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DURATION OF ANTICOAGULATION THERAPY IN PATIENTS WITH GENETIC INHERITED THROMBOPHILIA

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ABSTRACT

Background: Genetic factors play an important role in deep vein thrombosis (DVT). The duration of anticoagulation therapy in patients with verified genetic inheritance and previous events of DVT is still questionable.

Case reports: We present three cases of siblings (two brothers and one sister) with verified Venous thromboembolism (VTE) and genetic inheritance. The first case is a 33 y.o. male who was admitted with bilateral massive pulmonary thromboembolism and DVT of the right femoral vein. He had an episode of DVT 4 years ago. Fibrinolytic therapy was introduced immediately. Afterwards, unfractionated heparin was introduced, and then switched to enoxaparin and acenocoumarol. Because of inappropriate INR, it was switched then to rivaroxaban. The imaging methods showed significant improvement, and the patient was discharged from the hospital with rivaroxaban at 2x15 mg/day for another 2 weeks and was instructed to continue 20 mg/day until his next control. In the meantime, the second case, a 36 y.o. male, brother to the first patient, came with vein thrombosis of vena saphena magna of the left leg. Treatment with Acenocoumarol was started and continued for 2 years until complete resolution of the thrombi, and then it was changed to Aspirin. The third case is the sister of the first 2 cases, a 38 y.o female with symptoms and findings almost similar to those in the second case. She was treated with Acenocoumarol for 6 months. Doppler ultrasound showed complete resolution of the thrombosis and anticoagulation therapy was stopped. Genetic investigations for mutation showed presence of homozygous gene mutation for *Prothrombin* (*PTB G20210A*) in the first patient, his brother (the second case) was compound heterozygote for PTB and for *MTHFR C677T*, and his sister (third case) was heterozygous only for the *PTB* mutation. According to the clinical (recurrent unprovoked DVT with thromboembolic complications) and genetic testing (homozygous gene mutation for *PTB*) in the first patient, we decided to continue the secondary thromboprophylaxis with rivaroxaban 10 mg/day indefinitely.

Conclusion: Testing for genetically inherited thrombophilia should be included in the risk assessment for recurrence, and performed in all patients under 50 y.o. who have a first, non-provoked episode of thrombosis, in order to determine the duration of anticoagulation therapy.

Keywords: deep vein thrombosis, pulmonary embolism, anticoagulation therapy, genetic investigation, mutation, prothrombin, thrombophilia

INTRODUCTION

Venous thromboembolism (VTE), whose main clinical manifestations are deep vein thrombosis (DVT) and pulmonary embolism (PE), is a very common worldwide health problem. They can be caused by complex interactions of environmental and genetic factors. A combination of side effects (female hormone intake, immobilization, surgery or neoplasms) and variations in the genes responsible for the coagulation system can lead to thrombosis [1]. In some cases, only the presence of genetic mutations without the influence of external risk factors may lead to DVT with clinical manifestations. Thrombophilia is a medical condition that describes conditions where the blood has an increased tendency to clot. There are 2 types: acquired and inherited. People with inherited thrombophilia tend to form a thrombus due to a genetic predisposition inherited from their parents [2]. When a person under the age of 50 develops thrombosis, without any risk factor, the cause is often found in the genes. About half of the young DVT patients who come to our clinic have a close relative with the same condition (DVT). Therefore, testing for genetic variation and adequate prophylaxis helps to reduce the risk of thrombosis and its complications. Hereditary thrombophilia results when a mutation in certain genes occurs. Until now, the known hereditary risk factors are gene mutations of: *Factor V Leiden*, *Prothrombin 20210A, methylene tetrahydrofolate reductase (MTHFR) C677T*; then Protein S deficiency, Protein C deficiency, Antithrombin deficiency, and hyperhomocysteinemia. A homozygous abnormality or a combination of two or more heterozygous abnormalities can lead to a thrombotic event with clinical manifestation at an early age. Also, these conditions have a much higher percentage of possibility for recurrent occurrences of thrombotic events, and a high probability of thrombotic events in the closest family if they are also carriers of a certain gene mutation. Of particular importance in these patients with a proven genetic mutation and previous venous thromboembolic event is the treatment strategy and duration of anticoagulant therapy and it is still under discussion.

