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VENOUS THROMBOSES AND THROMBOEMBOLISM IN ONCOLOGY PATIENTS

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ABSTRACT

Deep vein thrombosis and pulmonary artery thromboembolism are the most commonly occurring cardio-vascular complications of oncological diseases, which may develop at any stage of the oncological process. These life-threatening complications take the leading positions within the structure of mortality among cancer patients, giving place only to the oncology disease itself. It is important to note that the patients with cancer-associated thromboses are the most difficult group of patients, in which the development of thromboses and thromboembolisms may not only delay the vitally important treatment of the main disease, but also to completely cease the treatment due to the lack of possibility for its adequate performing. This is an important social and economic task, taking into consideration the costs for the healthcare system required to treat the disease itself and its concomitant complications. Thus, there is a criticality factor of not only the treatment itself, but also of the prevention of oncology-associated thromboses and thromboembolisms. Currently, due to the wide spreading of the said complications, the therapy and the prevention of them undergo significant changes. The traditionally used warfarin is being switched to low molecular weight heparin. At the present moment, oral anticoagulants are used more and more often. The analysis of special scientific literature has allowed for evaluating the novel principles of treatment in cases of oncology-associated thromboses and thromboembolisms depending on the location of the process, on its stage, on the severity of the patient status, as well as to define the risk factors of oncology-associated thromboses, the practicability and possible methods of its prevention in various groups of patients.

Keywords: *deep vein thrombosis; pulmonary embolism; cancer-associated thrombosis.*

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BACKGROUND

Deep vein thrombosis and pulmonary artery thromboembolism are the most frequent cardio-vascular complications of oncological diseases, which may occur at any stage of tumor development [1, 2]. Thromboses, both venous and arterial, as well as the embolisms related to them, represent the second major cause of mortality among the oncology patients right after the complications related to cancer diseases. Venous thromboembolisms may precede the oncology disease or may occur at any stage of cancer development or even at the stage of its successful treatment [2, 3].

Thromboembolism affects the course of the oncology disease, compelling to pause or delay the vitally important anti-tumor therapy [4, 5]. The rate of venous thromboembolisms in oncology patients is 4–7-fold higher than in healthy individuals [6]. The improvement of the survival rate in oncology patients results in an increase in the rates of venous thromboembolisms, first of all, due to the extension of the survival among the oncology patients, secondly, due to the wide use of central venous catheters/ports and the increased rates of thromboses caused by them.

It is also important to note that the diagnostics of oncology-associated thromboses has become widely accessible [7]. In general, patients with oncology-associated thrombosis represent a more severe group of cancer patients: the morbidity levels among them are significantly higher comparing to the individuals of the same age and gender without oncology diseases [8]. About 15% of the patients with oncology diseases develop venous thromboembolisms and, on the contrary, 20% of non-induced venous thromboembolisms may be the first signs of malignant neoplasms [9]. Arterial thromboses and ischemic heart disease also occur more often among the oncology

ВЕНОЗНЫЕ ТРОМБОЗЫ И ТРОМБОЭМБОЛИИ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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АННОТАЦИЯ

Тромбоз глубоких вен и тромбоэмболия лёгочной артерии — наиболее часто встречающиеся сердечно-сосудистые осложнения онкологического заболевания, которые могут возникать на любой стадии онкологического процесса. Эти жизнеугрожающие осложнения занимают лидирующие позиции в структуре смертности у онкобольных, уступая место только самому онкозаболеванию. Необходимо заметить, что пациенты с онкоассоциированными тромбозами — это наиболее тяжёлая группа больных, у которых возникновение тромбозов и тромбоэмболий может не только отсрочить жизненно важное лечение основного заболевания, но и полностью исключить его ввиду невозможности проведения адекватной терапии. Это важная социальная и экономическая задача, учитывая затраты здравоохранения на лечение самого заболевания и сопутствующих осложнений. Таким образом, остро стоит вопрос не только самого лечения, но и профилактики онкоассоциированных тромбозов и тромбоэмболий. В настоящее время в связи с распространением данных осложнений лечение и профилактика претерпевают большие изменения. Традиционно использовался варфарин, на смену которому пришёл низкомолекулярный гепарин. На данный момент всё чаще используются пероральные антикоагулянты. Анализ специальной научной литературы позволил оценить новые принципы лечения онкоассоциированных тромбозов и тромбоэмболий в зависимости от локализации процесса, его стадии, тяжести состояния пациента, а также определить факторы риска онкоассоциированных тромбозов, целесообразность и возможные методы их профилактики в разных группах пациентов.

Ключевые слова: *тромбоз глубоких вен; тромбоэмболия лёгочной артерии; онкоассоциированные тромбозы.*

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patients comparing to the groups of individuals comparable by age but with no cancer diseases [10]. Venous thromboembolism in case of cancer is not limited to the deep vein thrombosis and pulmonary artery thromboembolism. There are also the so-called atypical thromboses in the veins of the upper limbs and of the visceral organs [11].

PREVENTION AND TREATMENT OF ONCOLOGY-ASSOCIATED VENOUS THROMBOSES: NEW TREATMENT SCHEMES, APPROACHES AND STRATEGIES

New trends in the treatment of oncology-associated thromboses

Anticoagulant therapy, primarily with low molecular weight heparins, was and still remains the basics of therapy for venous thromboembolisms. However, in recent years, a clear shift can be seen towards the use of direct oral anticoagulants in oncology patients with venous thromboembolisms. Large-scale randomized clinical trials in oncology patients with deep vein thrombosis, aimed for primary and secondary prophylaxis of pulmonary embolism, have demonstrated a comparable degree of safety and not lesser efficiency of low molecular weight heparins or vitamin K antagonists in secondary prophylaxis of pulmonary embolism and deep vein thrombosis. The heads of the professional communities of the Western countries, as well as the Russian Society of Cardiology have recently changed their approach to primary prevention and to the treatment of deep vein thrombosis and pulmonary embolism in oncology patients [12–16].

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Risk factors of venous thromboses and pulmonary embolism in oncology patients

A number of risk factors of venous thromboembolism, for example, age, smoking, obesity, inactive lifestyle, arterial hypertension and diabetes mellitus, are related to the patient [17]. Other risk factors are related to the type and the location of the oncology process. As it is shown in table 1, some types of antitumor therapy also increase the probability of developing thrombi [18].

