International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Heparin-Induced Thrombocytopenia in Cardiac Surgery

Dr. Boryana Mihalkova[1], Dr. Lyubomir Bakalivanov[2] MD, PhD, Maria Atanassova[3] M.D., PhD

[1] Resident at the Cardiovascular Anesthesia and Intensive Care Clinic (CVAICC), National Cardiology Hospital, Sofia, Bulgaria

[2]Associate Professor, Head ofthe Cardiovascular Anesthesia and Intensive Care Clinic, National Cardiology Hospital, Sofia, Bulgaria

[3]Associate Professor, Head of Clinic of anesthesiology and intensive care, University Multiprofile Hospital for active treatment "St. Anna" Sofia, Bulgaria

Abstract: ***Heparin is the most commonly used anticoagulant in the treatment of cardiac surgery patients. It is a preferred anticoagulant because of its ease of control by tracking patient-thromboplastin time and the presence of an antidote, Protamine. In addition to the increased risk of bleeding, the use of heparin can lead to a potentially life-threatening condition - heparin-induced thrombocytopenia (HIT). HIT is of two main types - type I HIT of non-immune genesis (also known as heparin-associated thrombocytopenia (HAT)) and type II HIT (a condition of immune genesis, whereby HIT is caused by antibodies that recognize platelet factor 4 (PF4) complexes. and heparin). HIT leads to a state of hypercoagulation, high risk of arterial and venous thrombosis and death. HIT is associated with increased morbidity and mortality rates, higher costs and significantly prolongs hospital stay. Cardiac surgery and resuscitation patients are a risk group for the development of HIT. The diagnosis of HIT in most cases is difficult, but once made, leads to a significant change in the patient's diagnostic and treatment plan and the forthcoming surgical interventions.***

Keywords: Heparin-induced thrombocytopenia type II, Cardiac surgery, Cardiac anesthesia

1. Introduction

Heparin is a mixture of glycosaminoglycans of different chain lengths, high in sulfate groups. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are widely used anticoagulants. Heparin is one of the most commonly used direct anticoagulants during the perioperative period in cardiovascular surgery, including at the CVAICC.

The presence of multiple sulfate groups makes the heparin molecules highly negatively charged and facilitates their interaction with positively charged molecules. [1]

UFH and LMWH have potential side effects, including bleeding and thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is the most common drug-induced immune-related adverse reaction and is potentially life-threatening to the patient. It is associated with a high risk of thromboembolic complications that can lead to limb gangrene (required limb amputation), venous and/or arterial thromboembolism, and even death. [2]

2. Epidemiology and incidence of complications

The overall incidence of HIT is low, ranging from 0.1% to 5%. The incidence may be as high as 3% in patients undergoing cardiac surgery. [3] The use of heparin during the perioperative period leads to an increase in the incidence of HIT. [4] HIT is associated with higher mortality and morbidity rates, higher costs and longer hospital stays. [5]Seigerman et al. in their retrospective multicenter analysis in the national inpatient sample (NIS) 2010-2014 examine the impact of HIT on the outcome of cardiac surgery. [6] HIT is associated with a 50% increase in morbidity and mortality after cardiac surgery, as well as with doubling of the risk of stroke, limb amputation, acute renal and respiratory failure, and tracheostomy. The development of HIT is also associated with an increase in perioperative mortality of up to 50%. Cardiac surgical patients who experience a new onset of thrombocytopenia or a thrombotic incident occurring around 5-10 postoperative days (POD) always have a suspected presence of HIT. In patients with HIT, the risk of bleeding is lower than the risk of thrombosis (arterial or intravenous). The incidence of deep vein thrombosis (DVT) is much higher, but cardiac surgery patients are inversely more likely to develop arterial thrombosis. Aortic and venous cannulation sites are areas of predilection for the development of thrombosis. Venous thrombosis is most commonly manifested as DVT of the upper and lower extremities and pulmonary thromboembolism (PTE) and arterial thrombosis - most often the upper and lower limbs, followed by stroke. In case of gangrene of the finger(s), it is necessary to first exclude a different etiology: use of vasopressors, hypotension, history of chronic arterial insufficiency of the limbs, or cannulation of an artery, in order to monitor invasive arterial pressure. Acute myocardial infarction is a very rare complication of HIT. Patients with HIT after aortic-coronary bypass surgery with clinical and laboratory data of myocardial ischemia have a high incidence of occlusion of venous graft (great saphenous vein). The incidence of occlusion of arterial graft (internal thoracic artery) is low. [3, 7]

