REVIEW ARTICLE

Importance of antithrombin evaluation and supplementation in clinical practice

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Summary

Antithrombin (AT) is a key natural anticoagulant that primarily inhibits thrombin, factor Xa, and other procoagulant proteases, maintaining hemostatic balance. Deficiency in AT, whether inherited or acquired, significantly increases the risk of venous thromboembolism, obstetric complications and sporadically arterial thrombosis. Individuals with AT deficiency are 15 times more likely to develop thrombosis.

Acquired deficiency is more common and may result from hypoproduction, excessive excretion or loss, increased consumption, or dilution of AT. In critically ill patients, acquired antithrombin deficiency may occur frequently; however, routine monitoring of antithrombin levels is not currently supported by strong evidence and should be reserved for selected clinical indications, especially with risk of thromboembolism. Antithrombin is essential for the action of unfractionated heparin, low-molecular-weight heparin, and fondaparinux, meaning deficiency can lead to resistance to these anticoagulants. Antithrombin deficiency is often detected in cases of resistance during the administration of antithrombin-dependent anticoagulants, typically indicated by insufficient levels of anti-Xa activity.

Supplementation of AT is indicated for preventing and treating thrombotic events in patients with congenital or acquired AT deficiencies.

Supratherapeutic antithrombin levels during heparin therapy can lead to bleeding. Its role in thromboembolism, anticoagulant resistance, and pleiotropic effects highlights its clinical importance and research potential.

Keywords: antithrombin, thromboembolism, heparin resistance, hemostasis

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INTRODUCTION

Antithrombin (AT) is an anticoagulant glycoprotein from the serpin superfamily, encoded by the SERPINCS-1 gene, which promotes the proteolytic activity of procoagulant proteases from both the extrinsic and intrinsic coagulation pathways. It represents the most potent natural inhibitor of coagulation, providing up to 80% of the potential to inhibit the formation of FIIa (thrombin). It also significantly inhibits FXa and, to a lesser extent, FIXa, FXIa, and FXIIa, thereby maintaining the fundamental balance of the hemostatic system (1,2).

In individuals with detected antithrombin deficiency, the risk of venous thromboembolism (VTE) is approximately 15 times higher. It is estimated that 50% of individuals with AT deficiency will experience a venous thromboembolic event before the age of fifty (3). About 8.8% of patients with AT deficiency and idiopathic VTE experience recurrent thromboembolic events annually (1,4).

CLINICAL PRESENTATION OF ANTITHROBIN DEFICIENCY

Antithrombin deficiency manifests through early onset of spontaneous (so-called idiopathic) venous thrombosis, with the fact that AT deficiency potentiates the formation of thrombosis in certain specific conditions (use of contraceptive therapy, pregnancy, trauma, immobilization, surgical interventions). AT deficiency can present as rare but potentially life-threatening forms of thromboembolism, such as cerebral venous sinus thrombosis, splenic vein thrombosis, Budd-Chiari syndrome, or thrombosis of the inferior vena cava. AT deficiency is also characterized by frequent recurrence of thrombosis. In addition to venous thromboembolism as the most common manifestation, antithrombin deficiency during pregnancy leads to certain obstetric complications, such as fetal growth restriction, placental abruption, fetal distress. It can also result in recurrent miscarriages and pregnancy loss. In rare cases, AT deficiency can present as arterial thrombosis, such as myocardial infarction. Congenital AT deficiency may be associated with a variety of other conditions and symptoms (developmental anomalies, psychomotor retardation, dysmorphic phenotype, microcephaly, small hands and feet, brachydactyly, clinodactyly of the fifth finger, facial dysmorphism, autoimmune symptoms, hypopituitarism, lipomatosis, skeletal and cardiac malformations, renal and hepatic insufficiency) (1).

The estimated prevalence of inherited antithrombin deficiency is between 1 in 2000 and 5000 individuals. It has been found that AT deficiency is detected in 2-3% of patients with thrombotic incidents. Given the clinical significance and the potentially life-threatening complications, it motivates physicians to always evaluate the presence of this type of thrombophilia. AT deficiency has been found in 4% of patients with recurrent VTE who are ≤ 50 years old, in 1% of patients with splenic vein thrombosis, and in 2% of cases associated with the use of combined oral contraceptives or pregnancy (1,5, 6).