The age is a risk factor of venous thromboembolism both in patients with malignant neoplasms [20] and in the general population. In one retrospective research, the patients aged above 70 years and receiving chemotherapy, had an increased risk of developing venous thromboembolism comparing to younger patients (11% versus 6%) [21]. The functional status of the patients is also important: the decreased working capacity due to hypodynamia can increase the risk of venous thromboembolism [2].

Hereditary trombophilia is a significant risk factor that increases the probability of venous thromboembolism in oncology patients. The presence of a rare genetic risk factor, such as the deficit of antithrombin, of protein C, of protein S or of the factor V Leiden, increases the risk of venous thromboembolism at the young age [22]. Concomitant diseases, such as chronic pulmonary and renal diseases, anemia, infections and obesity — all of these increase the risk of venous thromboembolism in oncology patients 1.5-fold [20]. Finally, oncology patients with a past medical history of venous thromboembolism have 6 to 7 times higher risk of repeated venous thromboembolism comparing to cancer patients without venous thromboembolism [23].

Tumor location also affects the rate of venous thromboembolisms. The tumors located in the brain and in the pancreatic gland, are associated with the highest risk of pulmonary embolism [24]. Cancers of the stomach, esophagus, ovaries and lungs are also associated with high risk of deep vein thrombosis and pulmonary embolism. Especially dangerous are the hemoblastoses, the non-Hodgkin lymphomas and multiple myelomas [18]. The risk of venous thromboembolism increases upon regional or metastatic spreading of the malignant tumor [25], and the number of such patients is constantly increasing. About 50% of the patients with venous thromboembolism at the time of diagnosis already have metastases. The highest risk of deep vein thrombosis is reported during

Table 1

Risk factors for venous thromboembolism in cancer patients (modified from source [19])

Risk factors	
Related to the patient	Demographic data: elderly age, female gender Obesity Smoking Low physical activity Concomitant diseases (ischemic heart disease, hypertensive disease, atrial fibrillations, atherosclerosis, cardiac insufficiency, infectious diseases, sepsis, diseases of kidneys and liver, lung diseases, systemic diseases, diabetes mellitus) Past history of venous thromboembolism Hereditary trombophilia Number of platelets before therapy: ≥350×10^9/l, number of leucocytes before therapy: >11×10^9/l, hemoglobin level <100 g/l
Related to the oncology disease	Primary focus of cancer (lungs, colon/rectum, stomach, pancreatic gland, ovaries, prostate gland, urinary bladder, kidneys, brain, lymphoma, myeloma) Histogenesis of the tumor (adenocarcinoma) Malignant neoplasm stage: late stage of the tumor process, metastatic process Time from the inset of the diseases: more often during the first 3–6 months of the disease Significant enlargement of regional lymph nodes with the compression of adjacent vessels
Related to therapy	Major surgery Hospitalization Chemotherapy and anti-angiogenic medications Hormonal therapy Blood transfusions Medicinal products stimulating the erythropoiesis Presence of central vein catheter

the first 3 months after setting the adenocarcinoma diagnosis, while the probability of deep vein thrombosis eventually becomes slightly decreased. Nevertheless, when comparing the population of oncology patients to the comparable group of population not having cancer diseases, the risk of venous thrombosis in oncology patients remains increased all the time (from the moment of setting the diagnosis to 15 years of follow-up) [26].

Factors of deep vein thrombosis and pulmonary embolism, related to the treatment

Sadly, but the probability of venous thromboembolism also increases with a background of successful treatment for malignant diseases. Surgical interventions, some types of antitumor therapy and other therapeutic procedures can result in venous and arterial thromboembolisms. Minor pelvis and abdominal surgeries in oncology patients increase the risk of postoperative deep vein thrombosis and pulmonary embolism 2–3-fold comparing to the patients without oncological diseases and with similar interventions [27–30]. Systemic chemotherapy increases the risk of venous thromboembolism by a factor of 2–6 [31]. It was found that Cisplatin therapy doubles the risk of thromboembolic complications comparing to Oxaliplatin in patients with stomach and esophageal cancer [32]. Immunomodulating medicines used for multiple myeloma (Thalidomide, Lenalidomide), increase the risk of venous and arterial thromboembolisms [33], while the medicinal products suppressing the angiogenesis, such as Bevacizumab, containing monoclonal antibodies against vascular endothelium growth factor receptors (VEGFR), increase the risk of developing arterial thromboembolisms [34, 35]. Targeted therapy agents Sorafenib and Sunitinib increase the risk of thromboses [36]. Immune checkpoint inhibitors also increase the risk of both venous and arterial thromboembolism due to the cellular type of immune response, due to the expression of inflammatory cytokines and due to complement-mediated inflammation [37]. Supporting therapy with Erythropoietins, blood transfusions, often so necessary for oncology patients, also promote to developing venous thromboses in them [38].

Laboratory markers of oncology-associated thromboses

Some biomarkers indicate the increased risk of oncology-associated thromboses. High degree leukocytosis/thrombocytosis and low hemoglobin levels before chemotherapy increase the risk of venous thromboembolism [39]. These tests that are available in practice can be successfully used for the purpose of defining the probability of venous thrombosis [40].

D-dimer, a small fragment of the protein produced upon the degradation of fibrin, was investigated as a prognostic biomarker of venous thromboembolism in cases of oncology disease. High D-dimer levels were associated with elevated risk of venous thromboembolism [41]. It is worth noting that D-dimer levels often become elevated in oncology patients, even without the thrombosis: the levels are variable from one laboratory to another, and there is no general consensus on what levels of D-dimer can be considered an indicator of high risk of thrombosis.

Other molecules were also studied, including the P-selectin and the microparticles forming the tissue factor, along with their potential role in predicting venous thromboembolism. P-selectin was integrated into the risk assessment models together with the clinical factors [42]. As of today, the research works on the evaluation of the prognostic benefits of tissue factor microparticles show controversial results, and, in clinical practice, the risk scales are more commonly used.