2.1 HIT risk factors

Advanced age and female sex (as in other immune-mediated disorders) increase the risk of HIT.[8]Anthropological Indicators: Increased Body Mass Index (BMI). Results of a prospective study by Bloom et al. between August 2007 and January 2014 in patients from surgical and cardiac wards with suspected HIT found a strong relationship between the patient's body weight and the diagnosis of HIT. White adipose tissue secretes a wide variety of highly active

adipocytokines that are involved in inflammatory and immunomodulant processes. [9]Patients with chronic kidney failure, chronic liver failure, congestive heart failure and atrial fibrillation are among the strongest independent risk factors for HIT, probably because the therapy of patients with these conditions is very likely include heparin. [1] Infection predisposes to the formation of anti-PF4 / heparin antibodies, which may increase the risk of disease. Gram-negative infections (Gr -) are associated with a higher seroconversion rate of anti-heparin / PF4 antibody. [8] Patients without a history of heparin exposure may develop HIT spontaneously. This is due to the induced antiplatelet factor 4 (PF4) / polyanionic antibodies from other polyanions such as bacterial surfaces and nucleic acids. [10]A genome-wide retrospective study suggests that TDAG8 and HLA-DRA single mononucleotide polymorphisms (SNPs) are potentially associated with the development of HIT. [10] Rollin et al. found that Arg-His131 FcγRIIa polymorphism affects the risk of HIT-associated thrombosis with a higher thrombosis rate in patients with Arg131 isoform [11].

There is 10 times higher risk of developing HIT when using a prophylactic dose of UFH than LWMH. The risk of HIT with the use of pentasaccharidefondaparinux is almost negligible. Of course, the duration of anticoagulation with heparin promotes HIT. [1,8] HIT is most commonly seen in surgical patients and more specifically in cardiac surgery, since heparin exposure is practically universal. [12] The use of UFH is the gold standard for anticoagulation during cardio-pulmonary bypass surgery in cardiac surgery [13].

Risk factors within cardiac surgery: higher incidence of HIT in emergency than planned operations, reoperation, mediastinal re-exploration, combined surgery, duration of extracorporeal circulation (ECC), duration of aortic clamping, low-flow syndrome development [14] Operations directly related to the aorta are unequivocally related to the postoperative presence of HIT antibodies.[15]

3. Pathogenesis

HIT is a prothrombotic syndrome in which antibodies against complexes of charged molecules are present. In HIT, antibody formation is induced by heparin. IgG antibodies are formed to target positively charged endogenous proteins - platelet factor 4 (PF4). HIT is a serious complication of heparin therapy. This condition is also called white clot syndrome because it presents a high risk of potentially catastrophic venous or arterial thrombosis. The mortality rate in patients with thrombosis is approximately 25%. Thrombocytopenia and thrombosis predominate. [16]There are two types of HIT:Nonimmune heparin-induced thrombocytopenia: type I andimmune HIT: type II.Type I nonimmune HIT is a benign disorder affecting up to 10% of patients on heparin anticoagulant therapy. The mechanism of action is direct interaction between heparin and platelets. Typically, platelet counts are greater than 100.00×10^{12}/L. About two days after the start of heparin therapy, there is a rapid decrease in platelet counts. Platelet counts increase to baseline within 5 days, despite continued heparin anticoagulation, and within 2 days if stopped. [15]Type II heparin-induced thrombocytopenia:HIT is caused by antibodies that recognize complexes of platelet factor 4 (PF4) and heparin.

3.1 HIT antigen: PF4 / heparin complex

PF4 is a positively charged platelet protein stored in platelet α-granules and released in large quantities at the sites of platelet activation. The released PF4 binds to negatively charged glycosaminoglycans (GAGs) on nearby endothelial cells, displaces bound antithrombin (AT) and makes the local environment prothrombotic. Due to the higher affinity of PF4 heparin to other GAGs (heparin >heparan sulfate > dermatan sulfate > chondroitin-6-sulfate > chondroitin-4-sulfate), heparin infusions displace released PF4 from vascular or other cell-binding sites in the blood circulation thus allowing the formation of immunogenic PF4 / heparin complexes. PF4 binds to the negatively charged heparin by electrostatic interactions resulting in the formation of extra-large complexes. Formation of complexes is only possible at strictly defined molar concentrations of PF4 and heparin. PF4-neo-epitopes are expressed upon binding of PF4 to heparin molecules of> 11 saccharide length. Heparin stabilizes the PF4 molecule in its tetrameric form. In the process of binding, heparin acquires a linear structure and allows the attachment of new PF4 tetramers to the growing complex, forming neo-epitopes that are recognized by anti-PF4/H antibodies.Antibodies (IgG class) recognize the neo-epitopes in the PF4 / H complex and activate platelets and monocytes by binding to cellular FcγRIIa receptors. TF, platelet-fibrin thrombus, procoagulantmicroparticles and further platelet activation and release of PF4. The immune response is more frequent than clinically pronounced thrombocytopenia and thrombosis (UFH 8-17%, LMWH 2-8% and ~ 50% in cardiac surgery). In approximately 8% of patients treated with heparin were detected antibodiespositive for HIT but without thrombocytopenia. Between 1 and 5% of patients treated with Heparin have antibodies to HIT and thrombocytopenia. At least 30% of patients with thrombocytopenia develop venous or arterial thromboembolism. Heparin-induced antibodies disappear 2 to 3 months after treatment with heparin is discontinued.[17]

