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VENOUS THROMBOSIS

Akmal A. Irnazarov[1], Vali R. Khasanov [2], Ilhom R. Beknazarov[3], Rustambek A. Karimov[4], Dinara Kh. Irnazarova[5]

1 Doctor of Medicine, professor of the Faculty and Hospital Surgery Department No.1, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: akmal.irnazarov1980@gmail.com

2 PhD, Specialist of the Endovascular Surgical Department, Multidisciplinary Clinic of Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: vali180978@gmail.com

3 Assistant lecturer of the Faculty and Hospital Surgery Department No.1, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: beknazarov.ilhomjon@gmail.com

4 Assistant lecturer of the Faculty and Hospital Surgery Department No.1, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: doc.karim0ff@gmail.com

5 Assistant lecturer of the Department of Obstetrics and Gynecology in Family Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: akmal.irnazarov1980@gmail.com

ABSTRACT

This paper describes the distribution and complications of venous thrombosis of deep veins of the lower extremities. It is emphasized that the main method of treatment for this pathology is surgical, namely endovascular. Endovascular treatment methods significantly reduce the risk of pulmonary embolism and the development of post-thrombophlebitic syndrome.

Key words: Deep vein thrombosis of lower extremities, pulmonary embolism, thrombolysis, thrombectomy.

INTRODUCTION

Epidemiology of deep vein thrombosis of the lower extremities.

Today, deep vein thrombosis (DVT) of the lower extremities is an urgent problem of modern medicine. The clinical picture, due to the fact that it is common

for DVT and pulmonary embolism (PE), is often “silent” and, therefore, is not diagnosed in time or is detected only at autopsy. Therefore, the incidence and prevalence of this disease are often underestimated.

The annual incidence of venous thromboembolism (VTE) is 0.1-0.27%, affecting up to 5% of the population during their lifetime. The risk of recurrent thromboembolism is higher in men than in women. It is believed that the annual incidence of DVT of the lower extremities is 80 cases per 100,000. About 900,000 cases of DVT are registered annually in the United States. Between 5% and 15% of patients with untreated DVT die from a pulmonary embolism. Venous thromboembolism occurs in almost every 2 cases per 1000 pregnancies and is the leading cause of maternal and morbidity mortality [23,25,30].

In Europe, the incidence of DVT of the lower extremities is detected in 4.8-9.6 people per 10,000 populations every year [24,28].

According to epidemiological data, VTE is characterized by a high recurrence rate: even in patients on anticoagulant therapy, the frequency of early recurrent episodes reaches 2% after 2 weeks from the manifestation of the first event, 6.4% - by 3 months, 8% - by 6 months and up to 25% - within 5 years. At the same time, the frequency of VTE relapses does not depend on the picture of the clinical manifestation of the first episode [29,37].

A third of patients with venous thrombosis develop PE. In the first month, mortality reaches up to 6% for DVT and 10% for PE, although autopsy studies show that the already high mortality rates are probably underestimated. Autopsy results have shown a mortality rate as high as 30% based on the observation that many PEs are not diagnosed at the time of death [9,11].

According to the results of the multicenter study ICOPER (Cooperative Pulmonary Embolism Registry) [26], the mortality of patients three months after the treatment was 17.4% [32].

S.A. Sushkov [20] in his study revealed the likelihood of PE in patients with floating thrombosis. In this case, the thrombus has one attachment point in the distal part, and in the proximal part - the area of the thrombus, the so-called embolus, sways freely in the bloodstream. To date, despite numerous developments in the search for a pathogenetic method for treating these complications, the issue of finding unified algorithms for the perioperative management of patients with embolism -prone DVT is also acute and is under active search by scientists [3,8].

Causes of acute venous thrombosis

The development of DVT of the lower limb depends on many factors, these include:

1) Age over 40 years.

2) Obesity.

3) Hospitalization in a hospital for the purpose of an operation or in case of a sudden exacerbation of a chronic disease.

4) Trauma and fractures of the lower extremities.

5) Pregnancy and postpartum period.

6) Bed rest (more than 3 days).

7) Air travel.

8) The use of oral contraceptives and hormone therapy.

9) Varicose veins of the lower extremities.

10) Oncological diseases.

11) Chronic heart failure.

12) Severe lung disease.

13) Postponed ischemic stroke.

14) Acute and chronic infections, sepsis.