Predicting the risk of venous thromboembolism using risk scales

It is very important to determine in advance, which patients with oncology diseases are subject to the highest risk of venous thromboembolism. For this purpose, the venous thromboembolism risk assessment models were developed [43]. The first and the most popular risk assessment model for venous thromboembolism in out-patient oncology patients was proposed in the research works headed by A.S. Khorana [39, 44]. The Khorana scale was developed based on the analysis of the data from 2701 patients, while its benefits were confirmed during the retrospective and prospective research works with the participation of more than 35,000 patients [45]. This scale was based on using 5 variables, such as the type of oncological disease, the values of clinical hematology panel parameters (hemoglobin, platelets and leucocytes) and the body mass index, which need to be evaluated before the initiation of chemotherapy. Each variable had a single point assigned, except for the high risk subclass, to which 2 points were assigned. The Khorana scale remains an instrument for risk assessment, which was included into practically all the recommendations.

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The novel research works show that using the Khorana scale can be useful for early detection of venous thromboembolism using ultrasound diagnostics. Despite this fact, currently, the international guidelines do not include this aspect, while in one of the multicenter research, the venous thromboembolism was detected in about 9% of the patients from the high risk group (>3 points of the Khorana scale) [46].

During the pilot research, it was shown that electronic alerting can be useful for early detection of deep vein thrombosis and may prevent hospitalization [47].

The evaluation of the risk of developing cancer-associated thromboses using the Vienna system, besides the five parameters mentioned above, also includes the levels of D-dimer and soluble P-selectin, which has increased the predicting value of the system, however, independent clinical trials have not confirmed it [42].

As for the arterial thromboses and embolisms, currently there is no verified instruments for risk assessment and predicting the arterial thromboembolisms in oncology patients.

Prophylaxis of venous thromboembolism in oncology patients during surgical intervention

Surgical intervention is a well-known risk factor for venous thromboembolism in oncology patients when compared to the patients without oncology diseases, undergoing surgical treatment [48]. All the patients with active malignant neoplasms with a past history of major surgical interventions, must receive medicinal prophylaxis of venous thromboembolism. The postoperative prophylaxis of thrombosis at the In-Patient Department is a currently accepted standard. But, in oncology patients, the risk of thrombosis is increased and, after the discharge from the in-patient department, the prolongation of thrombosis prevention in such patients at the out-patient phase would be logical. Several research works have studied the efficiency of prolonged anticoagulant therapy (up to 4 weeks) comparing to the intrahospital prevention of venous thromboembolisms (for 7 to 10 days) in oncology patients after surgery. The results have demonstrated a significant — from 12 to 4.8% (by 60%) — decrease in the rate of venous thromboembolism when using the prolonged prevention, with the risk of major hemorrhages and of fatal outcomes not being increased [49]. On that basis, the current standards of therapy from the American Society of Clinical Oncology (ASCO) recommend all the patients with malignant diseases scheduled for major surgical intervention, to use the pharmacological prevention of thromboses or unfractionated heparin at a dosage of 5000 U within 2 to 4 hours before surgery and every 8 hours after surgery, or low molecular weight heparin at a dosage of 40 mg from 10 to 12 hours before surgery and then 40 mg once daily after surgery in the absence of contraindications (active hemorrhage, risk of major hemorrhage and other contraindications).

The prevention of venous thromboembolism should be continued for 7 to 10 days. In high risk patients, for example, with restricted mobility, obesity, past episode of venous thromboembolism or in case of other additional risk factors, prevention of venous thromboembolism should be continued for up to 4 weeks after surgery. For patients with low risk level, the decision on the duration of the prophylaxis of venous thromboembolism shall be drawn up on an individual basis [12].

In some other recommendations, prolonged prophylaxis of venous thromboembolism after discharge from the in-patient department was also approved for up to 4 weeks for oncology patients with a history of major surgery in the abdominal cavity or in the minor pelvis [14, 16]. Practically all the recommendations for prolonged prophylaxis, as well as for the intrahospital prophylaxis, suppose the use of low molecular weight heparins.

Prophylaxis of venous thromboses in hospitalized oncology patients

Among the hospitalized patients with malignant neoplasms, a lot of concerns remain unclear regarding the issues of primary prevention of thrombosis, despite the fact that the interrelation between the oncology disease and the venous thrombosis is well known. According to the register of deep vein thrombosis in the USA, hospitalized patients with malignant neoplasms less often receive preventive treatment of venous thromboembolism comparing to other patients without oncology diseases (28% versus 35%). The main reasons include the active hemorrhage, the concerns on possible hemorrhages or thrombocytopenia [50].

As of today, there are no ideal medications and optimal schemes for preventing venous thromboembolisms among hospitalized oncology patients. J.I. Zwicker et al. [51] have confirmed the high efficiency of fixed dosages of Enoxaparin used for the prevention of deep vein thrombosis and have demonstrated that thrombo-prophylaxis with low molecular weight heparins with taking into consideration the weight of the patient is effective and safe.

For the purpose of the optimal prophylaxis of venous thrombosis, various scales are used, one of which is the Padua scale. In this scale, the maximum of 3 points is assigned in case of an active oncology disease and previous venous thromboembolism. In case of decreased mobility and the presence of known trombophilia, according to this scale, the risk grade is 2 points. One point is assigned in case of having a recent trauma and/or surgery (within a time period of 1 month), in case the patients are aged 70 years and older, in case of having a cardio-vascular disease or infectious/rheumatic disease, obesity (body mass index >30 kg/m^2) or concomitant hormonal therapy [52].

Sadly, despite the fact that all the abovementioned systems of estimation include the diagnosed oncology diseases, they do not take into account the risk probability depending on specific types of tumors. Besides, the analysis of literature sources shows that the preventive dosages of low molecular weight heparins, which are being ubiquitously used (Enoxaparin 40 mg; Dalteparin 5000 ME; Fondaparinux 2.5 mg), may be insufficient for decreasing the total rates of venous thromboembolisms and may be non-optimal for high risk groups of patients [53]. The capabilities of the Khorana scale to predict venous thromboembolisms in hospitalized patients were demonstrated during the retrospective research [54], where it was shown that higher benefits of preventing venous thromboembolisms were observed in patients with high Khorana indexes. However, it is quite evident that the existing scales are not comprehensive and there is a need for further research works on the implementation of risk assessment systems into clinical practice for hospitalized and out-patient oncology patients.

