Coagulation Disorders in Infective Endocarditis: Role of Pathogens, Biomarkers, Antithrombotic Therapy (Systematic Review)

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The issue of antithrombotic therapy in patients with infective endocarditis has been studied for over 75 years. During that time studying of pathogenesis of the disease and its embolic complications, lead to the introduction of the concept of "immunothrombosis". That mechanism allows infective agents (mostly bacteria) to be cloaked from the immune system and to multiply freely, leading to growth of vegetation, thus resulting in higher chance of fragmentation. Small-scale experimental and clinical studies on the correction of hemostatic disorders in infective endocarditis, that were performed in 20th century, didn't show any significant results, that could affect clinical practice. However, reinterpretation of available data on coagulative system will allow to have elements of hemostasis as an application point in treating infective endocarditis. The article will discuss latest insights on the role of hemostasis system in pathophysisology of infective endocarditis, its effects on the development of the embolic complications, perspectives for diagnostics and treatment.

Key words: infective endocarditis, immunothrombosis, hemostasis, embolic events, biomarkers of coagulation and fibrinolysis, prevention of embolism, antithrombotic therapy.

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Introduction

The high level of in-hospital mortality remains unchanged from 17.1% to 31.3%, despite all the advances in the diagnosis and treatment of infective endocarditis (IE) over the past decades [1-3]. According to official statistics, in 2010-2020 hospital mortality in hospitals was 23.11% in Russia and 34.71% in Moscow [4]. A significant contribution to the structure of mortality is made by frequent embolic events (EE) [5]. The blood coagulation system is involved at every stage of the disease: bacterial adhesion to the valve leaflets and formation of vegetation, growth of the vegetation in size, fragmentation of the vegetation with embolic events, and destruction of the valve leaflets. Thus, disorders in the hemostasis system are an attractive target for antithrombotic drugs, and at the same time, a high risk of hemorrhagic complications limits their use. The first study on the addition of heparin to the treatment of patients with IE was published in 1943 [6,7]. Since then, the understanding of the role of hemostasis system disorders in the pathogenesis of the disease and its complications has become much deeper, but the principles of correcting these disorders continue to raise more and more questions, despite the accumulated experimental and clinical data. In this article, we will consider ideas about the role of the state of the hemostasis system in the pathophysiology of IE, its effect on the development of embolic complications, diagnosis, treatment and prevention of disorders in the hemostasis system in such patients.

Methodology

Literature searches were performed in the MEDLINE/PubMed, EMBASE (Excerpta Medica) and Cochrane Central Register of Controlled Trials databases. We used the terms «antiplatelet agents» OR «anticoagulants» OR «fibrinolytic agents» AND «endocarditis» as the search term for antithrombotic therapy. The date of the last search is 01/09/2022. The medicines included in the search query are anticoagulants (UFH, LMWH, warfarin, dicumarol, dabigatran, apixaban, rivaroxaban), antiplatelet agents (aspirin, clopidogrel, abciximab, ticagrelor, ticlopidine, dipyridamole, pentoxifylline, tirofiban, eptifibatide, abciximab, sulfinpyrazone), fibrinolytics (urokinase, alteplase). They have been used in experimental animal studies or have been administered to patients with ethical approval, or have been studied in subgroups of patients who were prescribed these medications for other indications. 31 studies were selected for review from 926 studies requested: experimental animal studies, case series, retrospective and prospective cohort studies, randomized trials, one meta-analysis with any level of statistical processing. We performed standard search queries without systematization for the remaining sections of the review.

Pathophysiological mechanisms of hemostasis local disturbance and formation of valvular vegetations with the participation of infective endocarditis pathogens

A characteristic feature of IE is the presence of an infected vegetation that forms on the endocardium. Platelet microthrombus, which is a potential basis for small sterile endocardial vegetation, is formed upon local activation of the hemostasis system. Sterile vegetation can be infected by bacteria present in the bloodstream, either in a free state or associated with non-activated platelets or antibodies [8]. The conditions that promote the formation of vegetation and the contribution of the links of the hemostasis system to this process are extremely important (Fig. 1) [8-17].

Currently, IE is considered as a unique model of endocardial thromboinflammatory disease, reflecting the close relationship between the hemostasis system and innate immunity, which is referred to as «immunothrombosis» [14]. Immunothrombosis is a physiological process of activation of endothelial, platelet and plasma components of hemostasis, leading to the release of neutrophil extracellular traps (NETs), which serve to capture and destroy bacteria that have entered the bloodstream. Immunothrombosis causes local activation of blood clotting to fight bacterial infection and is considered one of the mechanisms of the innate immune response. At the same time, it's important that the resulting protective reaction of the body be adequate to the stimulus that caused it. This balance is often disturbed in acute infections, causing many of them to be complicated by either bleeding or thrombosis. IE is an example of such an imbalance. Immunothrombosis inadvertently creates optimal conditions for the pathogen to shelter from the immune system and allows some bacteria to grow almost unhindered, leading to septic complications and EE, instead of containing the infection (Fig. 2) [14].