AIM OF THE STUDY

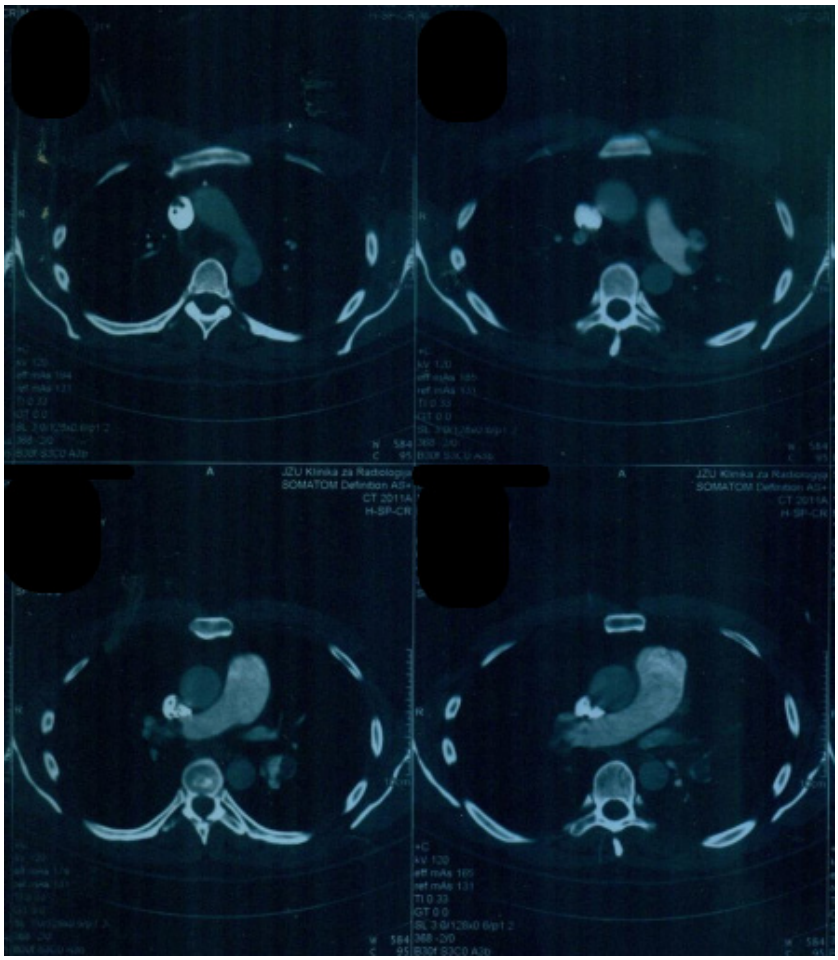
The aim of the study was to show how patients from the same family with genetically associated thrombophilia and (recurrent) non-provoked venous thrombosis should be managed in terms of anticoagulation choice and its duration as secondary prophylaxis.

CASE REPORTS

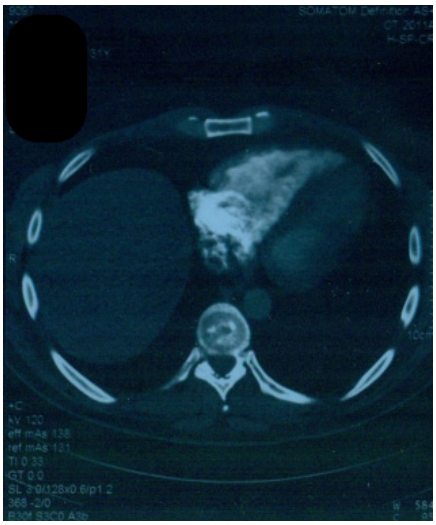
We present three cases from one family (two brothers and one sister) with proven venous thrombosis and genetic inheritance or thrombophilia.