3.2 Mechanisms of thrombosis in HIT

Once an immune response has started, thrombocytopenia and progress toward life-threatening complications of thrombosis are present in seropositive patients. The primary cellular target for HIT antibodies is platelets that express FcγRIIa receptors. These findings were confirmed in a mouse model by Reilly et al. demonstrating the presence of anti-PF4 / heparin antibodies and cellular FcyRIIA for disease manifestations. [18]Binding of HIT antibodies to platelets-FcyRIIA induces platelet activation by intracellular signaling including tyrosine kinase (Syk; 50) and release of procoagulantmicroparticles. Platelet activation in HIT is also accompanied by intense thrombin formation. The mechanisms of thrombin generation in HIT have not been fully elucidated, but recent studies indicate that cellular activation of FcyRIIA monocyte promotes the expression of a tissue factor that accelerates platelet activation through thrombin formation.

4. Clinical Manifestation

The clinical manifestation includes the following symptoms and complications of HIT:

Thrombocytopenia: 50% reduction of platelet counts compared to baseline or values less than 100x109/L.[19]

Hypercoagulable condition leading to the following complications: [7, 17, 19, 20, 21]

Thrombosis: Venous>>arterial(4:1), but in cardiac surgery patients this ratio is 1:1. Venous thrombosis includes:DVT in lower limbs (possibly bilateral), DVT in upper limbs (most commonly associated with intravenous catheters), PTE, a rare complication is adrenal venous thrombosis secondary to adrenal hemorrhagic infarction/hemorrhagic necrosis, cavernous sinus thrombosis; cerebral vein thrombosis. Arterial thrombosis includes: thrombosis of the lower limbs' arteries, thrombosis of the upper limbs' arteries, cerebral artery thrombosis – stroke, mesenteric thrombosis, myocardial infarction, venous graft occlusion.

Other serious complications are: disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), acute systemic reactions (chills, hypertension, tachycardia, dyspnea), thrombosis of a vascular prosthesis, thrombosis of a mechanical or biological valve prosthesis, intracardial thrombosis, vessel fistula.HIT is associated with skin lesions - most commonly necrosis near the points of s.c. injections of heparin, ecchymoses, petechiae, hematomas. Other complications of HIT include: Warfarin-associated limb gangrene, phlegmasiaceruleadolens, difficult cicatrization of an operative wound. Bleeding is a rare in patients with HIT. Patients with HIT may have heparin resistance due to high levels of circulating PF4 and other heparin-binding proteins.

Diagnosing HIT after cardiac surgery and scoring systems

Although the overall incidence of HIT in cardiac surgery patients is in the range of 1 to 2%, patients with HIT in this population are much more common. Nowadays, patients who have been referred for HIT laboratory tests due to suspected HIT are 36 to 51% of all cardiac surgery patients.[22]Thrombocytopenia during the first 72 hours is often present after cardiac surgery [23] requiring ECC. The diagnosis of HIT in cardiac surgery patients is difficult.There are several point systems for determining the probability of HIT. The most commonly used of these are Warkentin 4 T's scoring system [24], HIT expert probability score [25] and the score developed by Lillo-Le Louët et al. [26] for patients undergoing on-pump cardiac surgery with ECC.The high incidence of postoperative thrombocytopenia, the frequent detection of positive heparin-anti-PF4 antibodies during the early postoperative period, and the frequent occurrence of thrombotic and/or thromboembolic incidents make the diagnosis of HIT in cardiac surgery more difficult.Cardiac surgery patients very often experience hemodilution and platelet mechanical damage during cardio-pulmonary bypass (CPB). The presence of an intra-aortic balloon pump (IABP) also leads to thrombocytopenia [20] and is an independent risk factor for the development of HIT. Patients undergoing cardiac surgery are often in a severely impaired general condition (ASA III-IV), sepsis, multiple organ failure, taking various drugs that may alone cause thrombocytopenia. The assessment of the likelihood of HIT is based on a careful assessment of various clinical signs, including thrombocytopenia, the time it takes for platelet count to decrease relative to heparin exposure, the presence of thrombosis or other consequences of HIT, and the presence of other causes of thrombocytopenia. Each of these characteristics requires special care in patients undergoing cardiac surgery, especially with CPB.

