

New oral anticoagulants

Yeni oral antikoagülanlar

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ABSTRACT

Oral anticoagulants are medications that have an important place in the prevention and treatment of thromboembolic events that can be seen in the course of many diseases today. Warfarin, vitamin K antagonists are the most commonly known and used oral anticoagulants. Drugs known as new oral anticoagulants have emerged due to the difficulties in treatment and follow-up with warfarin. New oral anticoagulants exhibit anticoagulant effects, disrupting the structure and function of some factors in the coagulation cascade. There are many advantages such as monitorisation requirement, constant dose use, patient compliance and ease of follow-up. Meta-analyses of large studies with new oral anticoagulants have shown that they are non-inferior from warfarin in the prevention and treatment of thromboembolic events, and even superior in some cases. Due to the ease of use and advantages of these new agents, they have been rapidly spreading and taking place in the prevention and treatment of embolism and ischemic events. Therefore, the areas of use of these drugs, the location of treatment, follow-up, possible side effects and most importantly management of bleeding complications should be well known and applied.

Keywords: New oral anticoagulants, warfarin, thromboembolism, ischemia, bleeding

ÖZ

Oral antikoagülanlar günümüzde birçok hastalığın seyirinde görülebilen tromboembolik olayların engellenmesinde ve tedavisinde çok önemli yeri olan ilaçlardır. Varfarin vitamin k antagonistlerinden en çok bilinen ve kullanılan oral antikoagülanlardır. Varfarin ile yapılan tedavi ve takiplerinde görülen zorluklarından dolayı yeni oral antikoagülanlar olarak bilinen ilaçlar ortaya çıkmıştır. Yeni oral antikoagülanlar, koagülasyon kaskatında bazı faktörlerin yapı ve işlevlerini bozarak antikoagülan etki göstermektedirler. Monitorizasyon gerektirmemesi, sabit dozda kullanımı, hasta uyumu ve takip kolaylığı gibi birçok avantajları vardır. Yeni oral antikoagülanlar ile yapılan büyük çalışmaların meta-analizlerine bakıldığında, tromboembolik olaylardan koruma ve tedavisinde varfarinden aşağıda kalmadığı, hatta bazı durumlarda üstün olduğu saptanmıştır. Bu ajanların kullanım kolaylığı ve avantajlarından dolayı emboli ve iskemik olaylardan korunma ve tedavisinde hızlı bir şekilde yer bulmuş ve yaygınlaşmıştır. Bu nedenle bu ilaçların kullanımı, tedavideki yerleri, takipleri, olası yan etkileri ve en önemlisi kanama komplikasyonlarının yönetimi iyi bilinmeli ve uygulanmalıdır.

Anahtar Kelimeler: Yeni oral antikoagülanlar, varfarin, tromboemboli, iskemi, kanama

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ANTICOAGULANTS

Thromboembolic events is one of the leading causes of mortality and morbidity in this age. Thrombosis is caused by injury of the endothelium that provides vascular integrity, and induction of the tissue factor pathway and thrombocytes in the coagulation system. Anticoagulant drugs reduce blood coagulation ability by impairing the synthesis and efficacy of clotting factors and increasing anticoagulant factor activity. This prevents the formation of new thrombi or the further growth of the existing thrombus. Anticoagulant therapy is an important treatment modality in the prophylaxis and treatment of thromboembolic events seen in the course of many diseases (1).

Anticoagulant drugs are studied in two groups according to their mechanism of action; parenteral and oral. Parenteral anticoagulants; Low molecular weight heparins (LMWH) obtained by depolymerisation of polysaccharides in heparin or by fractionation of standard heparin, fondaparinux mediated by factor Xa inhibition by antithrombin, direct thrombin inhibitor lepirudin, bivaluridine (antithrombin III) and argotran. Parenteral anticoagulants are used in the acute phase of thromboembolic events and are difficult to use in the long term. Oral anticoagulants, which are easier to use and control in chronic period after thromboembolic event are used (1,2).

Protein C and protein S anticoagulant molecules increase the thrombosis tendency in the early phase of warfarin therapy, as their half-lives are shorter than coagulation factors. Risk of thrombotic events may be encountered if warfarin therapy is initiated without effective anticoagulation with a parenteral anticoagulant. The most important cause of warfarin-induced skin necrosis is inadequate parenteral anticoagulation therapy. The succession of the warfarin 2, 7, 9, and 10 of warfarin's effective dose is measured by measuring the prothrombin time (PT) following the activity. In order to be a standard parameter all over the world and not to be affected by laboratory differences, they need to be monitored using INR (international normalized rate), a laboratory parameter based on PT standardisation. The aim is to keep the PT or INR values within the limits of the thrombosis protection and treatment limitations and to prevent the occurrence of hemorrhagic complications due to the narrowness of the drug's therapeutic window. There are also many foods and medicines that interact with warfarin albumin and cause liver metabolism. Because of this, strict INR and dose follow-up is very important to protect both ischemia and embolism from hemorrhage complications (2-5).