3.1 The first case is a 33-year-old, non-smoking man who came to our clinic with data of syncope on the day of admission, as well as shortness of breath and dizziness in the last 2 days. From past diseases we could see the occurrence of DVT 4 years ago, treated with anticoagulant therapy for a period of 3 months. From the family history, he denied diseases of interest. On admission, he complained of dizziness and sweating with BP=95/60 mmHg, with about 30 breaths per minute and SpO2 of about 95% without oxygen support. On auscultation, there were no significant lung and heart findings, no swollen limbs, and no peripheral cyanosis. The electrocardiogram showed only sinus tachycardia with 115 bpm, with no other significant changes. An echocardiogram was performed immediately with normal left ventricular dimensions, with an ejection fraction (EF) of 56%. Notable were the moderate tricuspid regurgitation, moderate pulmonary arterial hypertension (PAH), and dilated right ventricle with the McConnel sign (reduced movement of the free wall of the right ventricle compared with the apex). Hypokinesia of the anterior wall of the right ventricle was seen on the interventricular septum, most likely caused by increased right ventricular pressure. The finding was highly suspected for pulmonary thromboembolism. During the echocardiography exam, the patient had another episode of syncope with bradypnea, but after short-term assisted ventilation, he regained his breathing and consciousness, after which he was transferred to the intensive care unit. It should be noted that, other than elevated d-dimers (5980 ng/ml), further laborato-

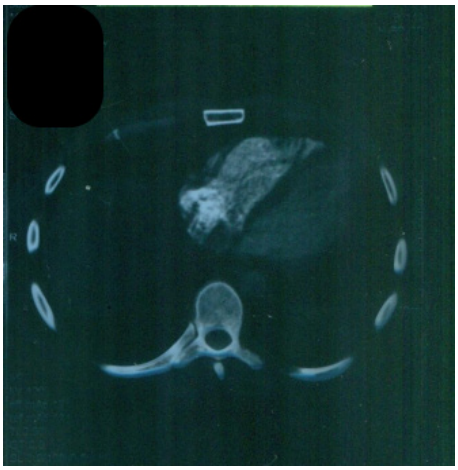
ry findings were within normal limits. A doppler ultrasound of the legs showed a non-occlusive thrombus of the right femoral vein. A CT angiography of the lungs was immediately performed (Picture 1), and proved the suspicion of bilateral pulmonary embolism (PE). Thrombi were also seen in the lobar and segmental branches of the inferior lobes bilaterally. The RV/LV ratio was > 1 (Picture 2).



Picture 1. *CT pulmonary angiograpy: occlusive embolus in the right pulmonary artery and subocclusive thrombus in one of the branches of the left pulmonary artery*