15) Venous thrombosis in history or in close relatives in the direct line of kinship [1,13].

The development of deep vein thrombosis in relatively young people in the absence of obvious prerequisites may be the result of genetically determined disorders of hemostasis [18]. The combination of several risk factors leads to a significant increase in the risk of thrombosis.

Back in 1865, R. Virchow described a combination of pathological factors that are the main trigger for intravascular thrombus formation and are known as the triad Virchow. It includes changes in the properties of blood, injury to the vessel wall and slowing down the blood flow.

Thrombophilia. An important point in the development of DVT belongs to the phenomenon of thrombophilia [10,16]. At the XV International Congress on Thrombosis and Hemostasis (Jerusalem, 1995) and at the XIII meeting of the European and African Sections of the International Society of Hematology (Istanbul, 1996), the terms “thromboembolic syndrome” and “hypercoagulemia” were combined into a single concept of “thrombophilia”. This term currently means disorders of hemostasis and hemorheology, characterized by an increased tendency to develop thrombosis of blood vessels, which are based on acquired and genetically determined disorders in various parts of hemostasis and hemorheology [5,39]. The role of hereditary thrombophilia in the genesis of DVT has been actively investigated since 1993, when the Dutch scientist B. Dahlback discovered resistance of factor V of the blood coagulation system to the inactivating effect of active protein C in members of a Swedish family [36].

Clinical diagnosis of deep thrombosis veins of the lower extremities.

In the scientific literature, when DVT is suspected, an external examination with a detailed history of the disease, taking into account intrafamilial morbidity and assessing risk factors is recommended. Attention should be paid to complaints of patients, such as: swelling in the lower leg or the entire lower limb; pain in static and in the calf muscle in motion; a combination of pain with asymmetric edema, which serve as predictors of the development of DVT.

May-Thurner syndrome is characterized by compression of the left common iliac vein, overlying the right common iliac artery. Vibratory pulsation is believed to cause hyperplasia in response, in a compressed segment of the vein, followed by progressive stenosis. Due to the slow and chronic nature of this process, the stenosis becomes hemodynamically significant, the collateral veins to the contralateral iliac veins and the inferior vena cava enlarge over time. When blood flow in a vein slows down, spontaneous thrombosis can occur, especially if the patient has a risk factor for developing DVT such as increased blood clotting.

The literature emphasizes that each symptom alone provides an 11-22% chance of DVT [2,23]. However, cases of DVT without pronounced signs of the disease, that is, without characteristic symptoms, are not uncommon, especially in bedridden patients. Considering that PE is a possible sign of the development of DVT, experts recommend an analysis of the level of D-dimer in the blood as a diagnosis and/or exclusion of DVT [38]. The sensitivity index of a specific blood test for D-dimer is 96-100% [22,33].

Ultrasound imaging of the veins is the most important diagnostic test for lower extremity DVT. Duplex ultrasound imaging has a mean sensitivity and specificity of 97% and 94%, respectively, with mean positive and negative predictive values of 97% and 98% for symptomatic proximal DVT [12,15].

Contrast-enhanced venography also does not show pelvic veins due to contrast dilution in deep pelvic veins. Pelvic vein thrombosis has been reported in the literature, diagnosed in 1-4% of studies using venography or ultrasound imaging. The authors convincingly show that the use of these diagnostic methods underestimates the true prevalence of isolated pelvic vein thrombosis.

Unlike ultrasound imaging or enhanced venography, ***CT venography*** (CTV) and magnetic resonance venography better reflect the picture of blood flow in the inferior vena cava and pelvic veins, which has been proven by various large studies [34,42]. CT can be performed by direct injection of contrast into the femoral or cubital vein. CT can be recommended as a standard for diagnosing PE [34].

Treatment of venous thrombosis

The treatment of patients in this category is aimed at solving the problems formulated back in 1998 by S. Haas from the Institute of Experimental Surgery. The essence of the solution is:

1) prevent the development of PE;

2) limit thrombotic damage and prevent its transition to venous lines of a larger caliber;

3) restore venous blood flow;

4) to carry out the prevention of retrombosis.

An important component of the therapy of patients with venous thrombosis of the lower extremities is the complexity, and the standards of treatment should be optimal for a particular patient, since DVT of the lower extremities in the absence of optimal therapy in 10-20% has a threat in the development of clinically manifesting PE. The basis of therapy is the use of indirect and direct anticoagulants. The effectiveness of anticoagulants reaches 70-80% [27].