4.1 Warkentin 4T's scoring system

It is an evaluation system based on the typical clinical features of HIT, consisting in timing of thrombocytopenia with regard to heparin exposure, the degree of platelet count drop (thrombocytopenia), the strong connection with thrombosis, including skin lesions at heparin injection sites and the presence or absence of an alternative differential diagnosis (other causes of thrombocytopenia). The results of the scoring system regarding the risk of developing HIT are interpreted as follows: high (6-8 points), intermediate (4-5 points) and low (<3 points). [23] In a systematic review and meta-analysis of 13 studies, the negative predictive value of the low probability 4Ts estimate was 99.8%. [22]

4.1.1. Timing– time for platelet count drop

In typical initial HIT, platelet counts begin to decline 5 to 10 days after heparin immunization exposure. [22] In patients after cardiac surgery, platelet count reductions due to HIT should be differentiated from reductions due to surgery and CPB (after CPB, platelet count decreases by 40% on average, [27] reaches its lowest point 48 -72 hours after surgery and then recovery begins). The risk of an immune response to modified PF4 is higher after CPB because the patient's blood is in prolonged contact with the artificial surface of the extracorporeal chain. This promotes the massive activation of platelets and the release of their granules contents as well as of large amounts of platelet factor 4 (PF4) [27]. The second drop in platelet counts between 5 and 10 PODs suggests HIT – the so-called biphasic model (figure 1). In contrast, platelet counts, which drop shortly after CPB and remain low without recovery, are rarely due to HIT and are much more likely to be of another genesis, most commonly infection. [22]

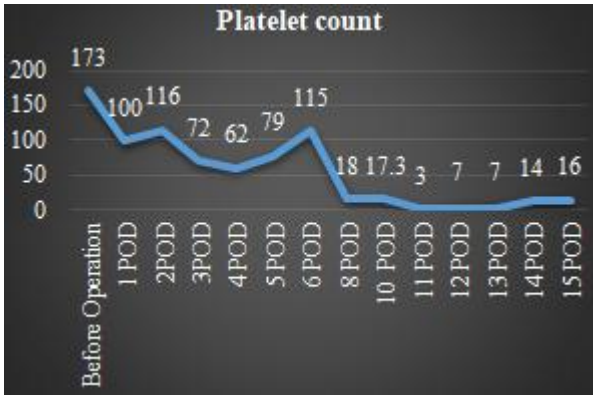

Figure 1: Biphasic platelet count model (59-year-old patient in our clinic after aortic-coronary bypass, mitral valve

prosthesis and IABP with clinical manifestation of HIT and positive anti-PF4-heparin antibodies proven at 8 POD)

In patients with pre-existing anti-PF4 - heparin antibodies, anticoagulation with heparin may lead to an immediate decrease in platelet counts or so-called rapid onset HIT. Such patients have always had been exposed to heparin in the recent past, usually within the last 30 days. In most cases, cardiac surgery patients have a history of recent heparin exposure (e.g., during preoperative cardiac catheterization). Therefore, the rapid onset of HIT should be considered in such patients.

4.1.2. Thrombocytopenia

The percentage drop in platelet count is measured by the peak platelet count after heparin exposure. Platelet count reduction is a major clinical manifestation of HIT. Thrombocytopenia may occur as either an absolute decrease in platelet count (<150 $x10^9$/L) or a relative decrease of 30-50% of the baseline platelet count.

Absolute thrombocytopenia in HIT is often moderate (50-70 $x10^9$/L) and is usually not associated with bleeding complications. Severe thrombocytopenia (<20 $x10^9$/L) may occur as a manifestation of fulminant DIC. [17] Following cardiac surgery, platelet counts usually exceed the baseline platelet count on postoperative days 5 to 7, peak approximately on day 14, and remain elevated above baseline for several weeks before returning to preoperative levels. In patients with baseline thrombocytosis, platelet counts may remain above 150 × 10^9/L, even if it decreases by more than 50%. [22]

4.1.3. Thrombosis and other manifestations

Thrombotic incidents in HIT patients are up to 70%, despite thrombocytopenia. Thrombotic complications can affect the venous and arterial vessels and/or microcirculation. Postoperative patients with HIT prone to venous thromboembolism are at higher risk of developing venous than arterial thrombosis. In contrast, arterial thrombotic complications are more common in patients with HIT who have cardiovascular disease or have undergone cardiac or vascular surgery. [1]Ischemic finger is a common occurrence among cardiac surgery patients and can be considered a sign of HIT. Although HIT may cause small vessel thromboembolism and digital ischemia, other etiologies, such as hypotension, vasopressors and underlying peripheral arterial disease, are likely to be more common in this setting. [22]

