INTRODUCTION
Thrombophilic states are a heterogeneous group of diseases that are characterized by increased blood predisposition to hypercoagulation and high risk of thromboembolic complications. There are congenital (primary) and acquired (secondary) thrombophilia. Blood coagulation is triggered by a tissue factor (TF) that activates the VII coagulation factor, which activates X and IX coagulation factors. In the center of the coagulation cascade is the synthesis of thrombin under the influence of the prothrombinase complex (factors Xa and Va). Thrombin activates the synthesis of fibrin, functioning of anticoagulation system (Pt C, S) in the presence of thrombomodulin and suppresses the fibrinolytic system (activates the inhibitor of fibrinolysis). Anticoagulants (Pt C, S, antithrombin III) inhibit the activity of V, VIII coagulation factors and thrombin. Violation of this balanced interaction leads to thrombosis or bleeding [1,2].

THE AIM
The purpose of this work is information analysis and results of clinical trials in thrombophilia, especially, investigation of pathogenesis peculiarities, clinical picture, prediction of thrombotic complications and systematization of approaches to primary, secondary prophylaxis and treatment of thrombotic complications.
liver failure, disseminated intravascular coagulation (DIC) and after treatment with L-asparaginase. Clinical presentation includes recurrent thrombosis of lower extremities deep veins (DVT), pulmonary embolism (PE), superficial thrombophlebitis, warfarin skin necrosis (in application of large doses of warfarin Pt C synthesis is suppressed faster than thrombin synthesis, therefore coagulant effect develops faster than anticoagulant effect); in homozygous newborns - fulminant purpura (DIC). Prevention and treatment: unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonist (VKA) - warfarin (long-term prophylaxis). For the prevention of warfarin-induced necrosis it should be prescribed in low gradually increasing doses [1,2].

PROTEIN S (PT S) DEFICIENCY
Protein S is a vitamin-K-dependent anticoagulant, which is synthesized by hepatocytes and megacarocytes, is a co-factor of Pt C. Clinical signs: recurrent venous thrombosis, especially DVT and superficial thrombophlebitis, fulminant purpura of newborns. Acquired reduction of Pt S production is possible in inflammation, increased content of coagulation factor VIII, autoimmune diseases, HIV and other infections.

FACTOR V LEIDEN MUTATION (FACTOR V RESISTANCE TO ACTIVATED PT C).
The pathology is caused by the appearance of an autosomal dominant mutation. Pt C inactivates the V factor of blood coagulation after binding to thrombomodulin, Pt S and thrombin. There are congenital factor V resistance to activated Pt C and acquired (leukemia, pregnancy, high levels of factor VIII, synthesis of autoantibodies to factor V). Clinical manifestation: DVT, cerebral vein thrombosis, PE, miscarriages in the second trimester of pregnancy, neonatal fulminant purpura in newborns.

PROTHROMBIN G 20210A MUTATION
Prothrombin G 20210A mutation promotes increasing amount and activity of the prothrombin. Clinically is manifested by arterial and venous thrombosis [2,3].

INCREASED CONCENTRATION OF FACTOR VIII
Factor VIII synthesis enhancement by endothelial cells is developed in acute inflammation, obesity, hyperestrogenemia, anti-diuretic hormone content increased, usage of OCP, during pregnancy. Clinically is manifested by DVT.

DEFICIENCY OF TROMBOMODULIN
Thrombomodulin is a membrane protein of EC that activates protein C, coagulation factor V and platelets. Deficiency of trombomodulin increases risk of myocardial infarction (MI), especially in young patients [2,4,5].

DEFICIENCY OF ANTITHROMBIN III (AT III)
AT III is synthesized by hepatocytes and endothelial cells. The mechanism of action is based on thrombin inactivation. Clinically manifested by DVT, mesenteric vascular thrombosis and transitory ischemic attacks (TIA). LMWH is used, because of resistance to UFH is developed. Primary prophylaxis of thrombosis is performed during pregnancy, before and after surgery. Long-life prophylactic use of anticoagulants is recommended for spontaneous and recurrent thrombosis [1,2,3].