The mechanism of action of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) drugs on blood coagulation factors is similar, but there are differences in the pharmacodynamic properties, bioavailability and pharmacokinetics of the drugs. LMWHs have predominantly anti-Xa activity and inhibit thrombin directly to a lesser extent. LMWHs have a long half-life, in connection with which the frequency of their appointment is reduced to once a day [6,31].

In modern practice, clinicians tend to use direct oral anticoagulants. Warfarin is the most commonly prescribed oral anticoagulant for the treatment and secondary prevention of venous thromboembolism, is a vitamin K antagonist. The anticoagulant effect develops due to the ability of drugs to reduce the formation of vitamin K-dependent coagulation factors. But the range of their therapeutic effects is narrow, when used, increased monitoring of the degree of coagulation is required, and there is a negative interdrug effect [21].

Rivaroxaban is another oral reversible direct acting factor X inhibitor with a rapid onset of action and dose - proportional pharmacokinetics and pharmacodynamics. The drug is fast-acting with high oral absorption [7]. The course of treatment with Rivaroxaban for PE and DVT is carried out according to the standard scheme: 15 mg 2 times a day for 3 weeks, then 20 mg 1 time per day for a period set individually. This treatment protocol eliminates the need for continuous monitoring of laboratory parameters, as well as the selection and adjustment of the dose of the drug depending on the age and weight categories of the patient.

Thrombolytic therapy (TLT) is a type of pharmacological therapy aimed at restoring blood flow in a vessel due to the lysis of a thrombus within the vascular bed. In 1938, the isolation of the enzyme streptokinase by β-hemolytic streptococcus group A was proven. In 1940, the mechanism of action of the enzyme was described, based on its binding to plasminogen in the blood, leading to its conversion into its active form - plasmin.

Thrombolytics with the conversion of the inactive protein plasminogen into the active proteolytic enzyme plasmin. Plasmin, in turn, provides fibrin lysis. Thrombolytics (fibrinolytics) are drugs whose action is aimed at the destruction of blood clots. Unlike antiplatelet agents and anticoagulants, which lower blood viscosity and prevent blood clots, thrombolytics are able to dissolve already formed blood clots. Therefore, antiplatelet agents and anticoagulants are the prevention of blood clots, and thrombolytics are their treatment.

Currently, there are five generations of thrombolytic drugs:

The first generation is the enzymes that are found in nature. They change blood plasmin and favor the acceleration of the synthesis of plasminogen into plasmin. The fibrinogen activators of the first generation are fibrinolysin, streptokinase, urokinase, which paved the way for the use of these enzymes as thrombolytic agents to destroy the fibrin network with the problem of systemic bleeding. Fibrinolysin is the most abundant plasma protein. Its effectiveness is characterized by early application. Streptokinase is a single-chain polypeptide that exhibits an indirect fibrinolytic effect by activating the circulating zymogen plasminogen, is a microbial plasminogen activator secreted by several strains of β-hemolytic Streptococci, can cause anaphylactic reactions, so repeated administration is often impossible [14].

Fibrin -specific agents are ***second-generation drugs*** that have been artificially produced using selective and genetic engineering. Acting directly on blood clots. The almost absence of shortcomings makes these funds the most popular at the present time. Second-generation plasminogen activators have a targeted thrombolysis, as first generation plasminogen activators showed non-specific degradation of fibrin and caused systemic fibrinolysis with concomitant destruction of hemostatic proteins resulting in bleeding. Alteplase has such advantages as increased stability in plasma, increased half-life (90-105 minutes), improved fibrin binding and reduced administration time from 60 to 2 minutes, affects thrombus formation without affecting hemostasis, does not cause bleeding. Prourokinase - designed as a fibrinolytic agent, can mediate specific clot lysis in the presence of fibrin, leading to better patency without any significant increase in bleeding.

Improved recombinant activators - ***third generation*** thrombolytic drugs. The advantage of these drugs: a relatively long-term effect, as well as an improvement in the ability to find a blood clot. Third generation plasminogen activators have been developed to improve structural and functional properties such as longer half-life, resistance to inhibitors, safety and increased efficacy, and increased fibrin specificity. Their long clearance makes it easy to administer one or two doses of the drug up to 3 hours after the formation of a blood clot. Later administration of the drug is fraught with a violation of the degree of vascular patency with the impossibility of their restoration and preservation of the valvular apparatus. Reteplase - is characterized by complete, rapid and stable thrombolysis and long-term effect, it is mostly used in hemorrhagic stroke. Tenecteplase - used as a method of thrombolysis in myocardial infarction, it has increased pharmacological properties and a stable effect without significant bleeding.