The duration of the prevention of venous thromboembolisms in oncology patients after hospitalization is also not yet defined conclusively. As shown by the EXCLAIM research (extended prophylaxis of venous thromboembolisms in patients with acute diseases and immobilization), the prolongation of anti-thrombotic prophylaxis for up to 28 days (comparing to standard 10 days) results in a statistically significant increase in the risk of hemorrhages with no additional decrease of the rates of venous thromboembolisms [55].

Despite the absence of specific data, also acknowledging the high risk of venous thromboembolisms in hospitalized oncology patients, the current recommendations from the professional societies, such as the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH), extrapolating the knowledge obtained during the research on the prevention of thromboses in patients with somatic diseases, include the following:

- in the absence of contraindications in the hospitalized patients with active malignant neoplasm and acute disease (cardiac insufficiency, acute respiratory disease with chronic pulmonary disease, acute infection, acute rheumatic disease and inflammatory intestinal disease), or in cases of their decreased mobility, the prescriptions shall include pharmacological prevention of venous thromboembolisms;
- the routine pharmacological prophylaxis of venous thromboembolisms is not indicated to patients admitted for undergoing minor procedures or chemotherapy, as well as to patients receiving administrations of stem cells or bone marrow transplantation [12, 16].

Prophylaxis of thrombosis in the out-patients with oncology diseases

Up to 74% of all the venous thromboembolisms related to cancer, occur exactly during the out-patient period [56]. The retrospective analysis of the medical insurance reports from the IMPACT (USA), conducted by G.H. Lyman et al. [57], indicates that the joint rate of venous thromboembolisms within 3.5 months from the initiation of chemotherapy is 7.3%, while in 12 months it reaches 13.5%. The rate of venous thromboembolisms varies significantly depending on the location of the oncology process and on the stage of diseases [57].

In the 1990-s, for the first time, the results were published on the thrombo-prophylaxis in oncology patients, and its was shown that the use of low Warfarin dosages in women with metastatic breast cancer results in a decrease of the relative risk of venous thromboembolism by 85%, with this, no increase was noted in the rate of hemorrhages comparing to the control group of patients [58]. Quite recently, several research works were carried out, devoted to the thrombo-prophylaxis in the out-patient settings among the patients with malignant neoplasms (pancreatic cancer and multiple myeloma), including the patients with high risk of venous thromboembolisms. During the PROTECHT trial (prophylaxis of thromboembolic during chemotherapy) [59], the participants included the patients with lung cancer, breast cancer, gastrointestinal tract cancers, as well as with the malignant tumors of the head /neck area and ovaries. The patients, according to the randomized sample,

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were receiving Nadroparin (3800 U) subcutaneously or placebo: venous thromboembolisms in patients of high risk group were reported in 4.5% and 11.1% of the cases, respectively. As for the rate of hemorrhages, the groups did not differ. Similar results were observed in the SAVE-ONCO research (Semuloparin for thromboprophylaxis in patients, receiving chemotherapy due to the presence of cancer), in which the patients with any metastatic or locally spreading solid tumor, receiving chemotherapeutic agents, were randomized into two groups, one of which was receiving the low molecular weight heparin Semuloparin, while the other group was receiving placebo. The research have demonstrated a significant decrease in the rate of developing venous thromboembolism in patients of the Semuloparin group without increasing the rate of serious hemorrhages [60]. The subgroup analysis of the data obtained in this research have shown that, for preventing a single case of thrombosis, it is sufficient to treat 25 patients from the high risk group.

In a recently updated Cochrane review [61] it was noted that primary thromboprophylaxis using low molecular weight heparins allows for significantly decreasing the rates of symptomatic venous thromboembolisms among the out-patients with oncology diseases, receiving chemotherapy. If the anticipated risk of venous thromboembolism is 7.1 per 100 patients, this means that 30 patients need to be treated in order to prevent a single thromboembolic event. These results once again confirm the necessity of stratifying the risk of thromboembolism in oncology patients for defining the groups of patients, in which the benefit significantly overweighs the risks of hemorrhages.

The benefits of anticoagulant therapy were proven during the research works in groups of patients with tumors showing high thromboembolic risk [62, 63]. The benefits of thromboprophylaxis were also reported in patients with multiple myeloma. In one of the research, a comparison was made of the efficiency and of the safety of thromboprophylaxis with low-dose aspirin or low molecular weight heparins in patients with newly diagnosed multiple myeloma, receiving Lenalidomide therapy. A decrease was shown in the rate of venous thromboembolism without serious hemorrhagic complications when using both the low molecular weight heparins and the aspirin [5]. Multiple myeloma is the only group of malignant neoplasms, in which it is justified to use aspirin for the prevention of venous thromboembolism.

Direct oral anticoagulants, especially factor Xa inhibitors, such as Apixaban, Rivaroxaban and Edoxaban, are well studied in patients with oncology diseases. Currently, three factor Xa inhibitors were approved by the regulating authorities in Europe and USA for the treatment of oncology-associated thromboses (in Russia — only Apixaban and Rivaroxaban). But the factor Xa inhibitors, or xabans (from the English Xa), were not certified for primary prophylaxis of venous thromboembolism, except for orthopedic surgery or some clinical situations. The dosage modes for factor Xa inhibitors for the prevention and treatment of venous thromboembolism are provided in table 2.

Data on the efficiency and safety of xabans during the primary prophylaxis of venous thromboembolism in oncology patients have been obtained at the beginning of 2019, when data became available from two large randomized controlled researches — CASSINI (Rivaroxaban for thromboprophylaxis in out-patients with cancer assigned to the high risk group) and AVERT (Apixaban for the prevention of venous thromboembolism in cancer patients), where the efficiency and the safety of xabans was evaluated for thromboprophylaxis in out-patients with active oncology disease and with high risks of venous thromboembolism. In general, both research works have shown the benefits of using direct oral anticoagulants in oncology patients for the purpose of primary prevention, which, however, is mitigated by the increased risk of hemorrhages. For the purpose

Table 2

Therapeutic and prophylactic doses of direct oral anticoagulants [19]

Drug	Dosage	
	Preventive	Therapeutic
Apixaban	2.5 mg twice daily	Initial dosage — 10 mg 2 times/day, 7 days, then 5 mg twice daily
Rivaroxaban	10 mg once daily	Initial dosage — 15 mg 2 times/day, 21 days, then 20 mg once daily
Edoxaban	Not used	60 mg/day, at least after 5 days of therapy, with low molecular weight heparin

of defining the role of direct oral anticoagulants in the primary prophylaxis of deep vein thrombosis and pulmonary embolism in oncology patients, further research is required. It must be stressed that the prescription of anticoagulants based only on the increase in the level of D-dimer, is insufficiently justified.