SUBTYPES OF ANTITHROMBIN DEFICIENCY

Inherited Antithrombin Deficiency

Inherited Type I antithrombin deficiency results from reduced synthesis or stability of antithrombin due to specific mutations. It is characterized by a proportional decrease in both the concentration and functional activity of antithrombin, with an antigen/activity ratio of approximately 1. In contrast, inherited Type II deficiency is characterized by the production of altered, nonfunctional antithrombin due to mutations that lead to a lack of functional activity. In this case, the level of antithrombin in the blood is normal, but the antigen/activity ratio is greater than 1 **(Table 1)** (2).

Inherited Type II antithrombin deficiency is further divided into three subtypes. Subtype IIa or Type II Reactive Site (II RS) is characterized by a reduced ability of antithrombin to bind to proteases like thrombin. Subtype IIb or Type II Heparin-Binding Site (II HBS) refers to a reduced ability of antithrombin to bind heparin, thereby diminishing its anticoagulant effect. Subtype IIc or Type II with Pleiotropic Effects (II PE) involves a structural defect in antithrombin near the thrombin-binding site. Individuals with Type IIc antithrombin deficiency usually have lower antithrombin levels compared to other subtypes. Subtypes IIa and IIc are associated with a more severe clinical picture of antithrombin deficiency, while individuals with subtype IIb deficiency have a lower risk of venous thromboembolism but a higher risk of arterial thromboembolism (3).

All inherited types of antithrombin deficiency occur in a heterozygous genotype, except for subtype IIb, which

Table 1. Types of inherited antithrombin deficiency

Types of inherited antithrombin deficiency	Disorder Characteristics	Genotype	Ag/Ac Ratio
Type I	Reduced AT concentration	Heterozygous	Approximately 1
Type IIa - *type II reactive site (II RS)*	Reduced AT binding to thrombin	Heterozygous	>1
Type IIb - *type II heparin-binding site (II HBS)*	Reduced AT binding to heparin	Heterozygous / homozygous	>1
Type IIc - *type II with pleiotropic effects (II PE)*	Multifunctional AT disorder	Heterozygous	>1

AT – antithrombin, IIRS - type II reactive site, IIHBS - type II heparin-binding site, IIPE - type II with pleiotropic effects

can be compatible with life even in a homozygous form. It is believed that Type II antithrombin deficiency is more common in the general population and carries a lower risk of thromboembolic events, except for subtype IIa, which carries a high risk for thromboembolic events. In contrast, individuals with symptomatic thrombophilia are more frequently diagnosed with Type I antithrombin deficiency (3).

Acquired Antithrombin Deficiency

Acquired antithrombin deficiency is significantly more common and is caused by: 1. Hypoproduction of antithrombin, such as in cases of acute and chronic liver insufficiency (e.g., liver cirrhosis), malnutrition, individuals undergoing L-asparaginase therapy, or premature infants. 2. Excessive excretion or loss of antithrombin, as seen in nephrotic syndrome, burns, inflammatory bowel diseases, and other enteropathies accompanied by protein loss. 3.Increased consumption, such as in disseminated intravascular coagulation (DIC), microangiopathy with thrombosis, malignancies, hematologic transfusion reactions, major surgeries (notably, the lowest levels of antithrombin are recorded on the third postoperative day), heparin therapy (after 4-5 days of heparin infusion antithrombin levels can be reduced to 50-60% of normal), massive thrombosis, severe sepsis, multiple trauma, hemolytic-uremic syndrome (HUS), preeclampsia, eclampsia. 4. Dilution, during massive transfusions, use of ECMO (extracorporeal membrane oxygenation), extensive use of intraoperative blood salvage devices, and extracorporeal circulation methods. 5. Complex and combined mechanisms, such as in sepsis, where there is a simultaneous process of decreased production and increased consumption, or in conditions like preeclampsia, eclampsia, and HELLP syndrome, which include reduced production and increased consumption of AT in combination with endothelial dysfunction **(Table 2)** (2,7).

Antithrombin levels lower than 50-60% in sepsis are generally associated with poorer prognosis, while levels below 20% correlate with fatal outcomes. In acquired forms of antithrombin deficiency, other anticoagulant proteins like protein C and protein S are often reduced as well (1). Postoperative chylothorax in children is associated with an increased risk of vascular thrombosis, believed to result from the loss of antithrombin in chyle fluid, leading to a hypercoagulable state (8).

