INVITED REVIEW

Anticoagulant therapy for acute venous thromboembolism

Akut venöz tromboembolide antikoagülan kullanımı

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Summary– Deep vein thrombosis (DVT) and pulmonary embolism (PE) are currently defined as venous thromboembolism (VTE) since they share pathophysiological features and the treatment is similar in many respects. It has been determined that more than 90% of PE cases originate from DVT in the legs. PE, which is difficult to diagnose, has a mortality rate of 12% when untreated. The worldwide increase in obesity, cancer diseases, and average survival time also contribute to the increase in the incidence of VTE. Traditional treatment of VTE includes heparin, low-molecular-weight heparin, and warfarin. Despite availability for oral use, warfarin has a narrow therapeutic range and a wide range of food interactions. After many years of research, new oral anticoagulant agents (NOACs) are expected to overcome these handicaps in treatment. In this review, the use of NOACs in the treatment of VTE is investigated in the light of current guidelines.

Özet– Derin ven trombozu (DVT) ve pulmoner emboli (PE) aynı patofizyolojik özellikleri taşımaları ve tedavilerinin de pek çok açıdan benzer olması nedeniyle günümüzde venöz tromboemboli (VTE) olarak tanımlanırlar. PE'li olguların %90'dan fazlasının bacaklardaki derin ven trombozu kaynaklı olduğu saptanmıştır. Tanısı zor olan PE'nin tedavisiz mortalitesi %12'lere ulaşmaktadır. Tüm dünyada obezite, kanser hastalıkları ve ortalama yaşam süresindeki artışın da VTE'nin görülme sıklığının artmasına katısı büyüktür. Geleneksel tedavi heparin, düşük molekül ağırlıklı heparin ve varfarin kullanımını kapsamaktadır. Varfarin oral kullanımına rağmen, dar bir terapötik aralığa ve geniş çaplı bir gıda etkileşimine sahiptir. Uzun yıllar süren araştırmalar sonucunda yeni oral antikoagülan ajanlar (YOAK) ile tedavideki bu handikapların üstesinden gelineceği düşünülmektedir. Bu derlemede, venöz tromboembolizm tedavisinde yeni kuşak antikoagülan ilaçların yeri güncel kılavuzlar ışığında incelenmiştir.

Venous thromboembolism (VTE), involving deep vein thrombosis (DVT) and acute pulmonary embolism (APE) is the third most common cardiovascular disease after coronary artery disease and stroke.[1] It is estimated that the annual incidence in Europe is approximately 100–200/100,000.[2] Only 41% of VTE-related deaths can be diagnosed and the remaining cases are thought to be undiagnosed.[1] It has usually been diagnosed postmortem. The frequency of VTE doubles in every decade of life over the age of forty.[3,4] Protection of patients at risk of VTE is as important as diagnosis and treatment of the disease. In recent years, new developments have been seen in the diagnosis and treatment of VTE. However, the methods used for diagnosis are not available at all centers, so no standard approach has been provided for diagnosis and treatment. There is a need for consensus on diagnosis, treatment, and prophylaxis of VTE and it requires a multidisciplinary approach.

Abbreviations:

APE	*Acute pulmonary embolism*
CI	*Confidence interval*
DVT	*Deep vein thrombosis*
ESC	*European Society of Cardiology*
HR	*Hazard ratio*
LMWH	*Low-molecular-weight heparin*
NOAC	*New oral anticoagulant*
PE	*Pulmonary embolism*
PESI	*Pulmonary embolism severity index*
sPESI	*Simplified pulmonary embolism severity index*
VKA	*Vitamin K antagonists*
VTE	*Venous thromboembolism*

VTE is often the result of patient-related persistent risk factors and the interaction of transient risk factors that may be associated with conditions such as surgery, trauma, pregnancy, oral contraceptive use, in-vitro fertilization, blood transfusion, and infections. If there is evidence of

Received: February 13, 2017 *Accepted:* June 22, 2017
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transient risk factors present 6 weeks to 3 months prior to the date of diagnosis, it is referred to as stimulated VTE.[5,6] It is important to differentiate between provoked and unprovoked VTE cases to determine the duration and type of anticoagulant therapy to be administered.

The risk factors for acute pulmonary embolism defined in the European Society of Cardiology (ESC) guidelines published in 2014 are presented in Table 1.