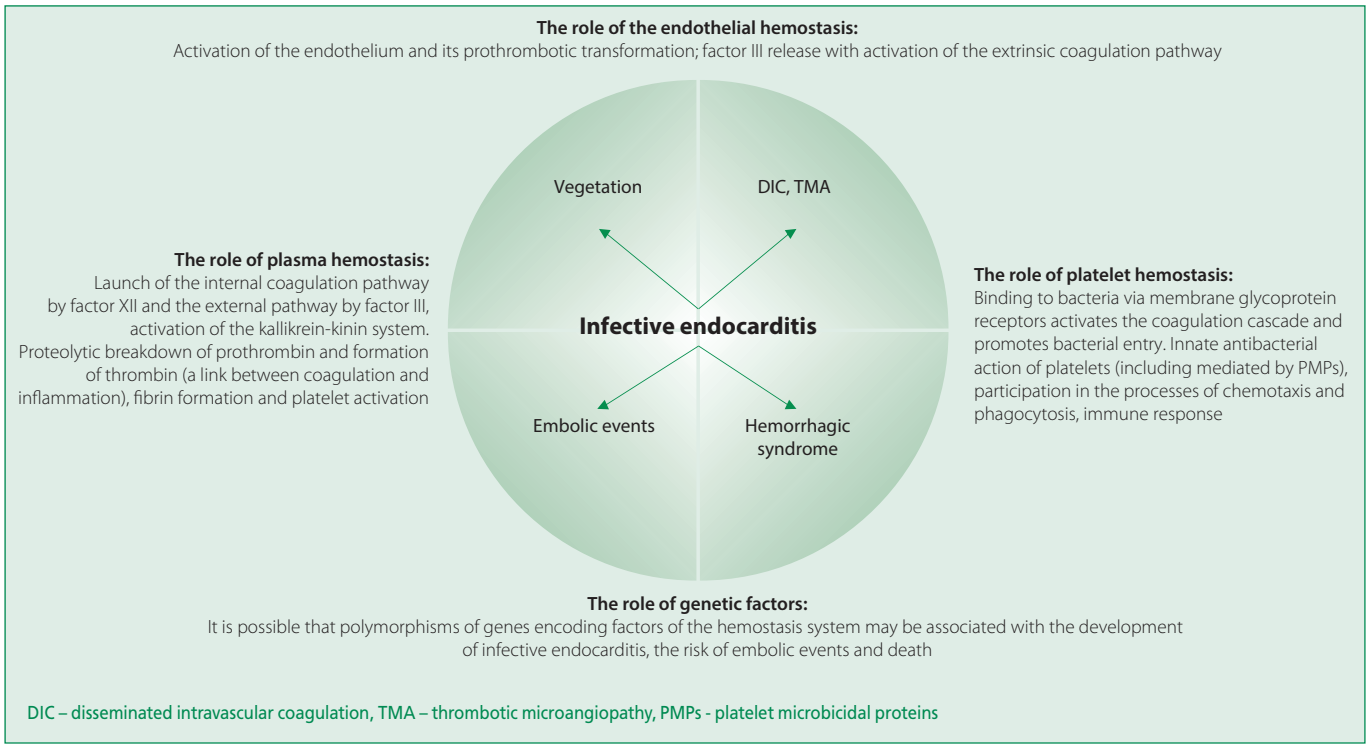

Figure 1. The role of platelets, coagulation cascade, endothelium and genetics in the process of vegetation formation and clinical manifestations of hemostasis disorders in patients with infective endocarditis

