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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

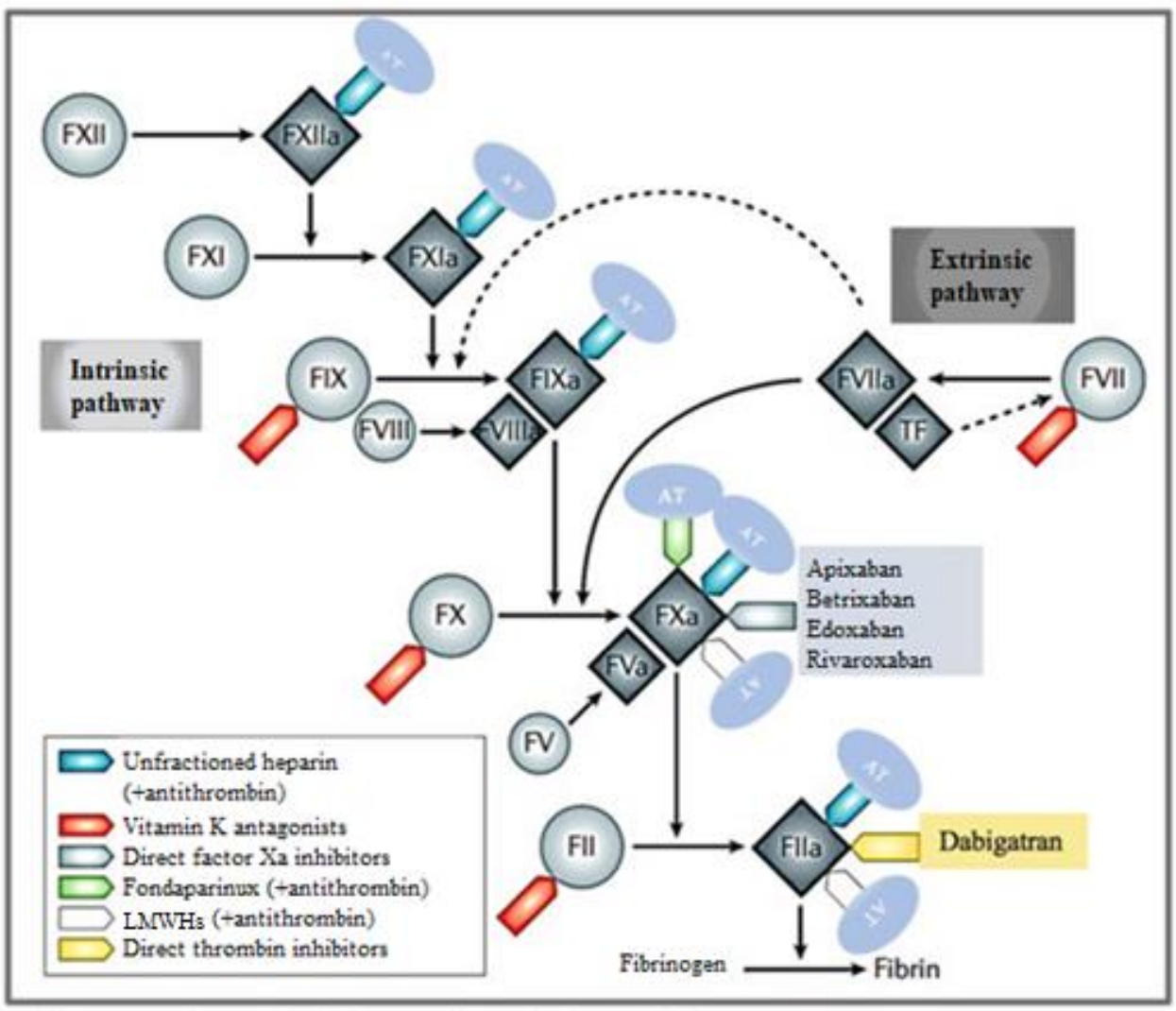



**Figure 1.** Coagulation cascade and the effects of anticoagulants*.
*Adapted from Perzborn E, Roehrig S, Straub A, et al. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Nat Rev Drug Discov. 2011;101:61-75. Abbreviations: AT: Anti-thrombin, LMWH: Low molecular weight 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)<br>11-13 hours (old) |
| **Other** | | Dyspepsia (5-10%) | | Must be taken with food |