APE occurs in about 40% to 50% of patients with symptomatic proximal DVT.[7] APE has a mortality rate of 9% to 11% for the early period (first 30 days) and there are series reporting 3-month mortality rate of over 15%.[8,9] Although it has been reported that 35% of patients have residual pulmonary artery occlusion in 1-year follow-up of APE, perfusion defects represent less than 15% in the majority of these patients. It is known that the risk of chronic thromboembolic pulmonary hypertension is approximately 1.5%.[10] The aim of using anticoagulants in the treatment of VTE, after the acute phase, is to prevent recurrence. The recurrence rate is 2% in 2-week period, 6.4% in 3 months, and 8% in 6 months.[11,12]

Risk Assessment and Prevention of Acute Pulmonary Embolism

It is important to define the severity of the disease for the treatment of APE. The ESC guideline recommendations for deciding which patient should undergo emergency revascularization, which patient requires close hemodynamic follow-up, and which patient would only be treated with anticoagulants, or a shorter length of stay in the hospital, are as follows:

If a patient with APE has hypotension or shock, s/he is considered to be at high risk. Shock or hypotension is defined as >15 minutes of systolic blood pressure <90 mmHg or systolic blood pressure >40 mmHg. These patients should be treated with unfractionated high-molecular-weight heparin immediately after the diagnosis.

The original pulmonary embolism severity index (PESI) and the simplified pulmonary embolism severity index (sPESI), which is the updated version, have long been used for rating patients without hypotension or shock. Patients with a PESI score >1 are considered to be at moderate risk. Patients who are at moderate risk and with elevated cardiac damage bio-

Table 1. Risk factors for venous thromboembolism

Strong risk factors (risk >10 fold)	Medium risk factors (risk 2-9-fold)	Weak risk factors (risk <2-fold)
Lower extremity fracture	Arthroscopic knee surgery	Extended bed rest (>3 days)
Hospitalization for heart failure or atrial fibrillation	Autoimmune disease	Diabetes mellitus
Hip or knee joint prosthesis	Blood transfusion	Hypertension
Myocardial infarction in the last 3 months	Presence of central venous line	Long trips without motion
Venous thromboembolism history	Chemotherapy	Advanced age
Spinal cord injury	Heart failure or pulmonary insufficiency	Laparoscopic surgery
	Excessive use of erythropoiesis stimulation	Obesity
	Hormone replacement therapy	Pregnancy
	In vitro fertilization	Varicose vein disease
	Infection (pneumonia, HIV and urinary tract)	
	Inflammatory bowel	
	Cancer (the risk of metastasis is higher)	
	Oral contraceptive use	
	Paralytic stroke	
	Postpartum period	
	Superficial vein thrombosis	
	Thrombophilia	

markers (especially cardiac troponin) and right heart dysfunction detected with cardiac imaging modalities are considered to be at moderate-high risk. If a patient is at moderate risk, but 1 or both of these conditions is absent, then s/he is considered to be at moderate-low risk. In addition, if the PESI score is 0 and cardiac damage biomarkers are elevated, the patient is considered to be at moderate-low risk. In the presence of shock or hypotension, monitoring right heart function or cardiac biomarkers has no additional contribution to evaluation of risk. Patients with moderate-high risk should be closely monitored in terms of risk of shock or hypotension in order to detect any indication for revascularization therapy. Patients at moderate-high risk should be followed up with administration of unfractionated heparin, which can be used with a thrombolytic agent. Low-molecular-weight heparin (LMWH) and fondaparinux, other parenteral anticoagulants, have not been tested in studies investigating the use of thrombolytics in pulmonary embolism.

Mechanisms of Action of Anticoagulants Used

The first member of this group, standard heparin, binds to antithrombin III and acts as an inhibitor of factor XIIa, XIa, IXa, and thrombin. Although LMWH anticoagulant medications exhibit their principal effect by blocking factor Xa, they also have anti-factor IIa effects. Fondaparinux is another parenteral anticoagulant used in a single daily dose. It acts as an anticoagulant by catalyzing the inhibitory effect of antithrombin factor Xa (Figure 1).

Rivaroxaban, apixaban, and edoxaban, which have been used in the treatment of atrial fibrillation and VTE, block free and bound factor Xa. Dabigatran acts by inhibiting direct thrombin (factor II).

