaban and Apixaban) in the Emergency Room Setting. Crit Care Explor 2019; 1(8): e0024.
118. Douxfils J, Chatelain B, Chatelain C, et al. Edoxaban: Impact on routine and specific coagulation assays. A practical laboratory guide. Thromb Haemost 2016; 115(2): 368-381.
119. Lippi G, Favaloro EJ. Recent guidelines and recommendations for laboratory assessment of the direct oral anticoagulants (DOACs): is there consensus? Clin Chem Lab Med 2015; 53(2): 185-197.
120. Douxfils J, Mullier F, Loosen C, Chatelain C, Chatelain B, Dogne JM. Assessment of the impact of rivaroxaban on coagulation assays: laboratory recommendations for the monitoring of rivaroxaban and review of the literature. Thromb Res 2012; 130(6): 956-966.
121. Bozic-Mijovski M, Malmstrom RE, Malovrh P, et al. Diluted thrombin time reliably measures low to intermediate plasma dabigatran concentrations. Ann Clin Biochem 2016; 53(Pt 4): 446-451.
122. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007; 64(3): 292-303.
123. Becker RC, Yang H, Barrett Y, et al. Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban--an oral, direct and selective factor Xa inhibitor. J Thromb Thrombolysis 2011; 32(2): 183-187.
124. Pratt J, Crispin P. Screening test for direct oral anticoagulants with the dilute Russell viper venom time. Eur J Haematol 2018; 100(6): 567-574.
125. Harder S, Parisius J, Picard-Willems B. Monitoring direct FXa-inhibitors and fondaparinux by Prothrombinase-induced Clotting Time (PiCT): relation to FXa-activity and influence of assay modifications. Thromb Res 2008; 123(2): 396-403.
126. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012; 126(20): 2381-2391.
127. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-

analysis of randomized controlled trials. Stroke 2012; 43(12): 3298-3304.
128. Raval AN, Cigarroa JE, Chung MK, et al. Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association. Circulation 2017; 135(10): e604-e33.
129. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019; 50(12): e344-e418.
130. Xian Y, Federspiel JJ, Hernandez AF, et al. Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non-Vitamin K Antagonist Oral Anticoagulants Before Stroke. Circulation 2017; 135(11): 1024-1035.
131. Jin C, Huang RJ, Peterson ED, et al. Intravenous tPA (Tissue-Type Plasminogen Activator) in Patients With Acute Ischemic Stroke Taking Non-Vitamin K Antagonist Oral Anticoagulants Preceding Stroke. Stroke 2018; 49(9): 2237-2240.
132. Wong JWP, Churilov L, Dowling R, et al. Safety of Endovascular Thrombectomy for Acute Ischaemic Stroke in Anticoagulated Patients Ineligible for Intravenous Thrombolysis. Cerebrovasc Dis 2018; 46(5-6): 193-199.
133. Shinoda N, Mori M, Tamura S, Korosue K, Kose S, Kohmura E. Risk of Recurrent Ischemic Stroke with Unintended Low-Dose Oral Anticoagulant Therapy and Optimal Timing of Review. J Stroke Cerebrovasc Dis 2018; 27(6): 1546-1551.
134. Paciaroni M, Agnelli G, Caso V, et al. Causes and Risk Factors of Cerebral Ischemic Events in Patients With Atrial Fibrillation Treated With Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention. Stroke 2019; 50(8): 2168-2174.
135. Essien UR, Holmes DN, Jackson LR, 2nd, et al. Association of Race/Ethnicity With Oral Anticoagulant Use in Patients With Atrial Fibrillation: Findings From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II. JAMA Cardiol 2018; 3(12): 1174-1182.
136. Xian Y, Hernandez AF, Harding T, et al. Acute management of stroke patients taking non-vitamin K antagonist oral anticoagulants Addressing Real-world Anticoagulant Management Issues in Stroke (ARAMIS) Registry: Design and rationale. Am Heart J 2016; 182: 28-35.
137. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 2010; 170(16): 1433-1441.
138. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012; 366(1): 9-19.
139. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011; 365(8): 699-708.
140. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013; 381(9872): 1107-1115.
141. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017; 377(16): 1513-1524.
142. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016; 375(25): 2423-2434.
143. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019; 380(16): 1509-1524.
144. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019; 394(10206): 1335-1343.
145. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009; 151(5): 297-305.
146. Alexander JH, Wojdyla D, Vora AN, et al. Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients With Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights From AUGUSTUS. Circulation 2020; 141(20): 1618-1627.
147. Brott TG, Howard G, Roubin GS, et al. Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis. N Engl J Med 2016; 374(11): 1021-1031.
148. Hawkins BM, Kennedy KF, Giri J, et al. Pre-procedural risk quantification for carotid stenting using the CAS score: a report from the NCDR CARE Registry. J Am Coll Cardiol 2012; 60(17): 1617-1622.
149. Nii K, Takemura Y, Inoue R, Morinaga Y, Mitsutake T, Higashi T. Safety of direct oral anticoagulant - and antiplatelet therapy in patients with atrial fibrillation treated by carotid artery stenting. J Stroke Cerebrovasc Dis 2020; 29(7): 104899.
150. Hindricks G, Potpara T, Dagres N, et al. 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 2020.
151. Hemphill JC, 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015; 46(7): 2032-2060.
152. Schulman S, Gross PL, Ritchie B, et al. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost 2018; 118(5): 842-851.
153. Beinart R, Heist EK, Newell JB, Holmvang G, Ruskin JN, Mansour M. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2011; 22(1): 10-15.
154. Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart 2014; 100(5): 396-405.
155. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007; 146(12): 857-867.
156. Ding WY, Harrison S, Gupta D, Lip GYH, Lane DA. Stroke and Bleeding Risk Assessments in Patients With Atrial Fibrillation: Concepts and Controversies. Front Med

