INVITED REVIEW / DAVETLİ DERLEME

A practical and case-based approach to thrombocytopenia in cardiology practice

Kardiyoloji pratiğinde trombositopeniye olgu bazlı ve pratik yaklaşım

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Summary– In cardiology practice, anticoagulation and antiplatelet therapies are essential for most patients. As of yet, there is no high quality evidence regarding these treatments in thrombocytopenic patients, which continues to be an issue. Thrombocytopenia is defined as a platelet count of <150x10^9/L and is classified as severe when the platelet count is <50x10^9/L. Pseudothrombocytopenia, drug-induced thrombocytopenia, immune thrombocytopenia, heparin-induced thrombocytopenia, and thrombotic thrombocytopenic purpura are some of the main causes of thrombocytopenia. The current treatment suggestions are conservative, as a result of the lack of evidence, built on defensive treatment strategies and the fear of bleeding complications. Many patients with acute myocardial infarction with thrombocytopenia have undergone percutaneous coronary intervention successfully with adjunctive antiplatelet and anticoagulant use, as has been described in case reports. A risk-benefit ratio should be evaluated for antiplatelet therapy. In the relevant guidelines, while full dose low-molecular-weight heparin (LMWH) is recommended for patients with a thrombocyte count of >50x10^9/L, a half-dose of LMWH is recommended in patients with thrombocytopenia between 25 and 50x10^9/L. According to the current guidelines, avoiding antiplatelet and anticoagulant treatment should be restricted to patients with very severe thrombocytopenia (i.e., a platelet count <25x10^9/L), but new data and recommendations are needed.

Özet– Kardiyoloji pratiğinde atikoagülan ve antitrombosit tedaviler birçok hasta için vazgeçilmezdir. Bu tedaviler trombositopenik hastalarda büyük bir sorundur ve bu hastalarda kanıt derecesi yüksek veriler bulunmamaktadır. Trombositopeni, trombosit sayısı <150x10^9/L olarak tanımlanırken, ciddi trombositopeni, trombosit sayısı <50x10^9/L olarak tanımlanmıştır. Psödotrombositopeni, ilaca bağlı trombositopeni, immün trombositopeni, heparine bağlı trombositopeni, trombotik trombositopenik purpura trombositopeninin ana nedenlerinden bazılarıdır. Kanıt yokluğunda tedavi önerileri konservatif, kanama komplikasyonundan çekinilen, defansif tedavi stratejilerinin üzerine kurulmuştur. Trombositopenisi olan birçok akut miyokart enfarktüslü hastanın başarılı acil perkütan koroner girişime gittiği olgu sunumları ile rapor edilmiştir. Bu nedenle antitrombosit tedaviler fayda zarar oranına göre verilmelidir. Konuyla ilgili rehberlerde de düşük molekül ağırlıklı heparinlerin trombosit sayısı >50x10^9/L olan hastalarda tam doz, trombosit sayısı 25–50x10^9/L olan hastalarda da yarı dozda verilmesi önerilmektedir. Güncel rehberlerde ciddi trombositopenisi olan hastalarda (trombosit sayısı <25x10^9/L) antitrombosit ve antikoagülan tedavilerin kesilmesi önerilmektedir fakat bu konuda yeni kanıtlara ihtiyaç duyulmaktadır.

Anticoagulants and antiplatelets are the mainstays of treatment for vascular pathologies and have an important role in the practice of cardiology. However, in thrombocytopenic patients, these treatments pose a problem. Thrombocytopenia is defined as a platelet count <150x10^9/L and is classified as severe when the count is <50x10^9/L, which develops in 5% to 20% of patients in intensive care units.[1–3] Thrombocytopenia may be present at hospital admission or may develop during the hospital stay.[4]

There are no evidence-based recommendations on antiplatelet therapy for thrombocytopenic patients because of the exclusion of these patients and the lack of randomized, controlled trials specifically conducted

Received: February 13, 2018 *Accepted:* February 28, 2018
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with this particular group. The recommendations are based on case reports and the extrapolation of findings from other patient groups. Thrombocytopenia in patients with acute coronary syndrome (ACS) leads to greater mortality and morbidity, compared with those without thrombocytopenia.[5,6] Therefore, medical professionals face challenges in discovering the etiology of thrombocytopenia (Fig. 1) and the management of cardiovascular disease in these patients. The aim of this article was to discuss the approach to thrombocytopenia in 3 cardiac case examples.