The areas of use of anticoagulants are quite extensive. However, the most common uses are (4,5);

- Atrial fibrillation
- Mechanical heart valve
- Prolonged immobilisation
- Venous disease
- Deep vein thrombosis
- Pulmonary thromboemboli
- Cerebrovascular Disease
- Left ventricular mural thrombus

There are many difficulties in using warfarin from oral anticoagulants. These can be summarized as follows (5);

- Narrow treatment interval
- Interaction with drugs and foods
- Side effect
- Dose adjustment and laboratory monitoring
- Patient incompatibility
- Slow effect
- Late termination of effect after stop
- Parenteral anticoagulation needs to be achieved until efficacy is achieved

These difficulties and limitations are due to new medications that are easier to use and do not require follow-up. Thereby, new oral anticoagulants have been developed that affect different coagulation factors in different regions of the coagulation cascade. Currently there are four different drugs approved by the FDA (5,6).

NEW ORAL ANTICOAGULANS (NOAC)

New oral anticoagulants are classified into two groups as F IIa inhibitors and FXa inhibitors (Table 1).

Table 1. New oral anticoagulants

F IIa inhibitors	FXa inhibitors
Dabigatran	Rivaroxaban Apixaban Edoxaban

(If these new oral anticoagulants are compared with warfarin); (5) it is more effective and quicker, and its use is stable, and there is very few interaction with food and drugs. The four existing oral anticoagulant drugs are used as rivaroxaban, edoxaban and apixaban as direct oral factor Xa inhibitors and dabigatran as a factor 2a inhibitor. The oral bioavailability is high with the cause of being active drugs (>50%). Approximately 1-3 hours after oral ingestion, the plasma reaches the peak level. Direct oral thrombin inhibitor, dabigatran is activated by esterases in the plasma and thus bioavailability is low (6,5%) (6). However, due to the addition of tartaric acid to inc-

Table 2. Comparison of new oral anticoagulants and warfarin

	Varfarin	Dabigatran	Rivaroxaban	Edoxaban
Target	Vit K Epoxide reduktase	Thrombin (Faktör IIa)	Factor Xa	Factor Xa
Pre drug	No	Yes	No	No
Bioavailability%	100	6	80	50
Effect peak	4-5 days	1-3 hours	2-4 hours	1-3 hours
Dose	Variable	2x1 tb	1x1 tb	1x1 tb
Half life	40 hours	12-17 hours	9-12 hours	9-14 hours
Renal excretion%	No	80	65	25
Antidote	Yes	No	Yes	No
Dialysis breakthrough	No	Yes	No	No

rease the absorption of the drug, the initial effect is rapid and plasma peak times are similar to other new agents (7) (Table 2).

About the renal metabolism of new oral anticoagulants, 80% of the dabigatran, one third of the rivaroxaban, one fourth of the apixaban were throw away as from the body by the kidneys. All new agents, especially dabigatran, are in the presence of severe renal impairment (creatinine clearance <30 mL / min) accumulation in the body and dose adjustment is required according to creatinine clearance. However, this is not suitable in warfarin. Because the inactive metabolites of warfarin are excreted through the kidney and the dose is adjusted according to the INR follow-up (8).

Many drugs and foods interactions alter plasma activity and INR value by affecting heparin metabolism and pharmacodynamics in vivo, especially in the liver. However, new anticoagulants do not have less known drug interactions and there is no need for laboratory parameters to monitor plasma activity. There is no specific coagulation test to determine the efficacy of NOAC drugs. For this purpose; Determining the time of thrombin or 'ecarin clotting time' in dabigatran patients is considered to be the most beneficial approach. Another test that can be used during dabigatran treatment is active partial thromboplastin time. However, it should be kept in mind that aPTT may give false results at high blood levels of the drug. The coagulation test to be used in patients using Rivaroxaban is prothrombin time. Another test that can be used for rivaroxaban, edoxaban and apixaban monitoring is to determine the factor Xa level (9).