Summarizing the accumulated experience and the currently available international recommendations, the following can be summed up:

- the routine pharmacological prophylaxis is not indicated to all the patients with oncology diseases;
- the out-patients with oncology disease of high risk group (≥2 points of the Khorana scale before the initiation of chemotherapy) can be a justified group for using thromboprophylaxis with Apixaban, Rivaroxaban or low molecular weight heparins: the decision on the use of anticoagulants should be conferred with the patient taking into consideration the benefits and harms, the cost of medicinal products and the therapy duration;
- patients with multiple myeloma, receiving Talidomide or Lenalidomide (in combination with dexamethasone), shall receive thromboprophylaxis with Aspirin or low molecular weight heparin in case of low risk and with low molecular weight heparin in high risk situations [12, 16].

Treatment and secondary prophylaxis of venous thrombosis and pulmonary embolism: the choice of therapy and therapy duration

The correct treatment for venous thromboembolism in oncology patients is critically important, for both the recurrent venous thromboembolisms and the hemorrhages negatively affect the survival [5]. Currently, there are various available variants for antithrombotic therapy for oncology patients with thromboses. Traditionally, for the treatment of oncology-associated venous thromboembolism, Vitamin K antagonists were used. Low molecular weight heparins are superior comparing to vitamin K antagonists by the efficiency and the safety, and they still remain the main means for the treatment of thromboembolic events in oncology patients within the two last decades. The foundational CLOT research (comparison of low molecular weight heparins and Warfarin in cases of venous thromboembolism) was carried out in patients with oncology diseases and with acute symptomatic venous thromboembolism, compellingly proving the superior efficiency of low molecular weight heparins versus vitamin K antagonists during the long-term (6 months) treatment [64]. During the treatment period of 6 months, 8.0% of the patients in the Dalteparin group had recurrences of venous thromboembolisms, while in the group receiving vitamin K antagonists, recurrences of venous thromboembolisms were reported in 15.8% of the cases (p=0.002). No significant difference was found between the two groups in terms of the rate of any types of hemorrhages.

In a later CATCH research (comparison of hemostasis treatment methods in cancer patients), comparison was made of treatment results obtained with using low molecular weight heparin Tinzaparin at a dosage of 175 IU/kg once daily for 6 months and with using the treatment with Tinzaparin, initially for 5 to 10 days with further transition to Warfarin with achieving the target INR levels (international normalized ratio) of 2–3. Just like in the CLOT research, the rate of venous thromboembolisms has decreased from 10% in the Warfarin group to 6.9% in the Tinzaparin group, though the results were not statistically significant (p=0.07). The occurrence rate of serious hemorrhages was similar in both groups, while the rate of minor hemorrhages was significantly lower in the Tinzaparin group (11% and 16%; p <0.03) [65].

Based on the data from the CLOT research [64] and from the Cochrane review [66], international associations recommend low molecular weight heparins as the first line therapy for short-term and long-term therapy of oncology-associated venous thromboses and pulmonary embolism [12, 14]. However, such a therapy is not always applicable: frequent subcutaneous injections are the evident impediment for following the correct treatment mode. Besides, the presence of renal failure and the cost of low molecular weight heparins restrict the possibilities of their wide use. In real-life clinical practice, vitamin K antagonists are still often used in oncology patients with venous thromboses, taking into consideration the simplicity of oral intake and the relatively low cost, despite the fact that they are not recommended as the preferable treatment for oncology-associated venous thromboembolisms [67].

Currently, direct oral anticoagulants are recommended as the first line therapy in patients with deep vein thrombosis and pulmonary embolism without oncological diseases. Up until recently, their use in cases of oncology-associated thromboses was not recommended, however, the results of three research works on the direct comparison of direct oral anticoagulants and low molecular weight heparins became widely accessible. The HOKUSAI-VTE

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research (Edoxaban for the treatment of venous thromboembolism, associated with cancer) had randomized 1050 patients with oncology diseases and with acute symptoms or accidentally diagnosed venous thromboembolisms. One group was receiving Edoxaban (at a daily dosage of 60 mg) after the initiation of therapy with low molecular weight heparin — Dalteparin, while the comparison group continued Dalteparin therapy for 6 to 12 months. The follow-up duration was 9 months [6]. The main endpoint (cases of first repeated venous thromboembolism or major hemorrhage within 12 months) was observed in 12.8% of the patients in the Edoxaban group and in 13.5% in the Dalteparin group (OP=0.97; p=0.006). Edoxaban was not inferior comparing to Dalteparin in terms of anti-thrombotic efficiency regardless of the therapy duration (OP=0.97; p=0.006 for non-inferiority). By the recurrence rates of venous thromboembolisms, the groups of Edoxaban and Dalteparin did not differ (7.9% versus 11.3%; p=0.09), while the rate of major hemorrhages was higher when taking Edoxaban comparing to Dalteparin (6.9% versus 4.0% respectively; p=0.04). Hemorrhages were especially often observed in patients with gastrointestinal tract cancers (12.5% versus 3.6%; p=0.005).

The proofs of efficiency of direct oral anticoagulants were also obtained in the randomized SELECT-D research [68], in which 406 patients with symptomatic or asymptomatic venous thromboembolisms were randomized to receive Rivaroxaban (with a dosage of 15 mg twice daily for 3 weeks with further transition to 20 mg once daily) or Dalteparin (with a dosage of 200 IU/kg daily for 1 month, then 150 IU/kg daily for 6 months). After six months of follow-up, the cumulative rate of venous thromboembolism recurrences was significantly lower in the Rivaroxaban group comparing to the Dalteparin group (4% versus 11%; OR=0.43). By the rate of serious hemorrhages, the groups did not differ (6% versus 4% respectively; OR=1.83), while the rate of clinically significant small hemorrhages was significantly higher in patients receiving Rivaroxaban therapy (13% versus 4%, respectively; OR=3.76). Just like in the HOKUSAI research, the most serious hemorrhages in the Rivaroxaban group (in 7 out of 11) were reported in patients with tumors of the gastrointestinal tract, clinically significant small hemorrhages were also developing in the gastrointestinal tract (in 9 out of 25) or in the urogenital tract (in 11 of 25). When taking Rivaroxaban, hemorrhages were reported 3 times more often (36% versus 11%) then in the Dalteparin treatment group. More than half of the patients in these research works had metastases (53% and 58% respectively), of which about 70% were receiving active anti-tumor therapy. Moreover, the rate of venous thromboembolism in the group of low molecular weight heparins within the HOKUSAI-VTE and SELECT-D research works (11.3% and 11.0% respectively) was matching with the data obtained in similar research works — CLOT and CATCH (9% and 7.2%, respectively), and the rate of major hemorrhages was also similar (4% for HOKUSAI-VTE and SELECT-D versus 6% and 3% for CLOT and CATCH, respectively).