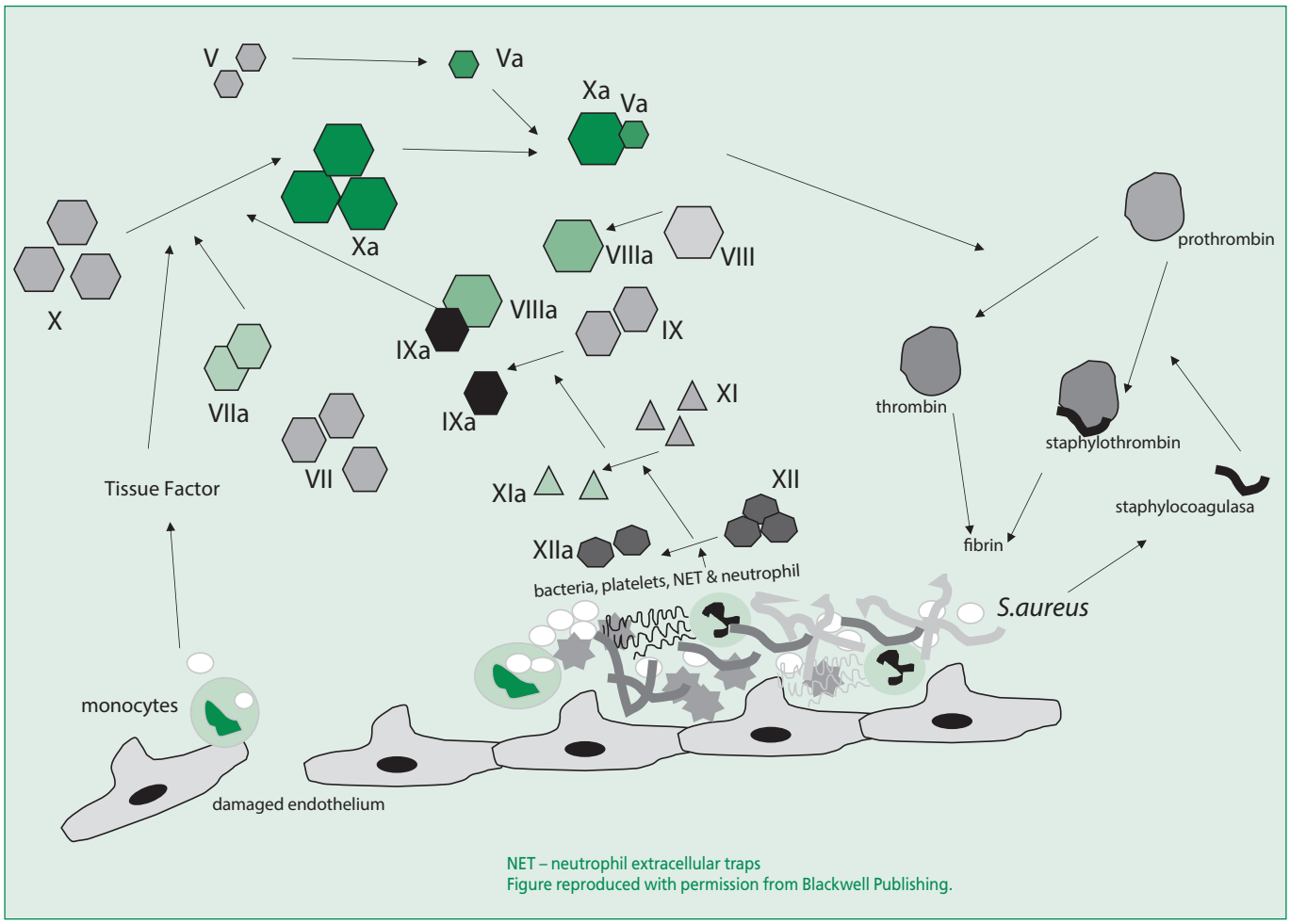

Figure 2. Pathogenesis of vegetation formation by immunothrombosis in infective endocarditis caused by S. aureus [14]

Bacteremia is a prerequisite for the occurrence of infection of the endocardium of valvular structures and the parietal endocardium of the heart. However, only a limited number of gram-positive bacteria from all types of microorganisms that enter the bloodstream easily colonize the endocardium. Most cases of IE are caused by staphylococci, streptococci, or enterococci. Gram-negative bacteria (*Escherichia coli*, etc.) can cause sepsis, but rarely cause IE [14]. The causative agents of IE can be various pathogenic and opportunistic microorganisms [18].

The endothelium of the heart valve is highly resistant to infection in healthy individuals, and IE is rare. Previously, IE was thought to occur only in damaged heart valves (eg, rheumatic or congenital disease) when turbulent blood flow occurs, damaging the endothelium, as well as areas of slow blood flow, which increases the contact time between the endothelium, bacteria and circulating proteins. Nowadays, rheumatic heart disease has become rare, and new risk factors for IE have emerged: prosthetic valves, the presence of pacemakers and intracardiac devices, degenerative valvular disease, and intravenous drug use. Almost half of patients with IE have structurally normal valves before the onset of the disease, so a new concept has emerged that not only damage, but also inflammation of the endothelium makes the valves vulnerable to infection (especially for *Staphylococcus aureus,* since streptococcal infection is much less common in this case) [14]. But Cbm+/PA- strains of *Streptococcus mutans* (a pathogen that causes caries) are highly virulent strains that also lead to the development of IE. These strains have significantly higher fibrinogen binding rates and induce an increased level of platelet aggregation in the presence of fibrinogen [19].

In the *Streptococcus mutans* model, layers of NETs that connect and capture bacterial-thrombotic aggregates within the vegetation and promote their growth were identified in the rat body. Activated platelets and specific IgG adsorbing bacteria are required for the formation of these neutrophil traps. Prophylactic administration of DNase I (an endonuclease that cleaves phosphodiester bonds in DNA) intravenously before infection reduced the size of the vegetation and the number of bacteria in the vegetation, and it also reduced aortic valve insufficiency. The introduction of DNase I 4 hours after infection also demonstrated a therapeutic effect in the experiment: there was a decrease in the size of the vegetation and the number of colonizing bacteria. The effect of DNase I, most likely, was due not to a bactericidal effect on *Streptococcus mutans*, but to the cleavage of NETs formed under the action of activated platelets. This study by C.J. Jung et al. showed that bacteria stimulate the formation of NETs, causing an increase in the amount of P-selectin on platelets, which activates signaling molecules such as the Src, PI3K and p38 MAPK family kinases. NETs, in turn, serve as a scaffold for further enhancing the capture of bacterial thrombotic aggregates and promote their formation and growth [20].