The fourth generation of drugs has not been studied enough. Compared to previous generations, these means of combined action. The difference is a quick and intense effect on the thrombus.

The fifth generation is a combination of natural and recombinant active substances.

The most popular and widely used as thrombolytic therapy are drugs of the 2nd generation. The decisive arguments in their use are numerous studies, minimal side effects, and most importantly, the release by the pharmaceutical industry on an industrial scale.

In many clinical guidelines for the treatment of DVT, the active tactics of surgical and catheter methods of treatment in selected patients with the level of evidence are classified as class 2.

Regional catheter thrombolytic therapy allows to achieve a high concentration of the drug in the thrombus, use the introduction of small doses of fibrinolytics, which contributes to a significant reduction in hemorrhagic complications, treatment time. Any proposed regimen for the treatment of DVT aims for the fastest and most complete thrombolytic effect in the venous system, but in practice, as a rule, partial recanalization is detected rather than complete restoration of vein patency.

Surgical methods are aimed at restoring vein patency and thrombo -reduction, they can be performed both by traditional and rapidly developing endovascular methods. catheter technologies [38].

Currently, the main surgical methods include: application of NVC; thrombectomy; ligation of the femoral vein, which is due to many reasons [19].

Promising is the widespread introduction of the so-called hybrid technology, the essence of which is thrombectomy from the iliac-femoral segment, with stenting of the iliac vein with the imposition of a temporary arteriovenous fistula [4].

Meanwhile, surgical (direct) thrombectomy can be performed only through a wide laparotomic approach; it is technically complex, accompanied by significant surgical trauma, blood loss, and the risk of intraoperative thromboembolism. Prospects for effective treatment of this category of patients were opened by endovascular catheter thrombectomy after the installation of temporary cava filters [17,35].

Indications for endovascular treatment are: <14 days old lower extremity DVT, without severe comorbidities and phlegmasia.

Endovascular thrombectomy can be divided into two groups, depending on how the thrombus is removed - in its entirety or by aspiration of thrombotic masses after their disobstruction. And the use of modern devices for thrombectomy, rheolytic systems thrombectomy Angiojet, systems with ultrasound support, rotary aspiration devices show encouraging results and significantly reduce the time of the procedure [15].

There is a controversy in clinician circles about the search for an effective thrombolytic, the duration of its administration. There is also no consensus on the use of a temporary cavafilter during catheter-guided thrombolysis (Haig Y. et al., 2016). Some authors, when using it, show low invasiveness and safety of the installation, achieving positive results in terms of reducing complications (Gurman P. et al., 2015). In contrast, the data of other authors indicate that its use is ineffective; moreover, the risk of thromboembolic complications does not decrease with this method [42].

In the work of K. Ksirajan et al. in 17 patients on the Angiojet device thrombus lysis was achieved (>50%) in 59% of cases. R.L. Bush et al. (2018), presented complete and partial thrombus resolution in 65% and 35% of cases. Martinez Trabal. et al. achieved a positive result in 92% of the veins of the lower extremities. When comparing the results of fibrinolytic therapy in the hospital period of complex treatment according to the randomized clinical trial “ATTRACT” (2017), the picture is as follows: significant bleeding was in 1.7%. According to some authors, such as: N. Meneveau (1998), the maximum applied dose of streptokinase was 1.45 ml units. in 25 patients - 12%, S. Patra (2014) in 105 patients, the maximum dose of streptokinase was 2.65-5.05 ml units, bleeding was observed in 1.9% [40].

Thus, DVT and PE are the leading causes of morbidity and mortality worldwide, which are in the field of view of modern clinical medicine. The relevance and significance of this problem is expressed in the constant growth, the presence of thrombotic complications, in the "silent" course, which makes early diagnosis difficult. The available treatment and prevention protocols do not always lead to effective results, which requires further scientific research in this direction.