HYPERHOMOCYSTEINEMIA
Congenital pathology is caused by a deficiency of one of the enzymes of homocysteine transformation to methionine (methionine synthase, 5,10-methylenetetrahydrofolate reductase, betaine-methionine methyltransferase) or the enzyme for conversion of methionine to cysteine (cystathionin-β-synthase). Mechanisms of thrombosis: endothelial dysfunction leads to reducing thrombomodulin expression, inhibition synthesis of nitric oxide, prostacyclin, leads to PtC and factor V activation and increasing expression of the TF, synthesis of thrombin, adhesion of monocytes to the EC, inhibition tissue plasminogen activator (tPA). Clinical manifestation includes Marfan-like syndrome, lens dislocation, myopia, intellectual deficiency, VTE, early development of atherosclerosis, arterial thrombotic complications (MI, ischemic stroke). The content of homocysteine is 100-500 μmol /L. [6,7]. Relative risk of thrombotic complications for congenital thrombophilia has been shown in table I., for acquired thrombophilia has been shown in table II.

### Table I. Relative risk of thrombotic complications for congenital thrombophilia.

<table>
<thead>
<tr>
<th>Hypercoagulability state</th>
<th>Relative risk of primary VTE *</th>
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<tbody>
<tr>
<td>FV Leiden mutation</td>
<td>2-10</td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td>5-40</td>
</tr>
<tr>
<td>PTC deficiency</td>
<td>6.5-31</td>
</tr>
<tr>
<td>P Ts deficiency</td>
<td>2-36</td>
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<tr>
<td>Prothrombin G 20210A mutation</td>
<td>2-6</td>
</tr>
<tr>
<td>FV Leiden + prothrombin G 20210A mutation</td>
<td>20,0</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>2-4</td>
</tr>
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*Relative risks are compared to persons without thrombophilia
SECONDARY (ACQUIRED) THROMBOPHILIA

Malignancy. Pathogenetic mechanisms of hypercoagulation: 1) hyperproduction of TF by activated monocytes, activation of coagulation factor X by sialic acids; 2) the synthesis of proinflammatory cytokines (TNF, IL-6) enhance the synthesis of TF, fibrinogen, adhesion molecules, free radicals. Clinical picture of paraneoplastic thrombophilia includes DVT, migratory thrombophlebitis (Trouseau's syndrome), chronic DIC and arterial thrombosis (thrombosis of cerebral artery with development of TIA, ischemic stroke, thrombosis of the arteries of upper and lower extremities). According to NCCN recommendations treatment of VTE is performed with using LMWH (dalteparin 200 U/kg OD, enoxaparin 1 mg/kg BID), fondaparinux (5mg (<50 kg), 7,5-10 mg (50-100 kg), 10 mg (>100 kg) OD), UFH; secondary prevention: LMWH, warfarin (2,5-5 mg/day), direct oral anticoagulants (DOACs) for at least 3 months (NCCN 2013) or 6 months (ASCO 2014). [9,10].

Antiphospholipid syndrome (APS). Antiphospholipid antibodies (APAs) are heterogeneous antibodies that include lupus anticoagulant (LA), antiphospholipid antibodies (aCL), and antibodies against β2GPI (a component that inhibits complement activity, suppresses cells apoptosis). β2GPI binds to the membrane of ECs, monocytes, platelets, trophoblast cells through receptors: the Toll-like receptor, Annexin A2, GP Ibα, and triggers signaling pathways regulating the cell cycle (proliferation, differentiation, apoptosis of cells), receptor expression, pathophysiological processes (inflammation, lipids peroxidation), activity of anticoagulants (Pt C). Antibodies to β2GPI activate expression of adhesion proteins (ICAM, VCAM, e-Selectin), TF on ECs and monocytes; synthesis of thromboxane A2 (Tx A2) and expression of GPIIb/IIIa on platelets; reduce activity of anticoagulants (PtC, Anexin A5), activate the complement, enhance synthesis of proinflammatory mediators, free radicals, stimulate proliferation of ECs (via the signaling pathway PI3K-AKT-miTOR). In the case of pregnancy, APA activates apoptosis and inhibits proliferation, differentiation and maturation of trophoblast and decidual cells, and thus impair placental formation and fetus development. Clinical presentation: thrombosis of arteries and veins of skin, musculoskeletal system and visceral organs; pregnancy and fetus pathology; systemic thrombotic microangiopathy [11].