Staphylococcus aureus is the main pathogen causing IE. *Staphylococcus aureus* can adhere to the heart valve without preexisting valvular disease, but the exact mechanism of adhesion remains unknown. Recent evidence suggests that Willebrand factor (UL-vWF) ultra-large multimers may promote bacterial adhesion to intact valvular endocardium (*Staphylococcus aureus* binds to the A1 and A3 domains on UL-vWF molecules) [21]. *Staphylococcus aureus* coagulases directly induce coagulation by activating prothrombin. Staphylococcus aureus also affects the process of fibrinolysis, causing the activation of plasminogen through staphylokinase. In addition, *Staphylococcus aureus* expresses clumping factor A (ClfA), a fibrinogen-binding adhesin that binds bacteria to platelets and induces platelet aggregation and activation via the αIIbβ3 receptor [22].

Direct binding of Staphylococcus aureus to platelets is a major virulence factor in the pathogenesis of IE and is critical for pathogenic events that occur after valve surface colonization, such as vegetation formation and septic emboli. P.M. Sullam et al. used insertional mutagenesis (transposon Tn551) of the parent strain of *Staphylococcus aureus* ISP479 in their study to create an isogenic variant (strain PS12) that binds platelets minimally. PS12 binding to platelet monolayers was reduced by 67.2% compared to ISP479. Also, PS12 binding to platelets in suspension was reduced by 71.3% by flow cytometry. The ISP479 and PS12 strains were phenotypically identical apart from differences in platelet binding as determined by numerous in vitro investigators, including their expression of two virulence factors: fibrinogen and fibronectin binding. A significantly lower likelihood of developing IE, lower microbial density in vegetation, and a lower incidence of renal abscesses compared to animals that were inoculated with the parental

line were found when testing in a rabbit model in animals that were inoculated with the PS12 strain [23].

Many researchers have concluded that fibronectin serves as a receptor that binds bacteria to various cell types. The binding area of *Staphylococcus aureus* to fibronectin is within the N-terminal peptide and can be degraded by plasmin. *Staphylococcus aureus* with reduced fibronectin binding capacity does not adhere well to valvular vegetations. Fibrinogen/fibronectin-binding FnBPA and FnBPB proteins are the main platelet-activating factors on the surface of *Staphylococcus aureus*, interacting with platelet surface receptors to form «bridges» [24].

Platelets alleviate the pathogenesis of endovascular infections through local secretion of antimicrobial peptides (tPMPs). The sensitivity profile of *Staphylococcus aureus* to tPMP in vitro significantly affects a number of cardiological and microbiological parameters associated with disease severity and prognosis in IE [25].

Changes in hemostasis parameters have been studied in bacteremia caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). The study included two groups of patients: group 1 – with IE and MSSA-bacteremia (n=21), group 2 – patients with thrombotic events (myocardial infarction, unstable angina, stroke, transient ischemic attack, infarcts of parenchymal organs, deep thrombosis vein or pulmonary embolism) and MSSA bacteremia without IE (n=8). Control groups of patients matched by age and gender were matched for each group [patients without IE with MSSA-bacteremia for group 1 (n=21), patients without thrombotic events with MSSA-bacteremia for group 2 (n=34)]. The results demonstrated that increased activity of the hemostasis system in the early stages (low level of antithrombin III, increased level of thrombin-antithrombin, prolongation of APTT) was observed in patients with IE compared with the control group, and also changes in the hemostasis system (increased level of thrombin-antithrombin) were observed in early terms in patients with thrombotic events compared with the control group. The authors concluded that changes in the hemostasis system in MSSA-bacteremia in the early stages of the disease may have a prognostic value for determining the risk of developing IE and/or thrombotic events [26].

The importance of determining biomarkers of the hemostasis system for diagnosing and predicting the risk of embolic events in infective endocarditis

The measurement of circulating biomarkers of coagulation and fibrinolysis may be useful in diagnosing and risk stratifying the development of EE in order to prevent them, given the key role of the hemostasis system in the pathogenesis of IE and EE, but these parameters are currently understudied. Table 1 presents information about the currently available studies on the role of biomarkers of the hemostasis system in IE.

Prevention and treatment of embolic events in infective endocarditis: risk assessment, antithrombotic therapy, current strategies

Prevention of embolic complications is a difficult task. Patients often come to the hospital with an already developed embolism. Embolism occur in 20-40% of IE cases, but their frequency decreases to 9-21% after the start of antibiotic therapy [5]. Embolism can be asymptomatic in about 20% of patients with IE and should be diagnosed using non-invasive imaging techniques (the brain and spleen are the most common organs to embolism in IE) [32].

The risk of embolism is also very high in the first 2 weeks of antibiotic therapy, which is associated with the size and mobility of the vegetation. Therefore, early surgical intervention (during the first days of antibiotic therapy) is considered to prevent embolic complications, significantly reducing the risk of death in patients with large vegetations, compared with conservative therapy. However, we must take into account the risk of surgery, the clinical status and comorbidities of the patient. Early surgical intervention reduces the incidence of embolism in patients with high-risk IE, but the quantitative assessment of embolic risk remains a difficult task, important for making decisions about the further treatment of the patient [33]. There are currently two clinical risk assessment calculators for developing EE. Factors associated with EE are age, diabetes mellitus, atrial fibrillation, previous embolism, vegetation length, and *Staphylococcus aureus*. A multivariate embolic risk prediction model was developed using these variables. It demonstrated high accuracy with a C index of 0.72 (95% confidence interval [CI] =0.65-0.81) and a significantly higher cumulative incidence