REFERENCES

1. Belova A.D. Evaluation of the effectiveness of outpatient and inpatient treatment of patients with thrombosis of the veins of the lower extremities. Ambulatory surgery: hospital -replacing technologies. - 2011. - No. 3/4. - S. 17-18.
2. Bokeria L.A., Zatevakhin I.I., Kirienko A.I. Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolic complications // Phlebology. - 2015. -T. 9, No. 4. - 42 p.
3. Borovsky S.P. Venous thromboembolic complications in patients with oncological pathology. View of the X-ray surgeon // Slavic venous forum: Mater. Intern. Congress (Vitebsk, May 28-29, 2015). - Vitebsk: VSMU, 2015. - P.94-95.
4. Ignatiev I.M., Akchurin F.R., Zanochkin A.V., Volodyukhin M.Yu., Bredikhin R.A., Khairullin R.N. Experience in the treatment of floating thrombosis in the system of the inferior vena cava // Journal named after Academician Petrovsky B.V. - 2015. - No. 3. - P.36-44.
5. Kirienko A.I., Panchenko E.P., Andriyashkin V.V. Venous thrombosis in the practice of a therapist and surgeon. - M.: Planida, 2012. -336 p.
6. Krivoshchekov E.P. Rivaroxaban in the treatment of acute vein thrombosis of the lower extremities // Slavic Venous Forum: Mater. Intern. Congress (Vitebsk, May 28-29, 2015). - Vitebsk: VSMU, 2015. - P.117-118.
7. Kurginyan Kh.M. Clinical cases of the effective use of rivaroxaban as a treatment for thrombotic complications in patients with oncological and systemic diseases.
8. Lobastov K.V., Barinov V.E., Schastlivtsev I.V., Laberko L.A. The Caprini scale as a tool for individual risk stratification of postoperative venous thromboembolism in a high-risk group. Khirurgiya. Journal them. N.I. Pirogov. - 2014. - No. 12. - P. 16-23.
9. Medvedev A.P., Nemirova S.V., Pichugin V.V., Shirokova O.R., Sobolev Yu.A. Open embolectomy in the treatment of massive pulmonary thromboembolism // Medical Almanac. - 2013. - No. 4 (28) - P. 35-37.

10. Momot A.P., Grigoryeva E.V., Panov M.Yu. et al. Predictors of venous thrombosis in medical thromboprophylaxis in orthopedics // Medicine and education in Siberia. - 2012. - No. 2. - From 45-50.

11. Muminov Sh.M., Akhmedov R.A., Kim D.L., Abdullaev Sh.M., Dadamyants N.G. Modern approaches in the diagnosis and treatment of thrombosis of the inferior vena cava system // Slavic Venous Forum. Mater. Intern. Congress. - Vitebsk, 2015. - S. 129.

12. Muminov Sh.M., Dadamyants N.G., Kim D.L. Database of color duplex scanning of patients with thrombosis of the veins of the lower extremities and pelvis // Certificate No. DG U 00322 on the official registration of the computer program dated 01/05/2016.

13. Muminov Sh.M., Khamidov B.P. et al. Immediate and long-term results of the treatment of thrombosis of the veins of the lower extremities and pelvis // Bulletin of Emergency Medicine. - 2018. - V.11, No. 2. - P.12-18.

14. Onuchin P.G., Nagovitsyn S.V., Motovilov M.A. thrombolysis urokinase and new oral anticoagulants in the treatment of patients with acute venous thrombosis. // Angiology and vascular surgery - 2015.- V.21, No. 2.- P.452-453.

15. Osiev A.G., Vishnyakova M.V., Gegenava B.B. Endovascular methods of treatment of pathology of the venous system // Almanac of Clinical Medicine. - 2015. - No. 43. - From 82-89.

16. Petrikov A.S., Shoikhet Ya.N., Belykh V.I., Kostyuchenko G.I. and others. Hyperhomocysteinemia and venous thromboembolic complications // Phlebology. - 2012. - No. 1. -S. 14–18.

17. Prozorov S.A. Complications observed during the implantation of cava filters and at different times after it. Indications for removal of kava filters. (literature review) // X-ray surgical methods of diagnosis and treatment. - 2016. - No. 45. – C.38-44.

18. Sadikova Sh.E., Muminov Sh.M., Abdullaev Sh.M., Shamsutdinova D.B. Molecular analysis of polymorphisms of the M T HFR, FV and FII genes in patients with deep vein thrombosis of the lower extremity // Bulletin of Hematology. - St. Petersburg, 2013. - V.9, No. 2. – From 45-51

19. Soroka V.V., Andreichuk K.A. Clinical recommendations (protocol) for the provision of emergency medical care for acute venous thrombosis. - M., 2014. - C. 10-11.