In another Apixaban research — CARAVAGGIO — a total of 1155 oncology patients with symptomatic or asymptomatic acute proximal deep vein thrombosis or pulmonary artery thromboembolism were randomized [69]. Patients were receiving Apixaban (at a dosage of 10 mg twice daily within the first 7 days, then 5 mg twice daily), or Dalteparin subcutaneously (at a dosage of 200 IU/kg once daily during the first month, then 150 IU/kg once daily). The groups were comparable by all the main clinical characteristics: about 60% of the patients were simultaneously receiving active anti-tumor therapy; 40% of the total number of patients in both groups had colorectal cancer and lung cancer. The recurrence of venous thromboembolism had occurred in 5.6% of the cases in the Apixaban group and in 7.9% in the Dalteparin group (OR=0.63; p <0.001 for non-inferiority). Major hemorrhages, the main clinical safety endpoint, were reported in 3.8% in the Apixaban group and in 4.0% for the Dalteparin group (HR=0.82; p=0.60). This is by what the CARAVAGGIO research differs from the previous similar research works, where the rate of hemorrhages in the group receiving direct oral anticoagulants was higher. Special mention should go to the hemorrhages in the gastrointestinal tract, the rate of which in the CARAVAGGIO research was similar in the Apixaban and Dalteparin groups.

In the ADAM-VTE small pilot research (Apixaban and Dalteparin for active venous thromboembolism, associated with malignant neoplasms), a decrease in the rate of venous thromboembolism recurrences was demonstrated in the Apixaban group without increasing the rate of hemorrhages [6].

Based on the accumulated data, the latest ASCO recommendations state that, for the purpose of long-term anticoagulant therapy (not less than 6 months) in cases of oncology-associated venous thromboembolisms, it is more preferably to use low molecular weight heparins or direct oral anticoagulants, which are more effective than vitamin K antagonists. Vitamin K antagonists can be used if low molecular weight heparins or direct oral

anticoagulants are not available. When using direct oral anticoagulants (except for Apixaban), the risk of serious gastro-intestinal hemorrhages is increased, just like the risk of hematuria in cases of urogenital tract tumors. The cautiousness when using the direct oral anticoagulants is also justified in other settings with a high risk of damage in the mucosal membranes. When selecting the direct oral anticoagulants, drug-to-drug interactions should be taken into account. Thus, factor Xa inhibitors should not be used simultaneously with potent inhibitors or inductors of P-glycoprotein or cytochrome P450 3A4 [12].

As of today, there are no research works that can evaluate the optimal duration of anticoagulant therapy in case of oncology-associated venous thromboembolisms. For the treatment of venous thromboembolisms in oncology patients, current guidelines have recommended using anticoagulants for at least 6 months. In patients with active oncology diseases, it is suggested to increase the duration of anticoagulant therapy. While the oncology process is active, the risk of venous thromboembolism recurrence in patients remains high, and the cessation of anticoagulant therapy due to the reasons not related to serious hemorrhage, results in the recurrences of venous thromboembolism [70]. Only in two prospective multicenter research works — DALTECAN (treatment for venous thromboembolism in oncology patients using Dalteparin for up to 12 months) and TiCAT (Tinzaparin in case of thromboses, related to cancer, lasting for more than 6 months) — the safety and the efficiency were proven for such an approach: the rate of venous thromboembolism recurrences has decreased from 4.5% and 5.7% to about 1% during the 7–12 months of therapy [71, 72]. These results indicate the benefits of prolonged treatment of venous thromboembolism in oncology patients. On the other hand, regardless of the medicinal product, the treatment of venous thromboembolism for some patients may become permanent. The necessity for long-term anticoagulation should be periodically revised, evaluating the additional risk factors, such as metastatic activity or progression of the disease, venous thromboembolisms in the past, current systemic chemotherapy or the use of thrombogenic drugs, on the one hand, and the risk of hemorrhages — on the other.

The current ASCO recommendations propose the following:

- anticoagulant therapy can be initiated with low molecular weight heparins (in case of normal renal functions, low molecular weight heparins are more preferable than non-fractioned heparin), with Fondaparinux, Apixaban or Rivaroxaban;
- low molecular weight heparin, Apixaban, Edoxaban or Rivaroxaban are more preferable than vitamin K antagonists for long-term anticoagulant therapy (for not less than 6 months);
- the use of direct oral anticoagulants is associated with an increased risk of hemorrhages, especially in cases of malignant neoplasms of the gastrointestinal tract;
- prolongation of anticoagulant therapy after the first 6 months should be taken into account for patients with metastatic tumors and/or when continuing the active antitumor therapy with periodical revision of the risk/benefit ratio of such therapy.

Asymptomatic and incidentally diagnosed venous thromboembolism

The venous thromboembolism that was detected upon scanning and that has no clinical manifestations at the moment of diagnosing, represents the half of all the cases of venous thromboembolism in oncology patients [6]. Besides the pulmonary embolism and deep vein thrombosis, the incidental findings also include thromboses of the visceral veins. In a group of patients with malignant neoplasms located in the gastrointestinal tract, deep vein thrombosis was incidentally diagnosed in half of the cases (35% of the total number of cases were pulmonary artery thromboembolisms), while the other thromboses were asymptomatic thromboses of the central vein catheter [73]. What should be done in situations like this, is not quite clear, however, retrospective research works and registers show that the data on the mortality and on the deep vein thrombosis recurrences do not differ in cases of asymptomatic and clinically manifesting venous thromboembolisms [74]. Based on this, the current recommendations propose a similar approach to therapy, meaning the long-term anticoagulant therapy both for incidentally diagnosed pulmonary embolism and in patients with symptomatic pulmonary artery thromboembolism.