(Lausanne) 2020; 7: 54.
157. Wilson D, Ambler G, Shakeshaft C, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. Lancet Neurol 2018; 17(6): 539-547.
158. Baş DF, Topçuoglu MA, Arsava EM. Yeni antikoagülasyonlar perspektifinde atriyal fibrilasyon ve inme. Türk Beyin Damar Hastalıkları Dergisi 2013; 19(2): 35-45.
159. Aytemiz F. Atriyal Fibrilasyonda Antikoagülan Tedavi ve Yeni Oral Antikoagülan İlaçlar. Türkiye Klinikleri Kardiyoloji-Özel Konular 2015; 8(1): 28-42.
160. Forslund T, Wettermark B, Andersen M, Hjemdahl P. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. Europace 2018; 20(3): 420-428.
161. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012; 33(12): 1500-1510.
162. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol 2011; 57(2): 173-180.
163. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138(5): 1093-1100.
164. Zulkifly H, Lip GYH, Lane DA. Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism. Am J Cardiol 2017; 120(7): 1139-1145.
165. Chao TF, Lip GYH, Lin YJ, et al. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. Int J Cardiol 2018; 254: 157-161.
166. Lioutas VA, Goyal N, Katsanos AH, et al. Optimization of risk stratification for anticoagulation-associated intracerebral hemorrhage: net risk estimation. J Neurol 2020; 267(4): 1053-1062.
167. İlacaBak. Pradaxa, Xeralto, Eliquis, Lixiana prospektüs bilgileri. 2020. https://www.ilacabak.com/pradaxa-110-mg-10-sert-kapsul-12312/kisa-urun-bilgisi, https://www.ilacabak.com/pradaxa-150-mg-60-sert-kapsul-13945/kisa-urun-bilgisi, https://www.ilacabak.com/xarelto-20-mg-28-film-kapli-tablet-14930/kisa-urun-bilgisi, https://www.ilacabak.com/lixiana-60-mg-28-film-kapli-tablet-18911/kisa-urun-bilgisi, https://www.ilacabak.com/eliquis-5-mg-film-kapli-tablet-56-tablet-23379/kisa-urun-bilgisi (accessed 19.9.2020.
168. TCSB. 16.06.2020 Değişiklik Tebliği İşlenmiş Güncel 2013 Sağlık Uygulama Tebliği (SUT). 2020. http://www.sgk.gov.tr/wps/portal/sgk/tr/kurumsal/merkez-teskilati/ana_hizmet_birimleri/gss_genel_mudurlugu/anasayfa_duyurular/duyuru_20200603_20 (accessed 19-9-2020.

Ethics

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