20. Sushkov S.A. et al. A differentiated approach to the treatment of patients with floating deep vein thrombosis of the lower extremities // Kharkov School of Surgery. - 2016. - No. 1 (76). - P.7-14.

21. Khruslov M.V. Efficiency of the system of centralized monitoring of INR in patients taking warfarin for venous thrombosis // Phlebology. - 2013. - No. 4. - P. 52-56.

22. Shulgina L.E. etc. Ultrasonic angioscanning and the level of D - dimer in the diagnosis of deep vein thrombosis in patients with central paresis and paralysis // Phlebology.- 2014. - V.8, No. 2.- P.104.

23. Beckman MG, Hooper WC, Critchley SE et al. Venous thromboembolism. A public health concern // Am. J. Prevent. Med. - 2010. - Vol. 38, Suppl. 4. – P.495–501.

24. Cuker A., Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia // Blood Adv. - 2018. - Vol.2, No. 22. - R.3360 - 3392.

25. Fowkes FGR Epidemiology of venous disorders. Venous and lymphatic diseases. - Elsevier, 2007. - P. 15-25.

26. Goldhaber S. Z., Visani L ., De Rosa M . Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER) // Lancet. - 1999. - Vol. 353, No. 9162. - R. _ 1386-1389.

27. Haas S. Management of venous thromboembolism // Hamostaseologie. - 1998. - Vol. 18. - P. 18-26.

28. Heit JA Predicting the risk of venous thromboembolism recurrence // Am. J. Hematol. - 2012. - Vol.87, Suppl 1. - R.63–67.

29. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden // Thromb. Res. - 2014. - Vol. 134. - P. 931-938.

30. John A., Heit1 Frederick A., Spencer Richard H. The epidemiology of venous thromboembolism // J. Thromb. Thrombolysis. - 2016. - No. 41. - R.3-14.

31. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients // Cochrane Database Syst Rev. - 2017. - N4. – CD 007557.

32. Kasper W., Konstantinides S., Geibel A., Olschewski M. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry // J. Am. Coll. Cardiol. - 997. - Vol. 30, no. 5. - R.1165-71.

33. Kelly J., Hunt BJ Role of D-dimers in diagnosis of venous thromboembolism // Lancet. - 2002. - N 359. - P.456-8.

34. Montgomery KD, Potter HG, Helfet D L. Magnetic resonance venography to evaluate the deep venous system of the pelvis in patients who have an acetabular fracture // J. Bone Joint Surg. Am. - 1995. - N77. –P.1639-49.

35. Othieno R., Okpo E., Forster R. Home versus in-patient treatment for deep vein thrombosis // Cochrane Database Syst Rev. - 2018. - No. 1. - CD003076.

36. Price DT, Ridker PM Factor V Leiden mutation increases risk for thromboembolism // Ann. Intern. Med. - 1997. - Vol. 127. - P. 895-903.

37. Schulman S., Lindmarker P., Holmstroom M. et al. Post-thrombotic syndrome, recurrence, and death 10 years after the fist episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months // J. Thromb. haemost. - 2006. - Vol.3. – P.734-742.

38. Schutgens RE, Ackermark P., Haas FJ, Nieuwenhuis HK, Peltenburg HG, Pijlman AH et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis // Circulation. - 2010. - Vol.107. – P.593-7.

39. Shaheen K., Ageno W., Bozzato S. et al. Role of factor V Leiden or G20210Aprothrombinmutation in patients with symptomatic pulmonary embolism and deep vein thrombosis: a meta-analysis of the literature // J. Thromb.Haemost. - 2012. - Vol. 10(4). - P. 732-737.

40. Sharifi M., Freeman W., Bay C. et al. Low incidence of post-thrombotic syndrome in patients treated with new oral anticoagulants and percutaneous endovenous intervention for lower extremity deep venous thrombosis // Vasc. Med. - 2015. - Vol. 20, No. 2. - P. 112–116.

41. Vedantham S., Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ at al. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis // The new england journal of medicine. - 2018. -N27. – P.2240-2252.

42. Witt DM, Nieuwlaat R., Clark NP et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy // Blood Adv. - 2018. - Vol.2, No.22. - P.3257 - 3291.