It is considered that in patients with Budd-Chiari syndrome, there are other causes of thrombosis in addition to antithrombin deficiency (8). The use of oral contraceptives and estrogens can, in certain predisposed individuals, lead to antithrombin deficiency (1,9).

Ovarian hyperstimulation syndrome (OHSS) is a severe complication that can occur in women undergoing controlled ovarian stimulation during in vitro fertilization (IVF). The estimated incidence of this syndrome is between 1%-5%, but it can reach 10% in individuals with risk factors (10). The clinical presentation of OHSS ranges from mild symptoms to potentially life-threatening thromboembolic complications. Arterial events predominantly involve cerebrovascular accidents, which typically occur at the onset of OHSS. Venous thromboses occur several weeks later and are often reported in unusual but specific locations, such as the large veins of the upper extremities and neck (11). According to current knowledge, hypercoagulability in OHSS is contributed to by vasoactive substances from the ovaries, hemoconcentration, hypovolemia leading to arterial hypotension, elevated 17β-estradiol levels due to induced ovulation, and the administration of human chorionic gonadotropin (hCG). Inherited thrombophilia and antithrombin deficiency can also contribute to the development of OHSS (7). On the other hand, studies indicate that hormonal stimulation with human chorionic gonadotropin can lead to a decrease in antithrombin concentration (11).

DIAGNOSIS OF ANTITHROMBIN DEFICIENCY

Evaluating antithrombin (AT) levels in the blood can help define the etiopathogenetic substrate of thromboembolic disease, enable substitution therapy, and significantly influence the outcome of the disease.AT activity levels between 70-80% are considered borderline and indicate a potential AT deficiency, while levels below 70% are considered diagnostic (12). The majority of patients with AT deficiency are detected by reduced anti-Xa levels during heparin derivatives therapy, but some patients with

Table 2. Causes of acquired antithrombiin deficiency

hypoproduction	acute and chronic liver insufficiency (e.g., liver cirrhosis), malnutrition, L-asparaginase therapy, in premature infants.
extreme excretion or loss of AT	nephrotic syndrome, burns, inflammatory bowel diseases, and other enteropathies associated with protein loss
increased consumption	disseminated intravascular coagulation, microangiopathy with thrombosis, malignancies, hematologic transfusion reactions, major surgeries, heparin therapy, massive thrombosis, severe sepsis, multiple traumas, hemolytic-uremic syndrome,
dilution	massive transfusions, use of extracorporeal membrane oxygenation, extensive use of intraoperative blood salvage devices, extracorporeal circulation methods
complex and combined mechanisms	sepsis, preeclampsia, eclampsia, *HELLP* syndrome, *OHSS*

AT – antithrombin, HELLP syndrome – hemolysis, elevated liver enzymes, low platelet count syndrome, OHSS – ovarian hyperstimulation syndrome

pathogenic mutations may not be diagnosed using this test, in which case molecular diagnostics is advised (1). When interpreting blood antithrombin levels, special attention should be paid to the fact that the use of AT analysis while on direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) can lead to falsely high AT levels, masking the diagnosis of AT deficiency. Additionally, bilirubin levels above 50 mg/dL, hypertriglyceridemia, and rheumatoid factor levels greater than 800 IU/mL can affect the AT level. Genetic testing can help identify patients with AT deficiency that standard tests may miss (13). To ensure accurate AT measurements, it is crucial to properly store samples. Freezer models with self-defrosting cycles may cause temperature fluctuations that can affect protein stability and test results. Therefore, freezers without automatic defrosting or ultralow-temperature freezers maintaining a constant temperature of -70°C are recommended (14).

Diagnostic algorithm in AT deficiency is presented in **Figure 1**.

THERAPEUTIC APPLICATION

In cases of significant antithrombin deficiency, AT substitution is performed using synthetic AT preparation. One of the formulas used to determine the required dose of AT is:

Dose (units required) = (120% - baseline %) × body weight (kg)/ 1.4 (2,3).