Table 1. Diagnostic and prognostic value of biomarkers of coagulation in infective endocarditis

Marker	Diagnostic value	Predictive value	Comment
D-dimer	An increase in plasma concentration [27]	D-dimer level >425 ng/dl has shown a sensitivity of 77% and a specificity of 62% in patients with IE and has been suggested to predict the risk of embolism	Potential role in predicting embolism. More studies are needed.
PF1+2	An increase in plasma concentrations in patients with IE and EE compared with patients with IE without EE [28]	No data	Suggestion of a potential role in predicting embolism based on detected hypercoagulability
TAT	An increase in plasma concentrations in patients with IE and EE compared with patients with IE without EE [26,28]	No data	Suggestion of a potential role in predicting embolism based on detected hypercoagulability
PAI-1	An increase in plasma concentrations in patients with IE and EE compared with patients with IE without EE [28]	No data	Suggestion of a potential role in predicting embolism based on detected hypercoagulability
β-TG	An increase in plasma concentrations in patients with IE and EE compared with patients with IE without EE [28]	No data	Suggestion of a potential role in predicting embolism based on detected hypercoagulability
PF4	An increase in plasma concentrations in patients with IE and EE compared with patients with IE without EE [28]	No data	Suggestion of a potential role in predicting embolism based on detected hypercoagulability
Antithrombin III	Activity decreased on day 4, increased on day 90 in patients with bacteremia who developed IE compared with patients without IE [26]	Changes in antithrombin III activity can predict the development of IE on the 4th day ($p<0.05$)	Potential role in predicting the development of IE in patients with bacteremia. Additional larger studies are needed.
APTT	Prolonged in patients with bacteremia who developed IE compared with patients without IE [26]	Changes in APTT can predict the development of IE on the 4th day ($p<0.05$)	Potential role in predicting the development of IE in patients with bacteremia. Additional larger studies are needed.
E-selectin	An increase in serum concentrations in patients with IE compared with patients without IE [29]	No data	Potential role in the diagnosis of IE
VCAM-1	An increase in serum concentrations in patients with IE compared with patients without IE [29]	No data	Potential role in the diagnosis of IE
SFMC	An increase in serum concentrations in patients with IE and EE compared with patients with IE without EE [30,31]	No data	Potential role in the diagnosis of embolism in IE

PF1+2 – fragments of prothrombin F1+2, TAT – thrombin-antithrombin III complex, PAI-1 – plasminogen activator-1 inhibitor, β-TG – beta-thromboglobulin, PF4 – platelet factor 4, APTT – activated partial thromboplastin time, VCAM-1 – vascular endothelial adhesion molecule-1, SFMC – soluble fibrin-monomeric complexes, IE – infective endocarditis, EE – embolic events

of EE observed in patients with a highly predictive embolic risk ($p<0.0001$). A strong correlation was found between predicted by the calculator (Hubert calculator) and observed EE [34]. Variables such as vegetation size ⩾ 13 mm and pathogen *Staphylococcus aureus* were included in another calculator model (Rizzi). Together they were used to predict the risk of EE. Each factor was assigned a point of 1 (overall risk score range: minimum 0 points; maximum 2 points), resulting in a three-tier rating: low risk, intermediate risk, and high risk. The 30-day cumulative embolic rate varied significantly across risk categories: 11.8% (95% CI=7.2-19.2) in the low risk category, 24.5% (95% CI=20.3-37, 0) in the intermediate risk category, 37.7% (95% CI=22.1-64.9) in the high risk category [35]. Both EE risk calculators have not yet been approved for routine use.

Methods for the prevention of EE with medicines using antiplatelet agents and anticoagulants are being studied in addition to tools for predicting EE. Experimental and clinical studies of antithrombotic therapy in patients with IE are presented in Table. 2.

The potential benefit of prescribing antithrombotic drugs in IE has been shown in experimental studies,

Table 2. Experimental and clinical studies of antithrombotic therapy in infective endocarditis