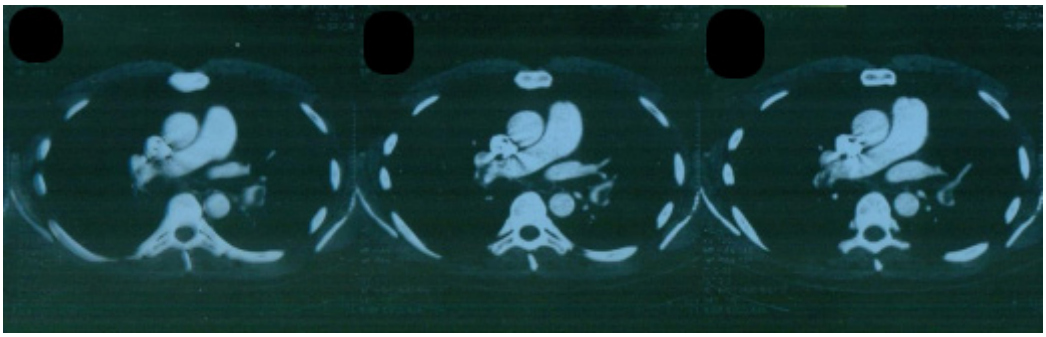


Picture 2. RV/LV ratio >1



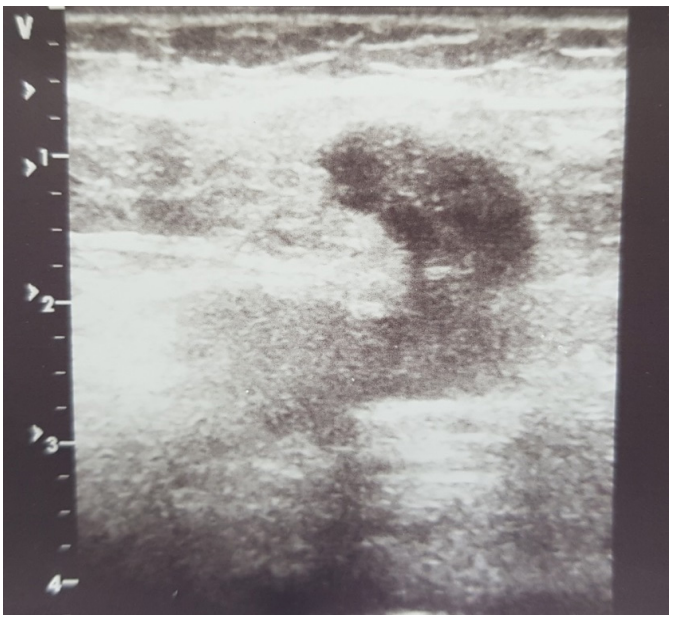
Picture 3. Normalizing the ratio RV/LV

Fibrinolytic therapy (Alteplase - tissue plasminogen activator - 100 mg iv/2 hours) was started immediately. Unfractionated heparin 30,000 IU/24 h was then continued as the anticoagulant therapy. Coagulation tests were satisfactory (extended Thrombin Time and APTT). The patient was then transferred to enoxaparin at 80mg/12h, overlapped with acenocoumarol. INR was monitored daily and the dose of acenocoumarol was adjusted to achieve a therapeutic value of INR (2-3). After one week, the INR value was still below 2 and the D-dimer value was still high (4156 ng/ml). It was decided to transfer the patient to therapy with novel oral anticoagulant (NOAC) - rivaroxaban 2x15mg (21 days), and then continued with 1x20mg until the next control. After 20 days of hospitalization (7 days of therapy with rivaroxaban), the doppler ultrasound and CT pulmonary angiography showed resolution of the thrombi in the femoral vein and pulmonary arteries (Picture 4). The patient was discharged from the clinic in good clinical condition. Genetic testing of the patient was performed during the stay, the results of which have not yet been obtained.



Picture 4. Control CT pulmonary angiography

3.2. The second case occurs during the hospitalization of the first. It is the brother of the first patient who came to our clinic with symptoms of pain, redness and swelling in his left leg during the previous month. Doppler ultrasound of the left leg lead to a diagnosis of thrombosis of the vena saphena magna (Picture 5). Therapy with Acenocoumarol was started. The INR reached its therapeutic value and Acenocoumarol was extended to complete thrombus resolution for about 2 years, and then replaced with Aspirin. No complications were reported in the meantime.



Picture 5. Doppler ultrasound: nonocclusive thrombus of the left great saphenous vein

3.3. The third case is a 38-year-old patient, the sister of the previous two patients with almost identical symptoms as the brother in the second case. The event takes place one year after the first 2 cases. Doppler ultrasound showed thrombosis of the v. saphena magna of the right leg. She was treated with Acenocoumarol, with a satisfactory INR response. After 6 months, Doppler showed complete resolution of thrombosis and anticoagulant therapy was discontinued.

Genetic testing was performed on all three patients and their parents. The presence of a homozygous mutation for Prothrombin (PTB) in the first patient was reported. Both of his parents were heterozygous for the same mutation. The sibling in the second case was heterozygote for Prothrombin and MTHFR, while the sister (the third case) was heterozygote for PTB. The first patient on control exam after 6 months felt great without any symptoms. He was still on therapy with Rivaroxaban 20mg/day. Due to the recurrent occurrence of thrombosis and the presence of a homozygous mutation for PTB, we decided to continue with secondary thromboprophylaxis, Rivaroxaban 20 mg/day for one year, and then 10 mg/day for an extended indefinite period.

DISCUSSION

Inherited thrombophilia has a prevalence of about 10 to 50%, and the total incidence of DVT thrombophilia is 24 to 50% [2]. The prothrombin mutation discussed in this paper is the second most common inherited mutation with a risk of thrombosis, after factor V Leiden. Heterozygotes have a 5 times higher risk of thrombosis than normal, while homozygotes have a 50 times higher risk [3]. However, these mutations are not very common, with heterozygotes accounting for about 2% of the US population and homozygotes around 1 in 100,000 [4]. Individuals with combined genetic mutations, such as heterozygotes for factor V Leiden and the prothrombin G20210A mutation, have a higher risk of venous thrombosis than the normal population [5]. Studies show that these individuals have a much higher risk of thrombosis than individuals with a single, heterozygous factor V Leiden or prothrombin G20210A mutation. These individuals also have a higher chance of recurrence, thus prolonged anticoagulation should be considered as secondary prophylaxis. Genetic testing should not be performed on patients with a known major provoking factor for thrombosis, but only in those with proven non-provoking thrombosis, where the test results will be useful for further strategy and duration of treatment with anticoagulant therapy.