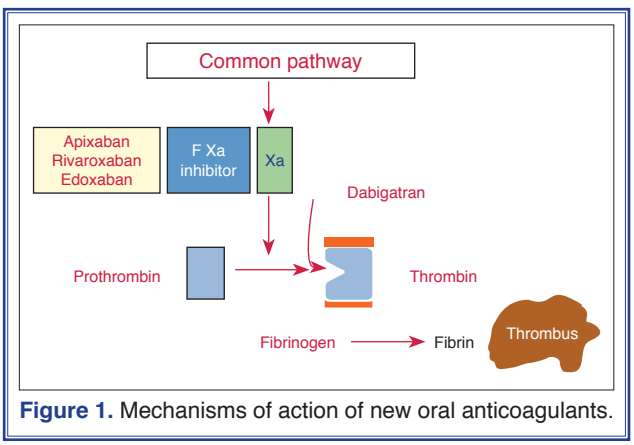

Figure 1. Mechanisms of action of new oral anticoagulants.

The Phases of Pulmonary Embolism and Anticoagulants Used

Acute phase anticoagulant therapy: The acute phase of APE usually involves treatment for the first 5 to 10 days, the determinant of mortality. Some authors have suggested that this period cover the first 14 days, which is the duration that thrombolytic therapy can be administered. It wouldn't be wrong to say that, at least until recently, the accepted anticoagulant therapy in acute phase treatment was fractionated heparin, LMWH, and fondaparinux.[13–16]

However, there are recent studies with new oral anticoagulants (NOACs), including the use of rivaroxaban and apixaban, at high doses.[17–19] The choice of initial parenteral anticoagulant therapy should depend on the risk assessment of the patient according to the PESI score. LMWHs and fondaparinux are recommended, especially in low-risk and moderate-low-risk patients, since in studies comparing these agents with standard heparin, bleeding safety points have been reported to be in favor of LMWH and fondaparinux, or similar.[13,14–16] In a series of 2213 patients that compared fondaparinux to unfractionated heparin in acute phase treatment of APE, the rate of recurrence of APE or DVT, which was the primary efficacy point, was reported to be 1.2% lower for fondaparinux group at the end of follow-up (3 months); major bleeding was similar in both groups (1.3% vs 1.1%; $p>0.05$).[20]

Indeed, the ESC APE guideline also determined parenteral use of fondaparinux and LMWH in the acute phase of APE to be Class I, Level of Evidence A, with reference to the risk of major bleeding and heparin-induced thrombocytopenia, except in high-risk cases. Table 2 lists the LMWHs and doses that can be used. All of these LMWHs are available in our country. Unfractionated heparin is suggested in acute phase therapy of high-risk patients with creatinine clearance <30 mL/minute and severe obesity. Therapy with LMWH may require periodic monitoring in pregnant women, whereas it is not indicated with fondaparinux.[21]

In monitoring such patients, the level of anti-factor Xa is controlled 4 hours after the last injection or immediately before the next injection. The required level of anti-factor Xa is 0.6–1.0 IU/mL for 2 doses of LMWH per day, and 1.0–2.0 IU/mL for a single dose. Anticoagulation with unfractionated heparin,

Table 2. The approved low-molecular-weight heparin anticoagulants and pentasaccharide (fondaparinux) in pulmonary embolism therapy

	Dose	Range
Enoxaparin	1.0 mg / Kg	12 hours
	Or 1.5 mg / kg[a]	Once a day[a]
Tinzaparin	175 U / kg	Once a day
Dalteparin	100 IU / kg[b] or	12 hours
	200 IU / kg[b]	Once a day
Nadroparin	86 IU / kg[c]	12 hours
	Or 171 IU / kg[c]	Once a day
Fondaparinux	5 mg (body weight <50 kg)	Once a day
	7.5 mg (body weight 50–100 kg)	
	10 mg (body weight >100 kg)	

All doses are administered subcutaneously. IU: International units; LMWH: Low molecular weight heparin.
[a]Once a day, 1.5 mg enoxaparin injection was approved for inpatient PE treatment in some, but not all, European countries.
[b]In cancer patients, dalteparin is given at a dose of 200 IU / kg body weight (maximum 18,000 IU) once daily for 1 month, followed by 150 IU/kg once daily for 5 months. After this period, anticoagulation with a VKA or LMWH should be continued indefinitely or until the cancer is thought to be treated.
[c]Nadroparin has been approved for PE treatment in the United States and in some, but not all, European countries.