Study (year) [referenc]	ATT	Population and study design	Key results
Experimental studies			
Hook E.W. (1974) [36]	Warfarin	Experimental animals: rabbits	The size of the vegetation was smaller in the group of experimental animals receiving warfarin, but life expectancy was lower in the same group.
Levison M.E. (1977) [37]	ASA	Experimental animals: rabbits	ASA at concentrations exceeding 50 mg/dl did not attenuate the development of IE in the group of experimental animals. No differences were found in the formation of vegetations and susceptibility to infection between rabbits receiving ASA and the control group.
Thörig L. (1977) [38]	Warfarin	Experimental animals: rabbits	Larger bacterial inoculums were required in the warfarin group of experimental animals to induce *Staphylococcus epidermidis* infection, and the infection rate of the vegetation was significantly lower. In the group of experimental animals, warfarin didn't affect the induction of *Streptococcus sanguis* infection and its course, however, treatment with warfarin led to rapidly progressive bacteremia.
Johnson C.E. (1982) [39]	Sulfinpyrazone	Experimental animals: rabbits	In the group of experimental animals, sulfinpyrazone reduced the total size of vegetations.
Pujadas R. (1988) [40]	ASA	Experimental animals: rabbits	Low doses of ASA (1-10 mg/kg/day) inhibit the formation of vegetations in the group of experimental animals, while high doses of ASA (50-500 mg/kg/day) have no effect.
Nicolau D.P. (1993) [41]	ASA	Experimental animals: rabbits	ASA significantly reduced the size of the vegetation in the group of experimental animals. The rate of microbial clearance of the vegetation was directly proportional to the observed size reduction. The authors concluded that the effect of ASA on the decrease in bacterial density and size of vegetation is a dose-dependent phenomenon.
Nicolau D.P. (1995) [42]	ASA	Experimental animals: rabbits	Experimental animals received ASA at doses of 2.5, 10, 20 and 50 mg/kg daily. The 2.5 and 10 mg/kg treatment groups had a statistically significant reduction in vegetative weight compared to the no-ASA control group (p=0.0001). The 10 mg/kg dose also resulted in a significant reduction in bacterial density compared to the control group (p=0.0084). Combination therapy with ASA and vancomycin resulted in a significant reduction in vegetation weight (p=0.002).
Nicolau D.P. (1998) [43]	Ticlopidin	Experimental animals: rabbits	Ticlopidine (10 mg/kg) in combination with vancomycin (50 mg/kg) reduced the progression of growth of aortic valve vegetation in the group of experimental animals. The effect was not related to the pharmacokinetic interaction of these two drugs.
Nicolau D.P. (1999) [44]	ASA Ticlopidin	Experimental animals: rabbits	In the group of experimental animals, the appointment of combination therapy (ASA 10 mg/kg + tiplopidin 10 mg/kg) significantly reduced the vegetation weight compared to the control group. The use of drugs in monotherapy also reduced the vegetation size, but no statistically significant results were obtained.
Kupferwasser L.I. (1999) [45]	ASA	Experimental animals: rabbits	In the group of experimental animals, ASA reduced the size of vegetation and growth rate, as well as the number and severity of embolic complications.
Veloso T.R. (2015) [46]	ASA Ticlopidin	Experimental animals: rats	In a group of experimental animals, the combination of ASA and ticlopidine effectively prevented the development of IE caused by *Str. gordonii*. The combination showed a borderline protective effect against IE caused by S. aureus.
	Abciximab	Experimental animals: rats	In a group of experimental animals, abciximab successfully prevented both IE caused by Str. gordonii and IE caused by S. aureus.
	Dabigatran etexilate	Experimental animals: rats	In a group of experimental animals, dabigatran etexilate at doses of 5 mg/kg and 10 mg/kg effectively prevented IE caused by S. aureus, but the drug was ineffective against IE caused by Str. gordonii.
	Eptifibatide Acenocoumarol	Experimental animals: rats	In a group of experimental animals, eptifibatide and acenocoumarol were ineffective in preventing the development of experimental IE caused by Str. gordonii or S. aureus.

Table 2. Experimental and clinical studies of antithrombotic therapy in infective endocarditis (continuation)

Study (year) [referenc]	ATT	Population and study design	Key results
Hannachi N. (2020) [47]	Ticagrelol	In vitro study	Ticagrelor showed the highest inhibitory effect on platelet activation (p<0.001) and aggregation (p<0.01) induced by Staphylococcus aureus
	ASA Ticagrelol	In vitro study	The combination of ASA and ticagrelor had the strongest inhibitory effect on platelet activation and aggregation (P<0.05 and P<0.001, respectively) in the case of Streptococcus sanguis
	Tirofiban	In vitro study	Tirofiban inhibited both platelet activation and aggregation induced by S. aureus but didn't inhibit activation induced by S. sanguinis.
Clinical studies			
Lichtman S. (1943) [6]	Heparin	Review of series of observations and clinical cases; Patients with IE of native valves (n=109)	6.5% of patients were cured
Katz L.N. (1944) [48]	Heparin	A series of observations; Patients with IE of native valves (n=4)	0% of patients were cured Intracranial hemorrhages were in 50% of patients.
Loewe L. (1946) [49]	Heparin	A series of observations; Patients with IE of native valves (n=4)	100% of patients were cured
Priest W.S. (1946) [50]	Heparin Dicoumarol	A series of observations; Patients with subacute IE of native valves (n=34) (8 patients received heparin, 3 patients received dicoumarol, 4 patients received heparin + dicoumarol,19 patients didn't receive anticoagulants). All patients received penicillin	65% of patients were cured. 2 fatal bleeding occurred, presumably due to the use of anticoagulants. The use of anticoagulants didn't prevent 5 major EEs.
Thill C.J. (1947) [51]	Dicoumarol	A series of observations; Patients with IE of native valves (n=22) (13 patients received penicillin + dicoumarol; 9 patients received penicillin)	54% of patients were cured
Wilson W.R. (1978) [52]	Warfarin or Heparin	Retrospective observational cohort study; Patients with IE of prosthetic valves (n=52) (38 patients with IE received adequate anticoagulant therapy)	Mortality was 57% versus 47% in patients without adequate anticoagulant therapy. 71% of EE in patients without adequate anticoagulant therapy of embolism in the brain caused 62.5% of deaths
Paschalisa C. (1990) [53]	Warfarin	Retrospective observational cohort study; Patients with IE (n=61) (20 patients with IE had prosthetic valves and received warfarin)	EE occurred in 30% of patients receiving warfarin with prosthetic valves versus 29% of patients with native valves not receiving anticoagulants
Taha T.H. (1992) [54]	ASA	Prospective observational cohort study; Patients with IE (n=9) (4 patients received low-dose ASA (75 mg/day).	Two symptomatic cerebral infarctions and one myocardial infarction occurred in the control group (not taking ASA). The average vegetation area decreased in the ASA group compared to its increase in the control group. There were no side effects or complications associated with taking ASA.
Мильто А.С. (1997) [55]	Ticlopidin Pentoxifylline ASA Dipyridamole Nicergoline Heparin Fresh frozen plasma	Prospective cohort intervention study; Patients with IE (n=84)	Blood clotting indicators quickly came to normocoagulation in the group of patients receiving antiplatelet agents. There were no hemorrhagic complications in the study group.
Chan K.I. (2003) [56]	ASA	Randomized clinical study; Patients with IE (n=115)	EE occurred more frequently in the ASA group (28.3% vs. 20.0%, OR=1.62, 95% CI=0.68-3.86, p=0.29). There was a trend towards higher bleeding rates in patients treated with ASA compared with placebo (OR=1.92; 95% CI=0.76-4.86; p=0.075).