In 2005, the European Genetics Foundation, the Cardiovascular Disease Educational and Research Trust, the Mediterranean League on Thromboembolism, and the International Union of Angiology convened a consensus conference to address diagnostic testing for thrombophilia. Recommended indications for testing include: a) a first episode of spontaneous VTE; b) VTE patients under the age of 50 even with a transient predisposing factor; c) those whose only risk factor is estrogen therapy or pregnancy; and d) those with recurrent VTE, irrespective of the presence of risk factors [6]. The RIETE (Registro Informatizado de la Enfermedad TromboEmbolica) registry, an ongoing, multicenter, observational registry of consecutive patients with confirmed VTE, completed a study whose purpose was to estimate the extent to which thrombophilia test ordering patterns are consistent with the above-mentioned recommendations. Their findings suggest that a substantial proportion of thrombophilia ordering is not consistent with the recommendations, thus laboratories and physicians need better mechanisms to promote appropriate utilization of thrombophilia tests [7]. Between January 2001 and December 2008, 22,847 patients with symptomatic, acute VTE had been enrolled in RIETE. Of these, 4503 (19.7%) patients were tested for thrombophilia: 41% presented positive results, of whom 8.4% had FVL, 6.8% had PTG20210A. They found an association between lower extremity DVT (LEDVT) and factor V Leiden, as well as association between LEDVT + PTE with PTG20210A [8].

The absolute risk of recurrent venous thromboembolic events in patients with non-provoked thrombosis is higher than in individuals with provoked thrombosis, with an approximately 30% higher 5-year risk, if the patient is not on prolonged anticoagulation [9]. A second episode of thrombosis has a 50 times higher risk of recurrence, compared to the first event [10]. Of particular importance is the treatment strategy and duration of anticoagulant therapy among these patients with a proven genetic mutation

and previous venous thromboembolic events. This is still under discussion [11]. According the guidelines from the American College of Chest Physicians (ACCP), the patients with a first episode of venous thromboembolism and low or moderate risk of bleeding should have extended anticoagulant therapy (grade 2B), while in patients with a second unprovoked episode of venous thromboembolism and low or moderate risk of bleeding, extended anticoagulant therapy is recommended (grades 1B and 2B, respectively). Patients who have venous thrombosis and preexisting irreversible risk factors, such as genetic mutations which are responsible for the venous thrombosis, should be placed on long-term anticoagulation [12, 13]. According the latest guideline for pulmonary thromboembolism from the European Society of Cardiology, oral anticoagulants are highly effective in preventing recurrent thrombosis during treatment, but they do not eliminate the risk of recurrence after discontinuation of treatment [14]. One analysis, with data from seven randomized trials, involving 2925 patients with a first venous thromboembolism who did not have cancer and received different durations of anticoagulant treatment, aims to determine how length of anticoagulation and clinical presentation of venous thromboembolism influence the risk of recurrence after anticoagulant treatment is stopped and to identify the shortest length of anticoagulation that reduces the risk of recurrence to its lowest level. The results show that unprovoked proximal DVT and PE have a high risk of recurrence whenever treatment is stopped [15]. Another multicenter, randomized, double-blind, controlled trial compares an additional 18 months of Warfarin with placebo in patients with unprovoked proximal deep-vein thrombosis initially treated for 6 months. The conclusion of the study was that an additional 18 months of warfarin therapy reduced the composite of recurrent venous thrombosis compared to the placebo, but the benefit was not maintained after stopping anticoagulation [16]. The objective of one meta-analysis of 18 randomized controlled trials and prospective cohort studies involving 7515 patients, was to determine the rate of a first recurrent VTE event after discontinuation of anticoagulant treatment in patients with a first episode of unprovoked VTE, and the cumulative incidence for recurrent VTE up to 10 years. The results show that in patients with a first episode of unprovoked VTE who completed at least three months of anticoagulant treatment, the risk of recurrent VTE was 10% in the first year after treatment, 16% at two years, 25% at five years, with 4% of recurrent VTE events resulting in death [17].