4.1.4. Othercausesofthrombocytopenia

In all patients with suspected HIT, it is appropriate to evaluate the possible presence of other probable causes of thrombocytopenia. As noted earlier, after CPB, platelet counts decreased by an average of 40% in the first 48 to 72 postoperative hours. A smaller drop is expected after off pump surgery. In one study, the use of an aortic balloon pump resulted in an average decrease in platelet count of 63% +/- 4% over 4 days. Platelet counts were restored rapidly after balloon pump removal. [28] Like CPBs, Extracorporeal membrane oxygenation (ECMO) and Ventricular Assist Devices (VADs) lead to high risk of developing HIT. Especially in cardiac patients, thrombocytopenia is due to the use of glycoprotein IIb / IIIa antagonists in 0.2 to 2% of patients and may occur within hours after the infusion. [29]The use of various drugs in resuscitation patients may also lead to thrombocytopenia. Vancomycin is a recognized cause of drug-induced immune thrombocytopenia, especially in resuscitation patients or the elderly. [30]

4.2 Lillo-Le Louët scoring system

The scoring system developed by Lillo-Le Louët et al. was specifically designed to evaluate the post-CPB HIT. The model was obtained from 84 patients with suspected HIT after CPB. Independent risk factors for HIT in the cohort under study include a two-phase platelet count profile, an interval of ≥5 days from CPB to putative HIT, and a CPB duration of> 118 minutes. These variables were used to construct a model that correctly classified 34 of 35 HIT-positive patients and 28 of 49 HIT-negative patients in the study group.[26]

4.3 Laboratory methods

The presence of HIT antibodies is a laboratory criterion confirming the diagnosis of HIT. There are two classes of laboratory methods: immunological and functional. Immunological tests are often used for initial evaluation. These include ELISA and PaGIA. Immunological tests can be polyspecific IgG/IgM/IgA and monospecific IgG. They deliver fast results, are easy to implement and affordable. Immunoassays measure the presence of anti-PF4 / heparin antibodies using various antibody capture platforms (enzyme-linked immunosorbent assay, particle gel, immunoturbidimetric, etc.).Advantages of immunoassays are technical simplicity and high sensitivity (> 99%). However, immunoassays have low specificity (30-70%) for the diagnosis of HIT due to the occurrence of seroconversions. The specificity of immunoassays can be enhanced by detection of IgG antibodies and numerical quantification of optical density (OD) and/or titers. [17]Negative result in immunological methods has up to 99% negative predictive value (NPV). Retesting is not necessary unless there is a change in the patient's clinical status. Immunological methods have an excellent sensitivity of 95-100% but low specificity (<90%), i.e. they have a low positive predictive value (PPV). [17]Antibodies against PF4 - heparin have been implicated in the pathogenesis of HIT. However, not all antibodies with this specificity are pathogenic. Therefore, a positive test result in an immunological assay such as PaGIA (or ELISA) should be taken with caution and functional assays should probably also be considered.On the other hand, the absence of antibodies makes HIT very unlikely.

Functional methods reflect the capacity of HIT antibodies to activate normal platelets. These include: serotonin release method (SRA) - gold standard [20], heparin-induced platelet activation (HIPA), argentometry, flow cytometry. Functional methods are useful in positive immunological tests and, if necessary, re-exposure to heparin. They are characterized by high specificity> 95%, sensitivity 56-100%, and PPV 89-100%. [17]

The difficult diagnosis of HIT makes close collaboration between the clinical laboratory and specialists extremely important. Rapid rejection or confirmation of HIT is useful for making the right therapeutic decisions.

5. Treatment

The goals of the treatment of HIT are: interruption of the pathological immune response, suppression of uncontrolled thrombin generation, initiation of an alternative non-heparin anticoagulant, avoidance of vitamin K antagonists, avoiding vena cava filter insertion, reduction of platelet transfusions. Immediate discontinuation of all forms of heparin administration, including s.c. injection, i.v. infusion and flushing of venous catheters with heparinized serum is required. The approximate risk of cross-reactivity with anti-PF4-heparin antibodies when using LMWH is about 90%. [20]

Stopping anticoagulation with heparin alone does not reduce the risk of thrombosis. Interruption of uncontrolled thrombin formation is required. Alternative non-heparin anticoagulants, direct and indirect thrombin inhibitors, are used for this purpose.