Table 2. Experimental and clinical studies of antithrombotic therapy in infective endocarditis (continuation)

Study (year) [referenc]	ATT	Population and study design	Key results
Anavekar N.S. (2007) [57]	ASA Dipyridamole Clopidogrel Ticlopidine (monotherapy or various drug combinations)	Retrospective observational cohort study; Patients with IE (n=600) (125 patients with IE received antiplatelet therapy)	EE occurred less frequently in the ATT group (12.0% vs. 27.8%; p<0.001). The intake of ATT was a protective factor against the onset of EE with an OR of 0.36 (95% CI=0.19-0.68; p=0.002).
Chan K.L. (2008) [58]	ASA	Randomized clinical study; Patients with IE (n=134) (84 patients received long-term ASA, 55 patients received placebo)	Long-term use of ASA may be associated with an increase in the number of bleeding (OR=2.35, p=0.065; AOR =2.08, p=0.059), while there is no significant decrease in the number of EE.
Pepin J. (2009) [59]	ASA and/or Clopidogrel	Retrospective observational cohort study; Patients with IE (n=241) (75 received with IE received antiplatelet therapy: 65 patients received ASA, 5 patients received ASA + clopidogrel, 3 patients received clopidogrel)	Long-term use of antiplatelet drugs before the development of IE is associated with lower mortality (AOR =0.27; 95% CI=0.11-0.64). There was a trend towards a decrease in mortality among patients who started taking antiplatelet drugs after admission to the hospital (AOR =0.29; 95% CI=0.08-1.13). The effect of ASA on mortality was almost the same in patients who received 325 mg per day (AOR =0.25; 95% CI=0.08-0.76) and those who received 80 mg per day (AOR =0. 23, 95% CI=0.07-0.70). Long-term antiplatelet therapy doesn't reduce the risk of major embolism.
Eisen D.P. (2009) [60]	ASA	International prospective observational cohort study; Patients with IE (n=670) (132 patients with IE received ASA)	ASA was associated with a reduction in the number of emergency valve replacements by multivariate analysis (OR=0.58; 95% CI=0.35-0.97; p<0.04). The number of EE in the ASA group didn't decrease, and the number of hemorrhagic events in the same group didn't increase.
Snygg-Martin U. (2011) [61]	Warfarin	Prospective observational cohort study; Patients with IE of native valves (n=587) (48 patients with IE of native valves received warfarin)	Embolism to the brain was significantly less common in patients in the warfarin group (6% vs. 26%; OR=0.20, 95% CI=0.06-0.6; p=0.006). At the same time, the risk of hemorrhagic complications didn't increase.
Habib A. (2013) [62]	ASA	Retrospective observational cohort study; Patients with suspected APU IE (n=392)	IE was confirmed in 21% of patients. Vegetations on valves or electrodes were less common in the ASA group (15% vs. 26%, p=0.01). There was no difference in survival between the two groups.
Ong E. (2013) [63]	Urokinase Alteplase (thrombolytic drugs)	Review of series of observations and clinical cases; Patients with IE (n=9)	55% of patients had intracranial hemorrhage
Eisen D.P. (2015) [64]	ASA	Meta-analysis of 9 observational studies of patients with IE (n=5400), of which 1230 patients received ASA, and in some studies other antiplatelet drugs were used, but it was ASA in 96%.	The risk of a major systemic embolism has been shown to be significantly reduced in patients who have previously received ASA, or started taking it after the diagnosis of IE (OR = 0.66; 95% CI = 0.54-0.81). There was a trend towards a decrease in the risk of bleeding in patients treated with ASA (OR=0.71; 95% CI=0.44-1.14). At the same time, the authors noticed a trend towards an increase in the risk of death close to significant (OR=1.20; 95% CI=0.97-1.50) and concluded that further studies in this area is unpromising.
Pathicka S.M. (2020) [65]	ASA Clopidogrel Warfarin Apixaban Dabigatran Rivaroxaban	Retrospective observational cohort study; Patients with IE (n=34) (20 patients with IE received ATT)	There were no statistically significant results in the study. EE were more common in the ATT group (30% vs. 7.1%, p=0.20). Bleeding was less common in the ATT group (0% vs. 7.1%, p=0.41). Mortality was lower in the ATT group (20% vs. 21.4%, p>0.99).