LMWH, or fondaparinux should continue for at least 5 days.

The aim of anticoagulant therapy after the acute phase is to prevent recurrence. This period covers a period of 3 to 6 months and the drugs that can be used during this period include LMWH (cancer, pregnancy), vitamin K antagonists (VKAs), and NOACs.[16,22–25]

Generally, anticoagulant drugs are discontinued at the end of this period. However, in some patient groups, such as unexplained APE, thrombophilia, or active cancer, it may be indicated to use anticoagulants for an extended period or lifelong. NOACs rivaroxaban, apixaban, and dabigatran, but not edoxaban, can be used for extended periods.[17,26,27]

Preventing Recurrence

VKAs, traditionally having been used in the acute phase, can be started immediately with parenteral anticoagulants, and it is recommended to use both agents together for 2 days after therapeutic level of international normalized ratio (2.0–3.0) is achieved, then to discontinue administration of parenteral anticoagulants in all patients except for those at high-risk.

NOACs, which have been used in atrial fibrillation in recent years, have been included in both the acute treatment of VTE and in the prevention of recurrence. The first member of this group is the direct thrombin inhibitor, dabigatran. In RE-COVER trial (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA) conducted with 2539 patients, one-third of whom were diagnosed with APE, dabigatran was compared to warfarin.[28] At 6-month follow-up, the ratio of recurrent VTE was reported to be 2.4% in the dabigatran group and 2.1% in the warfarin group (hazard ratio [HR]: 1.10; 95% confidence interval [CI], 0.65–1.84) and the ratio of major bleeding was reported to be 1.6% and 1.4%, respectively. The results of the RE-COVER II trial (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA) with 2589 patients are more recent; at 6-month follow-up, the ratio of mortality or recurrence of VTE was reported to be 2.3% in the dabigatran group and 2.2% in the warfarin group (HR: 1.08; 95% CI, 0.64–1.80), the ratio of major bleeding was reported to be 1.2% in the dabigatran group and 1.7% in the warfarin group (HR: 0.69; 95% CI, 0.36–1.32), and the ratio of bleeding due to any reason was 15.6% and 22.1%, respectively.[29] Based on these results, it can be concluded that dabigatran is as efficient as warfarin, but the risk of bleeding is lower with dabigatran. However, it should be noted that dabigatran was not used in the acute phase in these studies. The duration of parenteral anticoagulation was approximately 9 days in both studies.

The second member of this group is rivaroxsaban. The efficacy of rivaroxsaban in the treatment of DVT and APE was evaluated in the EINSTEIN-DVT and EINSTEIN-PE (pulmonary embolism) trials. In the EINSTEIN-DVT trial, 3449 patients were randomized into a rivaroxaban group and a LMWH with VKA group, and the patients were followed up for 3, 6, or 12 months, according to the treatment applied.[17] In this study rivaroxaban was used at doses of 2x15 mg/day during the acute phase (21 days) and then 1x20 mg/day for maintenance. The percentage of recurrent DVT was reported to be 2.1% in the rivaroxaban group and 3.0% in the enoxaparin-VKA group (HR: 0.68;

95% CI, 0.44–1.04). The percentage of any bleeding, which was the principal safety point, was the same in both groups (8.1%). Rivaroxaban was similarly used in the EINSTEIN-PE trial in 4832 patients with acute pulmonary embolism, and the percentage of recurrent VTE was reported to be 2.1% and 1.8%, respectively, in the 2 groups (HR: 1.12; 95% CI, 0.75–1.68).[18] Major bleeding percentage favored rivaroxaban (1.1% vs 2.1%; HR: 0.90; 95% CI, 0.76–1.07).

In the Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, which was an APE and DVT study, 5395 patients were randomized into a conventional enoxaparin + warfarin group and an apixaban group, with a dose of apixaban of 2x10 mg for the first 7 days and a 2x5 mg maintenance dose.[19] In this study, about one-third of the patients were diagnosed with DVT and the primary efficacy point was DVT or DVT-induced death. In this study, the percentage of primary efficacy events was 2.3% in the apixaban group and 2.7% in the conventional treatment group (relative risk: 0.84; 95% CI, 0.60–1.18). The major bleeding rate was better in the apixaban group (0.6% vs 1.8%; relative risk: 0.31; 95% CI, 0.17–0.55).