Direct thrombin inhibitors: (DTI) - inhibit free thrombin and fibrin-bound thrombin; the dose is easily predictable and the anticoagulation with them is stable with prolonged infusion, since they are not inhibited by plasma proteins. They have a short half-life and have no specific antidote. [29] The molecular structure of DTI does not allow cross-reactivity with anti-P4-heparin antibodies. FDA-approved are two drugs: Argatroban and Lepirudin. They are used according to different indications. Bivalirudin is also a DTI.

Bivalirudin: Authorized for PCI use only in patients without HIT. Its degradation is enzymatic and the degradation products are excreted by the kidneys. It is used with caution in the cardiac surgery of patients with HIT. Intraoperative control of anticoagulation - activated clotting time (ACT).

Argatroban: A synthetic molecule that inhibits the active part of thrombin. Its half-life is 30-50min. It is used for the prevention and treatment of HIT, as well as in percutaneous coronary intervention (PCI) in patients with HIT. It is metabolized in the liver, so the dose should be adjusted in patients with hepatic impairment. It affects INR more than other DTIs. [29]

Lepirudin: Used to treat HIT and HITT. Authorized for use only in the USA. It is excreted by the kidneys and the dose should be consistent with renal function. Half-life 90 min. It is extremely binding to thrombin, leading to an increased risk of bleeding compared to other DTIs. There is a narrow therapeutic window. Target APTT < 65 s, i.e. about 2.5 times the normal value. It is a recombinant protein obtained from yeast. In some cases, there is formation of antibodies against Lepirudin, which could lead to a change in dose. In cardiac operations under ECC, where prolonged hypotension leads to acute liver failure or correction of the abdominal aorta, which occasionally damage the renal vessels, Lepirudinshould be avoided because of its dependence on renal clearance. In such cases, the drug of choice may be Bivalirudin. [20,29]

Desirodin: FDA-approved for use in the prevention of DVT in hip surgery. Permitted for use outside the US. Formation of antibodies against Lepirudin is possible. [29]

Indirect thrombin inhibitors: They do not directly inhibit thrombin but are co-factors of antithrombin and potently potentiate its action. They are excreted by the kidneys and the dose is adjusted for renal failure. They have no sure antidote for bleeding. [29]

Fondaparinux: It is a synthetic pentasaccharide approved for the treatment and prevention of DVT and PTE. It only inhibits Factor Xa. It has excellent bioavailability and the standard dose has a very good predictive anticoagulation effect. Cases have been reported where, after treatment with Fondaparinux, patients had anti-platelet F4 / heparin antibodies without developing HIT. [29,31]

Danaparoid: A mixture of glycosaminoglycans. It mainly inhibits Factor Xa but also to a lesser extent inhibits Factor II (thrombin).

Direct oral anticoagulants: Apixaban, Rivaroxaban, edoxaban and betrixaban are oral inhibitors of Factor Xa, while Dabigatran is an oral DTI. Direct oral anticoagulants theoretically find their place in the treatment of HIT.

For patients with HIT in need of intravenous anticoagulation, the first-choice drugs are Argatroban and Lepirudin (evidence-based medicine). If positive antibodies are available for HIT, it is recommended to delay surgery until the values of the latter become negative. UFH can then be used. In a patient with a history of HIT and no time for antibody testing, UFH may be used if 100 days have elapsed since HIT was discovered. If an emergency cardiac surgery is required in a patient with HIT, off pump surgery is preferable given the lower dose of anticoagulant. In such cases, bivalirudin and lepirudin can be used. [29]

It is a paradoxical strategy to combine heparin with a strong short-acting anti-platelet agent such as iloprost or thyrophiban to inhibit or reduce the risk of developing a HIT response. However, when the effect of iloprost or thyrofiban is exhausted, patients may again be at risk for developing HIT-related complications. Preoperative or intraoperative plasmapheresis aims to reduce the level of HIT antibodies and thus reduce the thrombotic risk. In this case, it is possible to use UFH during CPB.

Switching to oral therapy: patients with acute HIT receiving vitamin K antagonists (VKA) are at risk of a thrombotic incident (often gangrene of the limb) due to protein C depletion. [22] VKA overlap starts with a low initial dose, lower than 5mg daily, whereas the overlapping period is about 5 days. [20]

High-dose IVIG may play a role in selected clinical situations as a way to reduce or eliminate heparin-dependent platelet activation in a patient who continues to have positive antibodies to HIT and who is intentionally re-

exposed to heparin due to need for cardiac or vascular surgery. [32]

6. Discussion

Patients in cardiac surgery and cardio-anesthesia are at risk of developing HIT. Anesthesia during cardiac surgery with CPB in a patient with HIT is a challenge and so is the follow-up and treatment in cardiac resuscitation. This is why UFH and LMWH should always be used with caution. Collaboration between different specialists - surgeon, anesthesiologist, hemostasis specialist is of particular importance. Knowledge of the risk factors and pathogenesis of HIT, as well as the interpretation of clinical manifestations, laboratory tests, and the application of rapid systems can lead to faster diagnosis of HIT and, accordingly, a change in patient treatment.