In a recent ASH review [75], the treatment of incidentally diagnosed venous thromboembolisms should differ depending on the location of the thrombus. Anticoagulant therapy is clearly recommended for proximal thrombosis of the deep veins, for segmental pulmonary embolism and multiple subsegmental pulmonary embolism, which are prognostically significant. However, in cases of isolated subsegmental pulmonary embolism without the ultrasonographic

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signs of deep vein thrombosis in the lower limbs, it could be sufficient just to arrange the dynamic clinical and radiological follow-up.

In the treatment of isolated distal deep vein thrombosis, there is also no certainty. At least, two research works [76, 77] have shown that the risk of fatal outcome, recurrence and major hemorrhage is similar for deep vein thrombosis in the proximal and distal segments. These results allow for supposing that the distal deep vein thrombosis may aggravate the prognosis in patients with oncology diseases, while the anticoagulant therapy could be more preferable than the follow-up tactics.

At the current stage, there is insufficient data confirming the benefits of anticoagulant therapy, as well as insufficient data on the treatment dosages and therapy duration for distal thromboses of the deep veins [76, 77]. Finally, anticoagulant therapy in cases of visceral vein thrombosis could be useful for oncology patients with no high risk of hemorrhages, but the scientific data regarding this aspect are insufficient. The recommendations encourage to take an individual decision in each specific case [78]: in particular, incidentally detected venous thromboembolisms should be treated in the same way as the symptomatic ones, taking into consideration their similar Clinical outcomes, except for isolated subsegmental pulmonary embolism.

Repeated venous thromboembolisms with a background of anticoagulant therapy

The recurrence of venous thromboembolism with a background of anticoagulant therapy in oncology patients is not a rare occasion. Low compliance, temporary cessation of therapy due to hemorrhages or surgical procedures, inadequate dosing of anticoagulants, cancer progression or heparin-induced thrombocytopenia — here is the non-inclusive list of the possible causes of recurrent venous thromboembolism. Evidences for each specific treatment are sparse, and the International Society on Thrombosis and Haemostasis (ISTH) have empirically proposed for such cases to use low molecular weight heparins [78]. Patients which have a recurrence of venous thromboembolism, should be switched to therapeutic dosages of low molecular weight heparins, if they are currently receiving therapy with unfractionated heparin, vitamin K antagonists (with adequate control of the international normalized ratio) or direct oral anticoagulants. In patients with oncology disease and with a symptomatic recurrent venous thromboembolism, despite the optimal anticoagulant therapy with low molecular weight heparins, it is necessary to increase the dosage of the latter by 25%. In case when an improvement is observed, the increased dosage of low molecular weight heparins shall remain for the whole treatment period, and, in the absence of clinical effect, further dosage increase can be performed based on the peak values of anti-Xa activity [7]. For the purpose of preventing repeated pulmonary embolisms, in certain situations, a removable cava-filter (IVC) can be implanted [12].

Thus, the specific recommendations for some clinical situations are not based on the evidences, but rather on the opinion from the experts. The International Society on Thrombosis and Haemostasis (ISTH) recommends the following approach: patients with the recurrence of venous thromboembolisms, despite the anticoagulant therapy, shall be switched to low molecular weight heparins, if they are taking other anticoagulants, or they should continue the intake of low molecular weight heparins at higher dosage, beginning from the increase of the current dosage by 25%.

Cases with high risk of hemorrhages, patients with thrombocytopenia

Thrombocytopenia (platelet count less than 100×10^9/l) is a frequent complication of both the oncological process itself and the certain types of chemotherapy, in particular, in patients with hemoblastoses, undergoing the transplantation of hematopoietic stem cells. Despite the increased risk of hemorrhages in cases of thrombocytopenia, the thromboembolic risk in them does not decrease. Besides, as it was shown by the retrospective research [79], long-term thrombocytopenia (more than 30 days) is associated with a quadruple increase of the risk of venous thromboembolism recurrence. To equilibrate the risk of oncology-associated thrombosis and the risk of hemorrhages — this is the main problem in the treatment of thrombocytopenia patients. Not having scientifically proven data for such cases, when evaluating the individual risk, one should take into account the thrombosis burden (dimensions and location), the time from the onset of the event, past episodes of venous thromboembolism and its etiology. For example, catheter-related thrombosis is associated with lower rate of recurrences or pulmonary artery thromboembolism comparing to the thrombotic events. In the same manner, the distal deep vein thrombosis and accidental subsegmental pulmonary artery thromboembolism are, apparently, being referred to the events with lesser risk of massive pulmonary

embolism [80]. On the other hand, hemorrhage is more commonly seen in cases of allogenic transplantation of hematopoietic stem cells, with concomitant coagulation disorders and hepatic/renal failure. However, the risk of hemorrhages is poorly studied in the situations, when the platelet count is within a range from 10×10^9/l to 50×10^9/l. According to the latest recommendations from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (SSC ISTH) [81], due to the higher risk of recurrence of venous thromboembolism at the acute phase (up to 30 days after the event), it is recommended to use the full dosage of the anticoagulant, if the platelet count exceeds 50×10^9/l. However, as soon as the number of platelets drops below this level, alternative strategies should be considered.

For patients with symptomatic segmental or more proximal pulmonary artery thromboembolism, proximal deep vein thrombosis or with the recurrence of deep vein thrombosis in the past, the indications may include a full-scale anticoagulant therapy and platelet transfusion (the threshold value is 40×10^9/l). On the contrary, for cases of distal deep vein thrombosis, asymptomatic subsegmental pulmonary embolism and catheter thromboses, the double decrease of the dosage is indicated or preventive administration of low molecular weight heparins, if the platelet count is from 25×10^9/l to 50×10^9/l. Generally, anticoagulant therapy shall be ceased in case of thrombocytopenia with less than 25×10^9/l of platelets. In some special situations, preventive dosages could be used even with the thrombocytopenia at the level of 10×10^9/l. The dosage modification strategy for anticoagulants is based on the consensus documents of the expert community and it has no sufficient evidence base [82].