Edoxaban, the last member of this group, was evaluated in the Hokusai-VTE trial. In this study, 8240 patients, 3319 of whom were diagnosed with APE, were randomized into warfarin and edoxaban groups after receiving heparin therapy for at least 5 days as initial treatment.[30] Edoxaban was used in a single daily dose of 60 mg, and in patients with reduced renal function (creatinine clearance 30–50 mL/minute) at a dose of 30 mg/day. Recurrent DVT or fatal APE, which was the primary efficacy point, was similar in the edoxaban and conventional treatment groups (3.5% versus 3.2%; HR: 0.89; 95% CI, 0.70–1.13) and major bleeding events reported were in favor of edoxaban (8.5% vs 10.3%; HR: 0.81; 95% CI, 0.71–0.94). These studies suggest that these 4 new anticoagulants are as efficient as conventional oral anticoagulants, and bleeding side effects are similar to or even less than for warfarin. Indirect comparable studies of new oral anticoagulants have demonstrated similar efficacy among drugs and no side effects. Table 3 provides a summary of the dosage and use of these drugs in the treatment of APE according to the ESC APE guideline.

Duration of Anticoagulation Therapy

The aim of anticoagulant therapy in VTE is to prevent recurrence. In many cases, warfarin and NOACs are used in this effort, but a LMWH is recommended under certain conditions, such as cancer and pregnancy.[16] The risk of recurrent VTE is 6.4% for 3 months, and 8% for 6 months.[5,11,12,31] In the presence of reversible risk factors, the annual recurrence rate of PE is 2.5% after completing anticoagulant therapy, and

Table 3. European Society of Cardiology recommendations for the use of new oral anticoagulants in acute pulmonary embolism

New oral anticoagulant	Class	Evidence Level
A combination of rivaroxaban with anticoagulation (15 mg twice daily for 3 weeks, then 20 mg once daily) is suggested as an alternative to the combination of parenteral anticoagulation with Vitamin K antagonist.	1	B
A combination of apixaban with anticoagulation (10 mg twice daily for 7 days, then 5 mg twice daily) is suggested as an alternative to the combination of parenteral anticoagulation with Vitamin K antagonist.	1	B
Dabigatran administration (150 mg twice daily, or 110 mg twice daily for patients over 80 years of age or on verapamil treatment) is suggested after parenteral anticoagulation, as an alternative to Vitamin K antagonist treatment.	1	B
Edoxaban* is suggested after acute phase parenteral anticoagulation, as an alternative to Vitamin K antagonist treatment.	1	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) should be avoided in patients with severe renal insufficiency recommended for.	1	B

after unprotected PE, it is 4.5%.[5,32] Although several studies of VTE treatment have used anticoagulants at different times, common points have emerged from these studies:

1. Patients with APE should take anticoagulants for at least 3 months.
2. There is no difference between 3-month use and 6-12-month use in terms of recurrence rate after 2-anticoagulant therapy has been completed.
3. Indefinite use of anticoagulants can prevent 90% of recurrences, but this positive effect seems to be offset by the risk of major bleeding rate of 1% per year.[5,33–35]

Active cancer is a major risk factor for VTE recurrence, with a 20% recurrence rate at 12 months.[5,36,37] Therefore, it is difficult to determine the duration of anticoagulant use in cancer patients, and it seems reasonable for these patients to take anticoagulants for an indefinite period of time, or at least continuing for as long as the disease is active. Dalteparin was used for 6 months in cancer patients diagnosed with DVT in a randomized trial and was found to be more successful than warfarin in decreasing recurrence.[22,23]

These studies were pointed out in the ESC 2014 guidelines, as well as the American College of Chest Physicians CHEST guidelines of 2016, and it is recommended that LMWH or warfarin should be given at least for 3 to 6 months, and anticoagulation can be continued as long as the disease is active. As mentioned earlier, VTE induced by transient risk factors other than cancer is called provoked VTE. In these patients, 3 months of anticoagulation is sufficient. The exception to this is the preservation of the temporary risk factor. The duration of treatment in unprovoked VTE has been clearly defined, whereas the situation in stimulated VTE is rather complicated. The presence of the following risk factors may provide guidance for this condition:

1. Having one or more VTE episodes,
2. Presence of antiphospholipid antibody syndrome,
3. Hereditary thrombophilia,
4. Presence of residual thrombus in proximal veins, or
5. Presence of ongoing RV dysfunction on echocardiography at discharge.[38] In addition, a negative D-dimer test 1 month after termination of anticoagulant therapy may indicate that risk of recurrence would be low.[39]

Patients with lupus anticoagulant presenting with molecular thrombophilia, those with confirmed protein C and S defects, and homozygous Factor V Leiden and prothrombin G20210A are candidates for indefinite use of oral anticoagulants after the first VTE episode. Currently, there is no evidence to demonstrate that anticoagulation therapy for longer than 3 months is effective in patients with heterozygous Factor V Leiden and prothrombin G20210A. There is no efficient risk score for bleeding due to use of anticoagulant for VTE, but the presence of the following risk factors may indicate a higher risk of bleeding:

1. Advanced age (>75 years),
2. Previous GIS bleeding,
3. History of ischemic-hemorrhagic stroke,
4. Chronic renal/hepatic insufficiency,
5. Concurrent antiplatelet therapy,
6. Severe acute or chronic disease,
7. Poor anticoagulant control, or
8. Suboptimal monitoring of anticoagulant therapy.

Therapeutic-dose LMWH is the first treatment of choice for VTE in pregnancy; LMWH does not cross the placenta, and is not associated with any teratogenicity.[40] The risks of LMWH use include postpartum hemorrhage (0.94%), severe antepartum bleeding (0.43%), wound hematoma (0.61%), allergic reaction (1.80%), and rarely, heparin-induced thrombocytopenia.[26]

Warfarin, rivaroxaban, apixaban, edoxaban, and dabigatran are contraindicated in pregnancy. Warfarin has known teratogenicity, with the risk of congenital anomalies, fetal hemorrhage, and pregnancy loss.[41] NOACs in pregnancy have been shown to cross the placenta and use of NOACs in animal studies have been associated with increased implantation loss, congenital malformations, altered ossification, and hemorrhage.[42,43]

Based on a consensus published in 2016 International Society on Thrombosis and Haemostasis guidance, women who are planning a pregnancy and al-

ready on a NOAC for treatment of VTE should be temporarily switched to warfarin or transitioned to a LMWH prior to conception instead of remaining on a NOAC until pregnancy is confirmed. If a woman becomes pregnant on a NOAC (or warfarin), she should be switched immediately to a LMWH.[44] Based on current data, exposure to a NOAC in pregnancy does not warrant elective termination of pregnancy. More data are needed before further conclusions can be drawn about the safety of NOACs in pregnancy.

In unprovoked VTE anticoagulation, therapy should be continued for at least 3 months, while paying attention to the risk of recurrence and the bleeding risk factors mentioned.

At the end of this 3 months of therapy, the ESC guideline recommends anticoagulation therapy to be continued for an indefinite period in first, unprovoked DVT or APE cases, provided that the risk of bleeding is low and taking the patient's preference into account. However, oral anticoagulation for an indefinite period does not have the same meaning as lifelong anticoagulation; it only points out that the treatment cannot be discontinued at the end of the first 3 months of follow-up. These patients should be evaluated at frequent intervals while taking the recurrence/bleeding balance into account before deciding to discontinue the anticoagulant therapy. Lifelong anticoagulation therapy should be considered in the second episode of unprovoked DVT or PE.

While there is an indication for using dabigatran, rivaroxaban and apixaban as prolonged anticoagulants, there is no indication yet in the guidelines for such use of edoxaban.[17,26,27]

Finally, we note that the Warfarin and Aspirin (WARFASA) and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) studies, in which anticoagulants were discontinued at the end of the treatment and aspirin was given for a long period, reported a positive effect on VTE recurrence. In these studies, 40% and 26% risk reduction was achieved with aspirin, which is equal to half of the efficacy of oral anticoagulants.[45,46]

Conclusion

If venous thromboembolism is not diagnosed and treated, it causes severe complications that can range from right heart failure to chronic thromboembolic pulmonary hypertension. Anticoagulant therapy has an important place in the prevention of these hard treatable diseases.

In our opinion, taking NOACs, which are easy to use and monitor, according to the guidelines would be useful in the prevention of recurrence and complications.

Conflict-of-interest: None declared.

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Keywords: Anticoagulant treatment; deep venous thrombosis; pulmonary embolism.

Anahtar sözcükler: Antikoagülan tedavi; derin ven trombozu; pulmoner emboli.