The authors declare that they have no source of funding.
The authors declare that they have no conflict of interest.

References

[1] Andreas Greinacher*, Theodore E. Warkentin†‡§ and Beng H. Chong¶, 41: Heparin-Induced Thrombocytopenia**,** Platelets (Fourth Edition), 2019, Pages 741-767
[2] B. H. Chong, Department of Haematology, St George Hospital, Kogarah, NSW 2217, Australia, BhdReGews (1988) 2, 108-114
[3] Jigna Solanki, Sundeep Shenoy, Emily Downs, Surabhi Palkimas, Svetlana Goldman, Aditya M. Sharma, Heparin-Induced Thrombocytopenia and Cardiac Surgery, Seminars in Thoracic and Cardiovascular Surgery (2018)
[4] Jerrold H. Levy and Anne M. Winkler, Heparin-induced thrombocytopenia and cardiac surgery, Current Opinion in Anaesthesiology 2010,23:74–79
[5] E. Aguayo et al., Heparin-induced thrombocytopenia in cardiac surgery: Incidence, costs, and duration of stay, Surgery (2018), https://doi.org/10.1016/j.surg.2018.07.013
[6] Seigerman M, Cavallaro P, Itagaki S, et al. Incidence and outcomes of heparin-inducedthrombocytopenia in patients undergoing cardiac surgery in North America: an analysis of thenationwide inpatient sample. Journal of cardiothoracic and vascular anesthesia. 2014;28(1):98-102
[7] Liu JC, Lewis BE, Steen LH, et al. Patency of coronary artery bypass grafts in patients withheparin-induced thrombocytopenia. The American journal of cardiology. 2002;89(8):979-981
[8] AllysonPishkoMDAdamCukerMD, MS. Transfusion Medicine and Hemostasis (Third Edition). Clinical and Laboratory Aspects. Chapter 104 – Heparin-Induced Thrombocytopenia. 2019, pages 627-640
[9] Matthew B. Bloom, MD, Andrea A. Zaw, MD, David M. Hoang, MD, Russell Mason, PharmD, Rodrigo F. Alban, MD, Rex Chung, MD, Nicolas Melo, MD, Oksana Volod, MD, Eric J. Ley, MD, and Daniel R. Margulies, MD, Los Angeles, California. Body mass index strongly impacts the diagnosis and incidence of heparin-induced thrombocytopenia in the surgical intensive care unit. J Trauma Acute Care Surg. 2016 Mar; 80(3):398-403; discussion 403-4. doi:10.1097/TA.0000000000000952.
[10] Takuya Okata1, Shigeki Miyata2, Fumio Miyashita1, Takuma Maeda2, & Kazunori Toyoda1. Spontaneous heparin-induced thrombocytopenia syndrome without any proximate heparin exposure, infection, or inflammatory condition: Atypical clinical features with heparin-dependent platelet activating antibodies Platelets, Early Online: 1–6 2014 Informa UK Ltd. DOI: 10.3109/09537104.2014.979338
[11] Rollin J, Pouplard C, Sung HC, et al. Increased risk of thrombosis in FcγRIIA 131RR patients with HIT due to defective control of platelet activation by plasma IgG2. Blood. 2015;125(15):2397–2404
[12] Natalia S. Ivascu MD, Meghann Fitzgerald MD, Kamrouz Ghadimi MD, Prakash Patel MD , Adam S. Evans MD, Lee A. Goeddel MD, MPH , ShazShaeÞ MD, John Klick MD , Angela Johnson MD, Jesse Raiten MD, Jiri Horak MD, Jacob Gutsche MD,Heparin Induced Thrombocytopenia: A Review for Cardiac Anesthesiologists and Intensivists, *Journal of Cardiothoracic and Vascular Anesthesia* (2018), doi: https://doi.org/10.1053/j.jvca.2018.10.035
[13] Pascale Piednoir, MD,* Nicolas Allou, MD,* Sophie Provenchère, MD,* Clarisse Berroeta, MD,†Marie-Geneviève Huisse, MD,‡ Ivan Philip, MD,† and Nadine Ajzenberg, MD, PhD. Heparin-Induced Thrombocytopenia After Cardiac Surgery: An ObservationalStudy of 1,722 Patients
[14] A. Assmann, U. Boeken, P. Feindt, P. Schurr, P. Akhyari, A. Lichtenberg, Heparin-induced Thrombocytopenia Type II after Cardiac Surgery: Predictors and Outcome, original cardiovascular/society paper, 463-465
[15] Xiumei Sun, MDa,*, Peter C. Hill, MDa, Sharon L. Taylor-PaneK, RNa, Paul J. Corso, MDa,and Joseph Lindsay, MDb, Heparin-Induced Thrombocytopenia in Contemporary Cardiac Surgical Practice and Experience With a Protocol for Early Identification. Am J Cardiol. 2016 Jan 15;117(2):305-9. doi: 10.1016/j.amjcard.2015.10.047. Epub 2015 Nov 6.
[16] Mary Louise Turgeon. Clinical Hematology Theory and practice. Fifth edition. 2012, 2005 by Lippincott Williams & Wilkins, a Wolters Kluwer businessPrinciples and Disorders of Hemostasis and Thrombosis 434
[17] Gowthami M. Arepally, MD. Heparin-Induced Thrombocytopenia. Blood First Edition Paper, prepublished online April 17, 2017; DOI 10.1182/blood-2016-11-709873
[18] Reilly MP, Taylor SM, Hartman NK, Arepally GM, Sachais BS, Cines DB, et al. Heparin-induced thrombocytopenia/thrombosisin a transgenic mouse model requires human platelet factor 4 and platelet activation through fcgammariia. Blood 2001; 98:2442–7.
[19] L. Bernardo Menajovsky, MD, MS. Heparin-induced thrombocytopenia: clinical manifestations and management strategies. The American Journal of Medicine (2005) Vol 118 (8A), 21S–30S
[20] Steele J, Kadosh B, Gulkarov IM, Salemi A (2011) Heparin Induced Thrombocytopenia and Cardiac