Usage of OCP, HRT. The synthesis of I, V, VII, VIII, IX, X, XI, XII blood coagulation factors is increased; the production of Pt S and AT III is reduced, the activity of the tPA is decreased, and the activity of the plasminogen activator inhibitor-1 (PAI-1) and the thrombin-activated fibrinolysis inhibitor (TAFI) is increased. There is a risk of MI, ischemic stroke, thrombosis of the peripheral arteries, DVT and PE [8,12].

Pregnancy. Hypercoagulation is due to increasing the content of I, V, VII, VIII, IX, X, XI, XII blood coagulation factors and decreasing activity of anticoagulants (Pt S and antithrombin III), inhibition of plasma fibrinolytic activity under the influence of estrogens and progestogens. Hypercoagulation status is maintained 6 weeks after childbirth. The risk of thrombotic complications is high in patients with simultaneous diagnosis of homozygous FV Leiden mutation and the prothrombin G20210A mutation, AT III deficiency, presence of APS and persistence of APA [8,12].

Acquired hyperhomocysteinemia. It is caused by a deficiency of vitamins B12, B9 and B6, which are cofactors of the enzymes of homocysteine transformation. Homocysteine enhances lipid peroxidation, induces dysfunction and apoptosis of ECs. Hyperhomocysteinemia is associated with increasing synthesis of adhesion molecules by ECs, enhancement synthesis of nitric oxide, prostacyclin, thrombomodulin, thromboxane A2; thrombin, TF, V and VII coagulation factors; reduction synthesis of adhesion molecules by ECs. Hyperhomocysteinemia enhances lipid peroxidation, induces dysfunction and apoptosis of ECs. Malignancy is a risk factor for pathologies associated with pregnant women, pregnancy and fetus: reducing fertility, preeclampsia, fetal nervous tube defects, anencephaly, and fetal development retardation. Prevention of thrombotic complication and pathogenetic treatment includes using vitamins B6, B9 and B12 [6,7].

ACUTE OR CHRONIC INFECTIOUS DISEASES, SEPSIS, AUTOIMMUNE PATHOLOGIES

The development of the systemic inflammation leads to the releasing of proinflammatory cytokines, including...
TGF, which increases the expression of the TF, molecules of adhesion and VIII coagulation factor synthesis. Systemic inflammation is associated with thrombocytosis, leukocytosis, increasing activity of leukocytes enzymes, provocation of lipid peroxidation, apoptosis of ECs and their dysfunction (inhibition production of nitricoxide and prostaglandins, activation Tx A2 production, reducing activity of anticoagulants). Risk factors of thrombosis include smoking, which provokes the development of endothelial dysfunction; surgical interventions involving TF releasing that activates VII and X blood coagulation factors, as well as immobilization, which results in decreasing venous outflow velocity, and also contributes to the development of hypoxia and endothelial dysfunction [8].

**OBESITY**

The accumulation of visceral fat contributes to the development of arterial thrombosis, subcutaneous fat - venous thrombosis. The production of reactive oxygen species is increased; activity of the antioxidant system is suppressed. Free radicals of oxygen cause chronic inflammation, endothelial dysfunction, activate synthesis of Tx A2. There is observed increasing synthesis of I, VII and VIII coagulation factors, TF and reducing activity of the fibrinolytic system (enhancement production of PAI-1; TAFI). Insulin resistance inhibits the synthesis of nitric oxide and causes platelet activation, hypercoagulation and vasospasm. Increasing the content of leptin via the Jak2 receptor activates the PI3K/Akt signaling pathway and results in the synthesis of Tx A2 and activation of GPIIb/IIIa platelet receptors. Lowering and normalizing weight correlates with normalization of hemostasis [13,14,15]. The usage of insulin sensitizers (glitazones, biguanides) reduces hypercoagulation, platelet hyperagregability and endothelial dysfunction [13,14,15].