The use of antithrombin is indicated for the prevention and treatment of thrombotic events in individuals with either congenital or acquired AT deficiency. In general, therapeutic approaches for patients with AT deficiency are considered in three groups:

1. Treatment of acute thromboembolic events
2. Short-term prophylaxis when exposed to high-risk situations
3. Long-term prophylaxis for symptomatic patients who have had a previously documented episode of thromboembolism caused by AT deficiency (3).

Antithrombin is essential for the action of unfractionated heparin, low-molecular-weight heparin, and fondaparinux (anticoagulants dependent on antithrombin), which are first-choice drugs in the treatment of VTE. In cases of patients with AT deficiency, resistance to these anticoagulants can develop (3).

Antithrombin deficiency is the most common cause of true heparin resistance, characterized by aPTT and anti-Xa activity levels measured during heparin therapy that are concordantly lower than expected, as opposed to pseudo-heparin resistance, where aPTT is lower than expected, but anti-Xa activity is appropriately reduced with prescribed heparin therapy. Predictors of heparin resis-

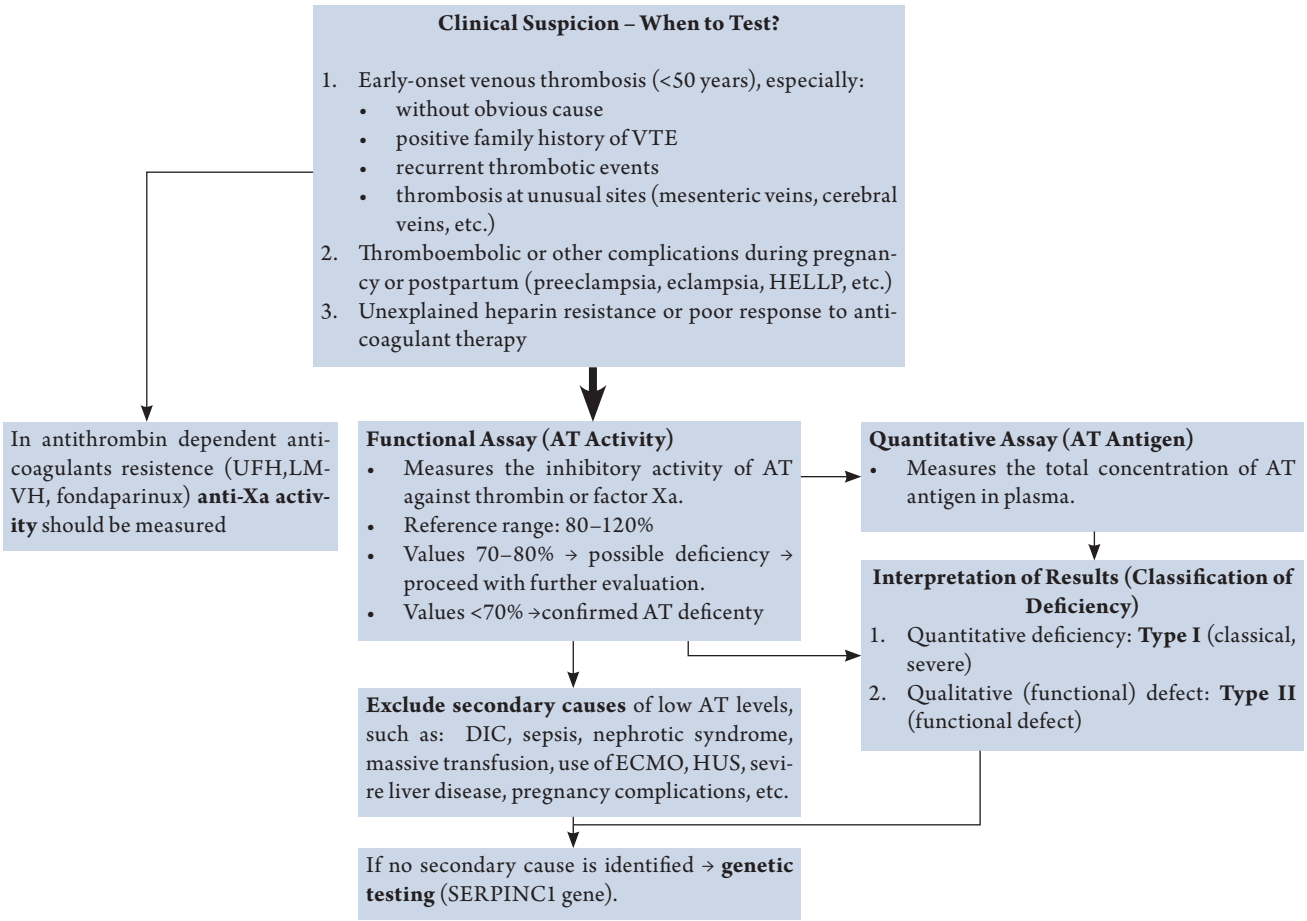

Figure 1. Diagnostic algorithm in AT deficiency

tance include AT activity ≤ 60%, platelet count >300 × 10^9/L, age (>65 years), and elevated levels of factor VIII and fibrinogen (15).

Optimizing heparin therapy based only on aPTT may lead to overdose and hemorrhagic events in cases of pseudo-heparin resistance, often caused by elevated FVIII levels and other acute-phase reactants (16). The laboratory-detected anti-Xa activity level, measured to optimize heparin therapy, does not depend on acute-phase reactants, unlike aPTT (16).

Heparin resistance is effectively resolved by AT supplementation, with preference given to AT concentrate (ATc). At the same time, in modern clinical practice, fresh frozen plasma is not recommended except when ATc is unavailable due to potential risks like allergic reactions, circulatory overload, infection transmission, hemolytic transfusion reactions, alloimmunization, and transfusion-related acute lung injury (TRALI) (3).

Long-term prophylaxis for symptomatic patients with AT deficiency involves the use of warfarin or direct oral anticoagulants (DOAC), which are AT-independent (3, 17, 18).

During pregnancy, especially in the postpartum period, women with AT deficiency are at high risk for developing VTE. Modern guidelines recommend pharmacological thromboprophylaxis with low-molecular-weight heparin in all women with mild AT deficiency during pregnancy and postpartum. AT substitution may also be considered for pregnant women and women in the postpartum period as adjunct therapy in high-risk cases or those with significantly reduced AT levels (19).