The recurrence risk for pulmonary embolism or deep vein thrombosis decreases after the first 30 days, which is why in the subacute or in the chronic period, the dosage of anticoagulants can be decreased for the purpose of decreasing the risk of hemorrhages and preventing unnecessary blood transfusions. In particular, the decreased dosage (50% of the therapeutic dosage or preventive dosage of low molecular weight heparins) is recommended for the platelet counts from 25×10^9/l to 50×10^9/l. The possibility of temporary cessation of treatment should be considered with the platelet counts less than 25×10^9/l. In some patients with low risk of thrombosis recurrence, it is acceptable to stop the anticoagulant therapy during the whole thrombocytopenia period (with the platelet count of less than 50×10^9/l).

Low molecular weight heparins are currently the preferable anticoagulant for patients with thrombocytopenia. The data on the use of direct oral anticoagulants in patients with oncology-associated thromboses and severe thrombocytopenia (less than 50×10^9/l) are not present currently, though some evidence appear concerning the benefits of such tactics [83]. Based on the available data, installation of the cava-filter should be considered only in patients with absolute contraindication for anticoagulant therapy [84]. In accordance with the recommendations, patients with venous thromboembolism and thrombocytopenia (less than 50×10^9/l) should receive a full dosage of the anticoagulant and, probably, a platelet transfusion within the first 30 days after setting the diagnosis of venous thromboembolism. The preventive dosage of the anticoagulant can be effective and safe during the chronic phase of venous thromboembolism in patients with the platelet count from 25×10^9/l to 50×10^9/l.

Oncology patients with lesions in the brain

Patients with brain tumors have the highest rates of venous thromboembolisms among all the patients with oncology diseases, with rate being just the same as the one in the patients with malignant neoplasms of pancreatic gland and gynecological tumors. Symptomatic venous thromboembolisms develop in 19–29% of the glioma patients — the most widespread primary tumor of the brain.

There are no systematic reviews in the relation of intracranial lesions and the rates of venous thromboembolisms. We can more often see patients with metastases in the brain. In this case, approximately 20% develop venous thromboembolism. Despite the fact that the majority of thrombotic events develop after surgery, the risk of venous thromboembolism persists for the whole follow-up period. In a prospective research by A.A. Brandes et al. [85] with 77 patients having tumors of the central nervous system, which were followed up for over 2 years after surgery, the risk of deep vein thrombosis in 24 months had reached 32%. Currently, for this group of patients, the primary prophylaxis with anticoagulants is not recommended. The treatment for venous thromboembolisms in such patients is complicated by multiple factors, including concomitant diseases and bad working capacity, drug-to-drug interactions and, primarily, the possibility of intracranial hemorrhages, which can be life-threatening. Sadly, but, as of today, there are very few data that could help in making the correct decision, because the patients with intracranial

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tumors are, generally, not being included into large prospective research programs on anticoagulant therapy. The CLOT research had only 27 patients with brain tumors, in 2 of which, intracranial hemorrhages have developed. Special caution should be exercised when prescribing anticoagulants in patients with metastases in the brain, especially in some types of tumors, such as non-small-cell lung cancer or renal cell carcinoma [86].

The retrospective research employing the case-control method (by J. Donato et al. [87]) had attempted to define specifically whether the therapeutic dosage of anticoagulant increases the risk of intracranial hemorrhage. The authors have analyzed the data from 104 patients with venous thromboembolism and parenchymatous solid tumors and metastases in the central nervous system, receiving therapeutic dosages of Enoxaparin, and have compared them to the data from 189 control oncology patients with no anticoagulant therapy. The primary tumor of the brain and hematological malignant neoplasms were the exclusion criteria in the research. The intracranial hemorrhage was defined as the measurable when the focus volume was >1 ml, or as traceable with the volumes of <1 ml. Besides, each hemorrhage was classified as significant, if the hemorrhage volume exceeded 10 ml, and symptomatic — in case of neurological deficit, headache or nausea, changes in the cognitive functions, or if it required surgical intervention [88]. Based on the results of this research, the mean rate of intracranial hemorrhages in 1 year from the moment of treatment initiation was 19% in the Enoxaparin group and 21% in the control group, no statistically significant difference was observed between the groups. No statistically significant differences were detected when evaluating the individual malignant neoplasms with a similar rate of events in the Enoxaparin group and in the control group. The overall survival was also similar in the Enoxaparin group and in the control group (8.4 versus 9.7 months; p=0.65). The data from this research give ground for suggesting that low molecular weight heparins can be safely prescribed to patients with metastatic tumors of the brain without increasing the risk of intracranial hemorrhages.

The current ASCO recommendations do not consider the presence of intracranial lesions as an absolute contraindication for anticoagulant therapy. It is recommended to use an individual approach in each specific case, while among the anticoagulants, the preferable ones shall include low molecular weight heparins.

CONCLUSION

The approaches to the prevention and treatment of oncology-associated venous thromboses are rapidly changing, with new treatment schemes developing. The universally applicable approach, based on using only low molecular weight heparins, is being changed to the individual approaches due to the appearance of new data on the efficiency and safety of direct oral anticoagulants. The initiation of treatment with using direct oral anticoagulants is a novel recommendation in the majority of professional communities — it represents a shift in the paradigm of the treatment for oncology-associated venous thromboembolism. However, this also means a more complex treatment scheme with new issues appearing. The physicians must more thoroughly select the anti-thrombotic drug, must take into account the risks of recurrences of venous thromboembolism and hemorrhages, the potential drug-to-drug interactions, the preferences of the patient and they also must try to define the best strategy in each specific case.

As of today, the role of primary prevention of oncology-associated thromboses is still unclear. The duration of anticoagulant therapy is not yet completely understood in oncology patients with venous thromboembolism. It is difficult to describe the actions to be taken by the specialist in cases of asymptomatic thromboses, detected in the oncology patients during the screening procedures. Taking into consideration the fact that the cancer patient is referred to the group of increased risk in terms of developing thrombi and hemorrhages, the risk stratification still requires perfection. At the current stage, active research on biomarkers are carried out, including the genetic markers, for the purpose of defining the individual risk. The science is focused on transferring the clinical tests and translation research works into healthcare practice. This is an important social task, taking into consideration the costs, related to the treatment of oncology-associated venous thromboembolisms, for the healthcare system.

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