**NEPHROTIC SYNDROME AND CHRONIC KIDNEY DISEASES**

Low molecular weight proteins (AT III, Pt C and S, plasminogen) are lost through the glomerular membrane. Loss of fluid in the process of edema development, leads to haemoconcentration. Systemic inflammation, hypercorticonemia, endothelial dysfunction are important factors of hypercoagulation. VTE dominate in clinic presentation. Primary and secondary prevention are not made. Thrombolytics, anticoagulants, antiplatelets, surgical thrombec- tomy, filter installation in the lower vena cava are used in the treatment of thrombosis. [16].

**BLOOD DISORDERS**

The increased risk of thrombotic complications in the case of myeloproliferative neoplasmas (MPN) - polycythemia vera (PV), essential thrombocythemia (ET), - is associated with leukocytosis, thrombocytosis, activation of leukocytes and platelets, high proinflammatory cyto-

kines content, that stimulate synthesis of free radicals, cause endothelial dysfunction, enhance the synthesis of TF, Tx A2 and adhesion molecules. Patients with acute leukemia, lymphoma and multiple myeloma (MM) have a high risk of thrombosis also. Pathogenetic pathways of hypercoagulation are the same as in malignancy and MPN. The use of drugs for treatment patient with leukemia and lymphoma (corticosteroid hormones (CS), L-asparaginase, thalidomide, erythropoietin) leads to hypercoagulation state [17,18,19]. Patients with haemolytic anemia (HA) and intravascular mechanism of hemolysis, including autoimmune hemolytic anemia with cold antibodies, sickle cell anemia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), paroxysmal nocturnal haemoglobinuria (PNH) ), less commonly, with intracellular hemolysis (thalsesemia) have a high risk of thrombosis. Clot formation is due to the releasing of the heme, that binds nitrogen oxide, increases synthesis of TF, and, in HUS, TTP and NPH, due to complement activation, which triggers coagulation cascade [20]. Clinical picture of thrombotic complication in blood disorder is characterized by development abdominal cavity veins thrombosis, DVT, PE, stroke, myocardial and spleen infarction in MPN; development of cerebral and upper extremities veins thrombosis in the usage of L-asparaginase, DVT in case of CS and thalidomide using, strokes and MI in using erythropoietin. There is a high risk DVT, PE, thrombosis of the microcirculation of kidneys, brain (in HUS, TTP, NPH), lung, liver in HA.

**PRIMARY PROPHYLAXIS OF THROMBOTIC COMPLICATIONS**

Primary prophylaxis of thrombotic complications is carried out after evaluation of the risk of thrombotic complications. When detecting congenital thrombophilia, OCP and RHT should be avoided. In the presence of a homozygous F V Leiden mutation, a homozygous prothrombin G20210A mutation, AT III or Pt C deficiency and the family history of VTE, primary prenatal and postpartum prophylaxis within 6 weeks is recommended. In Pt S deficiency it is recommended only postpartum prophylaxis within 6 weeks [3].

In acquired thrombophilia, risk of thrombotic complications in patients with MPN, MM, cancer, APS, HA and in case of using chemotherapeutic agents (CT) and corticosteroid hormones should be assessed.

Patients with myeloproliferative neoplasia (PV, ET) should receive antiplatelets. At the beginning of chemotherapy, in high risk of thrombosis (age over 60 years old, cardiovascular disease, mutation JAK2, history of thrombosis) should receive anticoagulants (LMWH). [17,18,19].

Patients during hemolytic crises with the intravascular mechanism of hemolysis should receive prophylactic therapy using anticoagulants (LMWH). [20].

In patients with MM presenting with a standard risk to develop VTE or treated with thalidomide as single-agent, antiplatelet therapy with low-dose acetylsalicylic acid (ASA) should be considered. In case of presence of addi-
tional risk factors or for all patients who receive thalidomide with high-dose dexamethasone or doxorubicin or multi-agent CT, LMWH or full-dose warfarin should be administered. Thromboprophylaxis should be continued for 3–6 months. [21,22].

Primary prophylaxis in case of APS is not prescribed in case of physiological course of pregnancy, absence history of obstetric pathology, absence of APA. But postpartum prophylaxis with UFH or LMWH is conducted within 6 weeks in presence of LA. [11].