Drug overdose, determined by antithrombin levels exceeding 120%, can cause a hemorrhagic tendency and lead to manifest bleeding, especially when AT preparations are given alongside heparin (1). If AT levels exceed 120%, it is recommended to reduce the dose by 30%. If the level is below 80%, the dose should be increased by 30%, with AT levels checked 2 hours after infusion completion. Before administration of the next dose, AT levels should be checked in order to optimize therapy. Patients with prior thrombosis and AT deficiency, should be considered for prolonged or lifelong anticoagulant therapy (1,2).

A specific problem for patients with undiagnosed AT deficiency is the use of low-molecular-weight heparin for anticoagulation therapy, whose therapeutic effect is rarely monitored by anti-Xa activity levels. Failure to achieve the target therapeutic effect with antithrombin-dependent anticoagulants prescribed for thrombosis prevention or treatment can endanger the patient's life. Clinicians should also be aware that heparin resistance can be caused by nitroglycerin infusion and the use of antidotes for direct anticoagulants, such as andexanet alfa (1,2,20,21).

In addition to its role as an anticoagulant protein and essential factor for the action of antithrombin-dependent anticoagulants, AT also may possess anti-inflammatory, anti-angiogenic, antimicrobial, and even antiplatelet properties, exerted through the release of prostacyclin from endothelial cells (1,2,20).

The mechanism of the anti-inflammatory response likely lies in the immunomodulatory effect of AT binding to heparan sulfate proteoglycans on the surface of endothelial cells, reducing the production of inflammatory and procoagulant mediators, while increasing the release of anticoagulant prostacyclins (PGI) (22).

Given the anticoagulant and anti-inflammatory effects of AT, its substitution may potentially benefit the treatment of individuals with sepsis-induced disseminated intravascular coagulation (DIC), sinusoidal obstruction syndrome, previously known as veno-occlusive liver disease, for patients undergoing ECMO therapy, therapy of acute lymphoblastic leukemia with asparaginase, and perioperative preparation of patients undergoing cardiopulmonary bypass. These indications for AT substitution are still under investigation (3).

Studies have shown that some cases of disseminated intravascular coagulation (DIC) associated with antithrombin deficiency (consumptive coagulopathy develops accompanied by low anticoagulant and fibrinolytic activity), present with the development of a severe prothrombotic state with significantly worse prognosis. In such cases, in addition to assessing the SOFA and DIC scores, monitoring antithrombin (AT) levels is recommended both for evaluating the severity and prognosis of the disease, as well as for selecting appropriate therapy (23).