Comparison of oral anticoagulants (10)

DABIGATRAN

Dabigatran is the first approved a new oral anticoagulant. It is a specific, reversible direct thrombin inhibitor. It is a prodrug and is activated by plasma esterases. It inhibits both free and fibrin-bound thrombin in plasma. Rapid absorption leads to plasma peak concentration in 1-3 hours. Oral bioavailability is 6.5%. However, due to the addition of tartaric acid to increase the absorption of the drug, the initial effect is rapid and the plasma peak times are similar to the other new agents. The plasma half-life is about 12-17 hours. aPTT is extended without dose-dependent. 80% of the kidney is removed. Dyspepsia is the most common side effect due to added tartaric acid for increased absorption. Dabigatran is also indicated for non-valvular AF reducing systemic emboli and pulmonary emboli, and for venous thrombophilia in the lower extremity. Dabigatran has also been approved for using in venous thromboemboli (9-11).

The largest study of dabigatran is the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) compared with warfarin. This is a prospective, randomized study comparing the efficacy and safety of dabigatran and warfarin for stroke and systemic embolism in patients with AF. In this study, dabigatran was given 110 mg or 150 mg twice a day and warfarin was adjusted to keep between INR 2-3. In the study, 18,113 patients with a mean CHADS2 score of 2.1 were included and followed for 2 years. In primary outcome, dabigatran 150 mg dose (1.11% / year) was superior to warfarin (1.71% / year) warfarin (1.71% / year) non-inferior in terms of stroke and systemic embolism. Dabigatran was found to be less risky about major and fatal hemorrhages than low dose warfarin, but higher risk was reported with high dose dabigatran than warfarin. Intracranial hemorrhages were observed less at both low and high doses dabigatran than warfarin. High doses dabigatran is a frequent gastrointestinal bleed-

ding reason than warfarin but low doses are similar to warfarin (10-12).

RIVAROXABAN

It is the first oral direct and recycled FXa inhibitor approved by the FDA and released to the market. It inhibits free and fibrin-bound FXa activity and prothrombinase activity. Oral bioavailability is 60-80%. The plasma half-life is about 5-13 hours. Drug is taken from the liver in two-thirds and kidney in one-third. The greatest study with Rivaroxaban is ROCKET-AF (Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). It is a double-blind randomized multicenter study comparing rivaroxaban with warfarin in non-valvular AF patients. This is a prospective, randomized trial comparing the efficacy and safety of rivaroxaban and warfarin for stroke and systemic embolism in patients with AF. Patients included 14,264 patients with a mean CHADS2 score of 3.5 to study for an average of 590 days; In the rivaroxaban group, warfarin was given a single dose of 20mg or 15mg daily (creatinine clearance 30-49 mL / min of disease) rivaroxaban, warfarin as held INR between 2-3. Both groups were given a placebo tablet to preserve blindness. In this study, CHADS2 scores of patients included in the study were higher than those of RE-LY, ARISTOTLE and AVERROES. In ROCKET-AF, primary outcome was noninferiority of rivaroxaban (1.7% / yr) warfarin (2.2% / yr) in terms of stroke and systemic embolism, but no superiority was detected. There was no significant difference between the rivaroxaban and warfarin groups in terms of major bleeding (3.6% and 3.4%, respectively; $p=0.58$), but the major bleeding in the rivaroxaban group (3.2%) and warfarin group ($p < 0.001$). Intracranial and lethal hemorrhages were significantly less frequent with rivaroxaban (12-15).

APIXABAN

It is a direct, reversible and competing inhibitor of Factor Xa. The oral bioavailability of the drug is 50%. The plasma half-life is about 9-14 hours. 25% of the drug taken from the body is excreted from the kidneys while the remaining 75% is excreted via the fecal route. INR and aPTT are dose dependent, but this effect is minimal in therapeutic doses. The largest study done with Apixaban is ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study (13). It is a randomized, double-blind study in which 18,201 patients who were compared with warfarin and apixaban in patients with AF were followed for an average of 1.8 years for patients with an average

CHADS2 score of 2.1. Dosimetric warfarin treatment was given to keep between 2x5 mg or INR 2-3 of apixaban. It was found that the primer outcomes including stroke and systemic embolism were superior to warfarin (1.60%) of apixaban (1.27% / year). Major bleeding occurred more frequently in the warfarin group (3.09% / year) than the apixaban group (2.13% / year). In addition, apixaban caused less intracranial hemorrhage and mortality. The superiority of the primitive primer on termination is also valid in the subgroup analysis (13-15).