Surgery: A Comprehensive Review. J Blood DisordTransfus S2:003. doi:10.4172/2155-9864.S2-003
[21] Ketha S, Smithedajkul P, Vella A, Pruthi R, Wysokinski W, McBane. Adrenal haemorrhage due to heparin-induced thrombocytopenia.Thromb Haemost.2013 Apr;109(4):669-75. Epub 2013 Feb 07
[22] Allyson M. Pishko, MD1 Adam Cuker, MD, MS1,2. Heparin-Induced Thrombocytopenia in Cardiac Surgery Patients.
[23] Linda J. Demma, PhD, and Jerrold H. Levy, MD, FAHA.Diagnosing Heparin-Induced Thrombocytopenia in Cardiac Surgical Patients: Not as Easy as You Think.
[24] Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J ThrombHaemost 2006; 4: 759–65.
[25] Cuker A, Arepally G, Crowther MA, Rice L, Datko F, Hook K, Propert KJ, Kuter DJ, Ortel TL, Konkle BA, Cines DB. The HITExpert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J ThrombHaemost 2010; 8: 2642–50.
[26] Lillo-Le Loue¨ t A, Boutouyrie P, Alhenc-Gelas M, Le Beller C, Gautier I, Aiach M, Lasne D. Diagnostic score for heparin-inducedthrombocytopenia after cardiopulmonary bypass. J ThrombHaemost 2004; 2: 1882–8.
[27] Gruel Y, Pouplard C. Post-operative platelet count profile: the most reliable tool for identifying patients with true heparininducedthrombocypenia after cardiac surgery. J ThrombHaemost 2010
[28] Vonderheide RH, Thadhani R, Kuter DJ. Association of thrombocytopenia with the use of intra-aortic balloon pumps. Am J Med. 1998;105(01):27–32.
[29] Matthai WH., Jr Thrombocytopenia in cardiovascular patients: diagnosis and management. Chest. 2005;127(2, Suppl):46S–52S.
[30] Platelets, June 2011; 22(4): 294–301; Piperacillin and vancomycin induced severe thrombocytopeniain a hospitalized patient
[31] Andreas Gevaert, Hilde Smets& Roeland Vercauteren (2013) Fondaparinuxin heparin-induced thrombocytopenia, ActaCardiologica, 68:5, 517-520, DOI: 10.1080/AC.68.5.2994477
[32] Theodore E. Warkentin (2019): High-dose intravenous immunoglobulin forthe treatment and prevention of heparin-induced thrombocytopenia: a review, Expert Review of Hematology, DOI: 10.1080/17474086.2019.1636645

Author Profile

Dr. Boryana Mihalkova graduated with honors medicine at Medical University –Sofia in January 2018. She has been part of anesthesiologists in National Heart Hospital since August 2018. She has been a resident in anesthesiology and intensive care since March 2019.