Some observation studies have shown improved treatment outcomes in sepsis-induced disseminated intravascular coagulopathy patients associated with AT deficiency; however, most global protocols and guidelines call for further research. Only in Japan's current guidelines is AT substitution approved for this indication (24,25).

There are some indicators of potential benefit from the use of AT in various malignancies, such as glioblastoma, lung cancer, and colorectal cancer, due to its observed anti-angiogenic effect, reduced tumor protein expression, and suppression of metastatic spread (3).

Routine substitution of antithrombin in critically ill patients is not standard practice. It is recommended only in cases of documented deficiency with a clear clinical indication, such as heparin resistance, planned invasive procedures, or active thrombosis.

The use of AT concentrates in patients with sepsis and disseminated intravascular coagulation (DIC) remains controversial, as clinical studies have shown inconsistent results. Many of these studies are methodologically limited, with heterogeneous primary outcomes, non-standardized dosing, and a lack of well-designed randomized controlled trials (26, 27, 28).

CONCLUSION

AT deficiency often goes unrecognized in everyday clinical practice, so more frequent evaluation is necessary. It is essential to evaluate the level of AT in order to define the exact pathogenetic mechanism of thrombotic events, especially major unprovoked thromboembolic episodes in a specific population. Although AT deficiency is commonly detected during heparin therapy and suspected of causing heparin resistance, it is crucial to recognize acquired conditions that carry a risk of AT deficiency. Regulating AT levels is critically important in the prophylaxis and therapy of thrombotic events. Although AT activity showed a strong positive correlation with higher heparin requirements, higher average AT activity did not show a significant difference in the rate of bleeding events. Therefore, future studies should compare the effects of higher endogenous AT activity with exogenously supplemented AT activity to differentiate between their contributions to the survival benefit.

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ZNAČAJ EVALUACIJE I SUPLEMENTACIJE ANTITROMBINA U KLINIČKOJ PRAKSI

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Sažetak

Antitrombin (AT) je ključni prirodni antikoagulans koji inhibira trombin (FIIa), faktor Xa (FXa), u manjoj meri i druge prokoagulantne proteaze, održavajući hemostatski balans.

Nedostatak AT, nasledni ili stečeni, značajno povećava rizik za nastanak venskog tromboembolizma (VTE), različitih opstetričkih komplikacija, a kod određenih subtipova i arterijskih tromboza. Osobe sa deficitom AT imaju 15 puta veći rizik za razvoj tromboza.

Stečeni deficit antitrombina nastaje usled hipoprodukcije, gubitka, povećane potrošnje, dilucijom ili kombinacijom navedenih patoloških procesa i dosta je češći u odnosu na urođeni deficit AT.

Kod kritično obolelih pacijenata često se detektuje stečena deficijencija antitrombina; međutim, rutinsko praćenje nivoa antitrombina trenutno nije podržano snažnim dokazima i trebalo bi da se sprovodi samo u odabranim kliničkim indikacijama posebno kod onih sa visokim rizikom od tromboembolije.

Antitrombin je neophodan za dejstvo nefrakcionisanog heparina, niskomolekulskog heparina i fondaparinuksa pa u slučaju njegovog nedostatka dolazi do razvoja rezistencije na dejstvo navedenih lekova. Deficit AT se često detektuje prilikom nalaza rezistencije na primenu gore pomenutih od antitrombina zavisnih antikoagulanasa kada se registruje insuficijentni nivo anti Xa aktivnosti.

Primena antitrombina indikovana je u prevenciji i terapiji trombotičnih događaja kod osoba sa urođenim ili stečenim deficitom.

Malo je poznato da supraterapijski nivoi antitrombina uz heparinsku terapiju mogu izazvati hemoragijsku tendenciju i dovesti do manifestnih krvarenja. Uloga AT u patogenezi tromboembolizma, rezistenciji na antikoagulanse, i njegova plejotropna dejstva upućuju na veliki klinički značaj i potencijal za dalja istraživanja.

Ključne reči: antitrombin, tromboembolizam, heparinska rezistencija, hemostaza

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