EDOXYBAN

Oral anticoagulant, a direct factor Xa inhibitor, is the latest FDA approved drug. The oral bioavailability of the drug is 62%. Oral uptake reaches the plasma peak concentration within about 1-2 hours. The plasma half-life is about 10-14 hours. 50% of the drug is excreted by the renal route. The greatest study with edoxaban is ENGAGE AF-TIMI 48 (14), which is a study of atrial fibrillation-thrombolysis in myocardial infarction 48. In this study, approximately 21,000 non-valvular AF patients were compared with Edoxaban 60 mg and 30 mg compared to warfarin INR 2-3. The mean CHADS2 score of the study subjects was 2.8 at the end of the study; Both doses were found to be as effective as warfarin in stroke and systemic embolism, and major bleeding and intracranial hemorrhage were found to be lower with both doses of edoxaban compared to warfarin. Compared with warfarin, high doses of edoxaban and gastrointestinal bleeding are more similar to lower doses of edoxaban. Bleeding and cardiac death were found to be significantly lower in the edoxaban group (14-16).

META-ANALYSIS OF STUDIES

AF studies have shown that the primary composite endpoint of stroke and systemic embolization is not worse than the challenge of the four new oral anticoagulants in preventing it. A relative risk reduction of 34% for dabigatran 150 mg arm warfarin and 21% for warfarin arm was determined. Thereby these two drugs are superior to vaccines in preventing primary outcome. When the causes of stroke were evaluated separately, only dabigatran 150 mg arm was superior to warfarin (24% relative risk reduction) in the prevention of ischemic stroke. On the other hand, there were significantly fewer haemorrhagic strokes compared to warfarin with four new oral anticoagulants. When we look at mortality rates due to all causes, we see that all new agents provide about 10% reduction compared to warfarin. Bleeding data at safety endpoints showed that dabigatran 110 mg, edoxaban and apixaban was superior to warfarin, dabigatran

150 mg and rivaroxaban were similar to warfarin in terms of major bleeding. When major bleeds are analyzed according to bleeding location; four new oral anticoagulants in intracranial hemorrhages are significantly more severe than warfarin. Dabigatran 150 mg, edoxaban 60 mg and rivaroxaban were observed more frequently than warfarin in the arm, while the gastrointestinal system bleeds were similar to warfarin in dabigatran 110 mg, edoxaban 30 mg and apixaban arm (15,16).

DRUG SELECTION

Warfarin should be preferred because NOAC (new oral anticoagulation drugs) don't have enough evidence with studies already in the case of AF with mechanical prosthetic valve or cap disease. If a patient is using long-lasting warfarin and their INR values are steady, there is no need to go to NOAC. The fact that new agents are not required to start with parenteral anticoagulants at the time of starting the new agents, the rapid onset of action and the rapid termination of the effect after cessation, the minimal effect of drug or food interactions is a significant advantage compared to warfarin. In patients with liver dysfunction, it is not appropriate to choose IACs. Because almost all of the NOACs are metabolized by the liver (17).

In general, those with creatinine clearance below 30 mL / min are not eligible candidates for this group of drugs. In patients with creatinine clearance ≤ 15 mL / min, NOAC should not be used. In patients with 15-30 mL / min, low doses of dabigatranian extrinsic factor Xa inhibitors should be preferred, and in patients with 30-50 mL / min, dose should be selected according to bleeding risk. Creatinine clearance should be measured every 3 months if renal dysfunction is present, and once a year if kidney function is normal. In patients at risk for gastrointestinal bleeding, apixaban and edoxaban 30mg are the most safe option. Dabigatran (150 mg twice a daily) over 75 years of age and rivaroxaban have been shown to cause more gastrointestinal system bleeding compared with warfarin. If we consider all of these conditions, there is no risk factor such as upper gastrointestinal bleeding story, past acute coronary syndrome, creatinine clearance 30-60 mL / min, HASBLED hemorrhage score ≥ 3 if we are under 75 years old, apixaban, dabigatran edoxaban or rivaroxaban any one can be preferred (18).

BLEEDING MANAGEMENT

In patients with NOAC, this treatment method is ineffective due to lack of factor deficiency in the environment and the presence of thrombin or factor Xa inhibitor. The best way to treat these drugs

is due to their short half-lives. The lower the creatinine clearance, the longer the time required for normalization of hemostasis. Different algorithms and recommendations are available for the treatment of patients with moderate, severe or life-threatening hemorrhage. As a general opinion, the first treatment that needs to be done is to skip the dose, to determine the area and size of the bleeding, to provide local and surgical bleeding control, liquid and if necessary blood products. Plasma coagulation factor level is normal in patients using IOP. Since the enzymatic mechanisms are blocked during thrombus formation, factor concentrate administration is limited to a limited extent. However, prothrombin complex concentration (PCC), recombinant FVIIa and active PCC activities may not be proven in cases of emergency or continuation of the bleeding. Since dabigatran is not bound to plasma proteins and is injected through the kidneys by 80%, hemodialysis can be useful if dialysis is performed in emergency conditions, especially if dabigatran has been taken within the last 4 hours (17).