SECONDARY PROPHYLAXIS OF THROMBOTIC COMPLICATIONS

1. Anticoagulation therapy (LMWH, DOAC, VKA).
   Secondary prophylaxis can last 3-6-12 months or be life-long. [23]. In case of history one thromboembolic event duration of secondary prophylaxis is 3 months; two events - 6 months; three and more events - life-long anticoagulation therapy.
2. The installation of a filter of the lower vena cava is considered if anticoagulant therapy is contraindicated.
3. Risk factors limitation: avoiding the use of OCP in patients with factor V Leiden mutation and women older than 35 years old and who smokes; stopping smoking; body weight correction [4, 23]. Secondary life-long prophylaxis of thromboembolic complication is recommended: 1) after the first episode of VTE in patients with AT III deficiency, homozygous form of factor V Leiden mutation or prothrombin gene 20210A mutation, as well as in the case of a combination of heterozygous forms of these disorders, in some patients with APS. 2) after the first episode of idiopathic thrombosis in thrombophilia another origin than the above in case of PE (especially high risk) and/or proximal thrombosis, if the risk of bleeding is low or moderate; 3) after the second episode of VTE or with coexistence of two causes of thrombophilia: a deficiency of Pt C or Pt S, as well as isolated heterozygous form of factor V Leiden mutation or prothrombin gene 20210A mutation; 4) three and more events of thrombosis. [23]. Secondary prophylaxis of arterial thrombotic complications in patients with blood disorders, cancer, APS, hyperhomocysteinemia, thalidomide using includes antiplatelets, in particular, inhibitors of Tx A2 synthesis - ASA, and thienopyridine-inhibitors of ADP-receptors (clopidogrel, prazugrel), in case of high risk of thrombotic complication is recommended to add anticoagulants (LMWH, AVK, DOAC) [6,7,17,21]. Low-dose aspirin (LDA) is recommended in patients with APS with history of arterial thrombotic complications and low titres of aCL, a combination of warfarin or LMWH and LDA is recommended for patients with arterial thrombotic complications history and high titre of aCL [11].

Treatment of arterial and venous thrombotic conditions is carried out in accordance with the protocols for the specific nosologies management. The use of UFH, fondaparinux, LMWH (enoxaparin (cleaxan), dalteparin (fragmin), nad-roparin (fraxiparin), DOAC (rivaroxaban, edoxaban, epixaban, dabigatran, argatroban, lepirudin), and the presence of a thrombophilia may affect the choice of anticoagulants. In AT III deficiency, UFH is ineffective and AT concentrate is recommended. In heparin-induced thrombocytopenia patients are prescribed argatroban or lepirudin. Patients with Pt C or S deficiency should be avoid using a high dose saturation of AVK and at the same time use heparin to reduce the risk of skin necrosis (when it has been occur, Pt C concentrate is also used) [1, 2, 3, 4, 22]. APS in a pregnant woman: in presence of obstetric APS, LDA and UFH or LMWH are prescribed [11] In catastrophic APS with systemic thrombotic microangiopathy treatment scheme includes fibrinolytics, anticoagulants (UFH, or LMWH, or DOAC), prostacyclin, CS, immunosuppressants (aminoguclidean, mTOR inhibitors or other immunosuppressants), intravenous immunoglobulin, plasmapheresis. In resistant cases - antibodies against B-lymphocytes (anti CD 20 – rituximab), antibodies against complement - eculizumab [24].

CONCLUSIONS

1. More than 60% of patients with spontaneous VTE have congenital thrombophilia.
2. Patients should be screened for congenital thrombophilia in the presence of indication.
3. Among patients with congenital thrombophilia, patients with a Pt C, S, antithrombin III deficiency and F V Leiden mutation have the highest risk of thrombotic complications.
4. Among the acquired thrombophilia, patients with malignancy, APS, HA, after surgical interventions, during pregnancy, postpartum period, or using of OCP and HRT have the highest risk of thrombotic complications.
5. The type of thrombophilia determines choice of anticoagulants, the character and duration primary and secondary prophylaxis.

REFERENCES


Authors’ contributions:
According to the order of the Authorship.

Conflict of interest:
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CORRESPONDING AUTHOR
Olha M. Bereziuk
National Pirogov Memorial Medical University
Academic Yushchenko street, 12/S2, Vinnytsya, 21018, Ukraine
tel: +380966980120
e-mail: olgabereziuk33@gmail.com

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