Due to the homozygous prothrombin mutation, as well as two non-provoked episodes of thrombosis in a patient without a high risk of bleeding, we decided to treat the first patient with prolonged anticoagulant therapy, rivaroxaban indefinitely. The dilemma we face is: to which patients will we recommend indefinite continuation of anticoagulant treatment? It is recommended to treat patients indefinitely who have a recurrent episode of thrombosis which is not associated with a major transient or reversible risk factor. If we opt for prolonged anticoagulation, the recommended doses for the novel oral anticoagulants (NOACs) are Apixaban 2.5mg 2x1 or Rivaroxaban 10mg 1x1 [14].

CONCLUSION

These cases indicate that the decision to determine the duration of anticoagulation in all patients with venous thrombosis should be individualized and based on the risk assessment for recurrence on the one hand and bleeding on the other. Testing for genetically inherited thrombophilia should be included in the risk assessment and performed in all patients under 50 years old who have a first, non-provoked episode of thrombosis, in order to determine the duration of anticoagulation.

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Резиме

ВРЕМЕТРАЕЊЕТО НА АНТИКОАГУЛАНТНАТА ТЕРАПИЈА КАЈ ПАЦИЕНТИТЕ СО ГЕНЕТСКИ АСОЦИРАНА ТРОМБОФИЛИЈА

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Вовед: Генетските фактори играат важна улога во длабоката венска тромбоза (ДВТ). Времетраењето на антикоагулантната терапија кај пациентите со верифицирана генетска наследност и претходен ДВТ настан сè уште е дилема и предмет на дискусија.

Приказ на случаи: Презентираме три случаи од едно семејство (двајца браќа и една сестра) со докажана венска тромбоза и генетска наследност или тромбофилија. Првиот случај е 33-годишен маж, примен на нашата клиника со билатерална масивна белодробна тромбоемболија и ДВТ на десната феморална вена, со податок за епизода на ДВТ пред 4 години. Веднаш беше поставен на фибринолитичка терапија, а потоа на антикоагулантна терапија, и тоа првично на нефракциониран хепарин, подоцна префрлен на enoxaparin и acenocoumarol. По неколку дена, поради неможност да се постигне адекватна вредност на ИНР, беше префрлен на Rivaroxaban. Дијагностичките методи покажаа значително подобрување на наодот пос една недела и пациентот беше испишан од болница со терапија: Rivaroxaban 2x15mg во следните 14 дена и да продолжи со 20mg/ден до следна контрола. Во меѓувреме, кај вториот случај, 36-годишен маж, брат на првиот пациент, дојде со венска тромбоза на vena saphena magna на левата нога. Беше започнат третман со Acenocoumarol и продолжен до комплетна резолуција на тромбовите, и потоа сменет со Aspirin. Третиот случај е сестра на првите два пациенти, 38-годишна жена со симптоми и наод многу слични како кај вториот случај. Таа беше третирана со Acenocoumarol 6 месеци. Контролниот доплер ултразвук покажа комплетна резолуција на тромбозата и антикоагулантната терапија беше стопирана. Генетските испитувања покажаа присуство на хомозиготна мутација за Prothrombin (PTB G20210A) кај првиот пациент, неговиот брат (вториот случај) беше хетерозигот за PTB и MTHFR C677T, а нивната сестра (третиот случај) беше хетерозигот само за PTB-мутација. Врз основа на клиничката состојба (рекурентна непровоцирачка ДВТ со тромбоемболична компликација) и генетското тестирање (хомозиготна мутација за PTB), кај првиот пациент се одлучивме да продолжиме со секундарна тромбопрофилакса на неопределено време, Rivaroxaban 10 mg/ден.

Заклучок: Генетско тестирање за тромбофилијата треба да биде направено кај сите пациенти под 50 години што имаат прва непровоцирачка епизода на венска тромбоза, и тоа треба да биде вклучено во проценатa на ризикот за рекурентност, како и за одредување на времетраењето на антикоагулантната терапија.

Клучни зборови: длабока венска тромбоза, белодробна емболија, антикоагулантна терапија, генетско тестирање, мутација, протромбин, тромбофилија