The search for antidotes has begun and antidote trials have begun to take place to control the bleeding caused by these drugs and to rapidly reverse the effects of these drugs, due to the fact that the number of new drugs and usage areas increase at the same time. Recent up-to-date important studies are idarucizumab, a specific antidote for dabigatran, class specific andexanet. Only idarucizumab, a specific antidote for dabigatran, was approved for use by the FDA in 2015 (19,20). Other studies and new antidote studies are still continuing (17,18).

There is no need for bridge treatment with the reason that the duration of the effect on preoperative evaluation is short in patients using IOP. Pre-treatment cessation times vary directly with the renal function of the patients. In patients with creatinine clearance > 50 mL / min, new oral anticoagulants should be removed approximately 24-36 hours prior to the procedure. If the operation to be performed is a process with a high risk of bleeding, it can be cut off 48 hours beforehand. In patients with lower creatinine clearance, this time can be extended to 72-96 hours. In the postoperative period, it is not decided when to start the treatment of NOAC by performing individual evaluation according to the bleeding risk and the stroke and embolism risk of the procedure. Patients with low risk of bleeding, high risk of stroke and embolism should be treated with intensive care after 24 hours postoperatively. If the risk of blood is high and the risk of stroke and emboli is low, this period can be extended to 48-72 hours. Bridge therapy with parenteral anticoagulant therapy may not be considered in patients who exceed these durations and have a high risk of stroke emboli (18-20).

DECLARATION OF CONFLICTING INTERESTS

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

REFERENCES

1. Kayaalp SO. Rasyonel tedavi yönünden tıbbi farmakoloji. 1. Cilt: Hacettepe-Taş Kitapçılık Limited Şti.; 2000.
2. Uzun S, Arslan F. Warfarin kullanan bireylerin eğitiminde hemşirenin rolü. *MN Kardiyoloji* 2006; 5: 352-4.
3. Poller L, Jacobson A, Deykin D, et al. Managing oral anticoagulant therapy. *Chest* 2001; 119: 22-38.
4. Kearon C, Hirsh J. Changing indications for warfarin therapy. Poller L, Ludlam CA (eds) *Recent Advances in Blood Coagulation* New York: Churchill Livingstone 1997: 141-60.
5. Weitz JI, Gross PL. New oral anticoagulants: which one should my patient use? *ASH Education Program Book* 2012; 2012: 536-40.
6. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor Xa inhibitors in development. *Clin Pharmacokinetics* 2009; 48: 1-22.
7. Hammersley D, Signy M. Navigating the choice of oral anticoagulation therapy for atrial fibrillation in the NOAC era. *Therapeutic Advances In Chronic Dis* 2017; 8: 165-76.
8. Gonsalves WI, Pruthi RK, Patnaik MM, editors. *The new oral anticoagulants in clinical practice*. Mayo Clinic Proceedings 2013: Elsevier.
9. Konkle BA. Direct oral anticoagulants: monitoring anticoagulant effect. *Hematology/Oncology Clinics* 2016; 30: 995-1006.
10. Thachil J. The newer direct oral anticoagulants: a practical guide. *Clin Med* 2014; 14: 165-75.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Eng J Med* 2009; 361: 1139-51.
12. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New Eng J Med* 2011; 365: 883-91.
13. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *New Eng J Med* 2011; 365: 981-92.
14. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *New Eng J Med* 2013; 369: 2093-104.
15. 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. *The Lancet* 2014; 383: 955-62.
16. Schulman S. New oral anticoagulant agents—general features and outcomes in subsets of patients. *Thrombosis Haemostasis* 2014; 112: 575-82.
17. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart J* 2016; 37: 2893-962.
18. Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. *Gastrointestinal Endoscopy* 2013; 78: 227-39.
19. Pollack CV, Reilly PA, van Ryn J, et al, editors. *Idarucizumab for dabigatran reversal: updated results of the re-verse ad study*. *Circulation*; 2016: Lippincott Williams & Wilkins Two Commerce Sq, 2001 Market St, Philadelphia, PA 19103 USA.
20. Pollack Jr CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *New Eng J Med* 2015; 373: 511-20.