ATT – antithrombotic therapy, ASA – acetylsalicylic acid, IE – infective endocarditis, EE – embolic events, OR – odds ratio, AOR – adjusted odds ratio, CI – confidence interval

Table 3. Guidelines for the use of antithrombotic therapy in infective endocarditis [5,18]

Guidelines	Grade/level of evidence	
	Ministry of Health of the Russian Federation [5]	ESC [18]
Withdrawal of antiplatelet therapy is recommended for major bleeding	B 1	I B
Withdrawal of anticoagulant therapy is recommended for intracranial hemorrhage	C 1	I C
Replacement of oral anticoagulants (warfarin) with LMWH/UFH for 1-2 weeks in ischemic cerebral infarction without hemorrhagic transformation should be performed under strict control.	C 3	IIa C
LMWH/UFH therapy should be restarted as soon as possible in a multidisciplinary discussion in patients with intracranial hemorrhage and a mechanical valve prosthesis.	C 5	IIa C
In the absence of ischemic cerebral infarction, replacement of oral anticoagulants with LMWH/UFH for 1-2 weeks in case of IE caused by Staphylococcus aureus is carried out under strict control	C 4	IIa C
Thrombolytic therapy is not recommended in patients with IE	C 4	III C

IE - infective endocarditis, ESC – European Society of Cardiology, LMWH – low molecular weight heparin, UFH – unfractionated heparin

but the available clinical estimates are conflicting (see Table 2). The number of patients in clinical studies is small due to the relatively low incidence of IE, and at the moment there are no reliable data indicating the need to start treatment with antithrombotic drugs in patients diagnosed with IE. It's considered that patients who have other indications for antithrombotic treatment (antiplatelet agents or anticoagulants), such as coronary artery disease, atrial fibrillation, or prosthetic heart valves, can continue this treatment if there are no contraindications (for example, bleeding). At the same time, if IE is caused by *Staphylococcus aureus*, it is advisable to replace oral anticoagulants with LMWH/UFH for 1-2 weeks according to experts [66] (Table 3). If embolism develops in the vessels of the brain (ischemic cerebral infarction without hemorrhagic transformation), we showed the replacement of oral anticoagulants, which patients received before the onset of IE, with LMWH/UFH for 1-2 weeks. The use of de novo anticoagulants in patients with IE and cerebral embolism remains an open question, although at the moment there are no negative effects of such therapy in several small non-randomized trials or case reports [67]. Mechanical thrombectomy may be a promising method for the treatment of embolism in cerebral arteries in IE, but there are limited data on the efficacy and safety of this method in proximal occlusions of large cerebral arteries [68]. Patients in whom IE is complicated by coronary artery embolism may undergo thrombus aspiration or mechanical thrombectomy, while balloon angioplasty and stenting, which are associated with the risk of developing mycotic aneurysms, may be required in selected cases [69]. Patients with embolic myocardial infarction in IE should receive antithrombotic therapy only in the case of stenting [69]. There are no data on the effectiveness of antithrombotic therapy in peripheral embolism. In these cases, surgical thrombectomy is recommended. Thrombolytic therapy is absolutely contraindicated in patients with IE.

If we take into account all the knowledge accumulated to date, planning and conducting future studies with the appointment of acetylsalicylic acid for the prevention of embolic events in infective endocarditis is not justified [64]. Ticagrelor and abciximab are currently being discussed as promising antiplatelet agents. Ticagrelor and abciximab emerged as potential antiplatelet drugs for clinical trials in patients with IE following several successful experimental studies in mice with abciximab [64] and the discovery of the antibacterial properties of ticagrelor in addition to its potent antiplatelet activity (a clinical case of reducing the severity of bacteremia caused by Staphylococcus aureus is described). [70]).

However, the best antiembolic strategies currently remain early diagnosis, timely adequate antibiotic therapy, and careful selection of patients who require early surgical intervention [71].

Conclusion

This disease continues to be controversial, despite all the advances in understanding the pathogenesis of IE, combining opposite mechanisms of hemostasis disorders, which is accompanied by a high risk of embolic complications and a consistently high mortality rate. The above explains the difficulties in treating IE:

antibiotic therapy and surgical treatment are traditionally used, and no new medicine class has been added to therapy in the last half century. The close relationship between bacterial virulence factors, the hemostasis system, immune response, and hemodynamics requires further study to better understand the protective and pathological mechanisms of immunothrombosis. Pharmacological interventions in this complex system can lead to various results: from the prevention of the development of IE and EE to the progression of infection and the development of major bleeding, as shown by the few experimental and clinical studies of antithrombotic therapy in IE, which look inconclusive given the low power. Of great importance in the progress of the treatment of this disease is the conduct of more basic research on the study of the hemostasis system, on the basis of which in the future more sensitive EE risk scales and protocols for clinical trials of new medicines can be developed.

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