Case 1

A 45-year-old male patient with a medical history of hypertension presented at the emergency department with worsening chest discomfort over the previous 7 hours. ST-segment depression was noted in the anterior precordial leads on electrocardiogram (ECG). His high-sensitivity troponin level was 117 ng/L (reference interval: 0–14 ng/L). The patient was diagnosed with non-ST-segment elevation ACS. Echocardiography revealed hypokinesis in the basal and mid segments of the anterior wall. No bleeding was documented in the patient history. There were no findings of petechia or ecchymosis. A coronary angiography was planned. The laboratory findings were as follows: a white blood cell (WBC) count of 9.5 x10^9/L, a neutrophil count (Neu) of 5x10^9/L, a hemoglobin (Hb) level of 15 g/dL, a mean corpuscular volume (MCV) of 85 fl, a platelet (Plt) count of 5x10^9/L, an activated partial thromboplastin time (aPTT) of 28 seconds, and a prothrombin time (PT) of 15 seconds. A hematology

Abbreviations:

ACS	*Acute coronary syndrome*
AMI	*Acute myocardial infarction*
aPTT	*Activated partial thromboplastin time*
ASA	*Acetyl salicylic acid*
ECG	*Electrocardiogram*
EDTA	*Ethylenediaminetetraacetic acid*
Hb	*Hemoglobin*
HIT	*Heparin induced thrombotic thrombocytopenia*
INR	*International normalized ratio*
ITP	*Immune thrombocytopenic purpura*
Ig	*Immunoglobulin*
IVIG	*Intravenous immunoglobulin*
LDH	*Lactate dehydrogenase*
LMWH	*Low-molecular-weight heparin*
MCV	*Mean corpuscular volume*
Neu	*Neutrophil*
PF4	*Platelet factor 4*
Plt	*Platelet*
PT	*Prothrombin time*
PTCP	*Pseudothrombocytopenia*
TTP	*Thrombotic thrombocytopenic purpura*
UFH	*Unfractionated heparin*
WBC	*White blood cell*

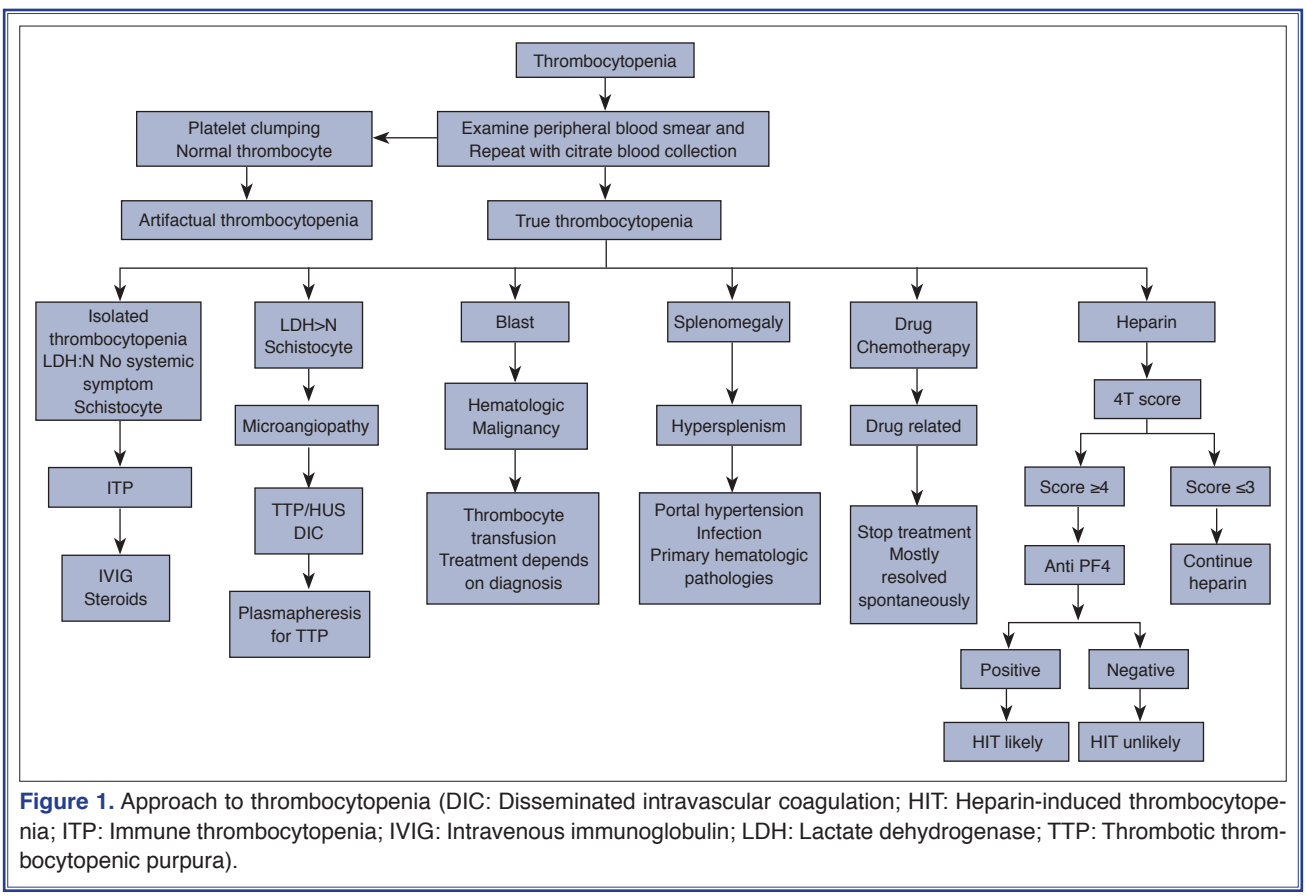

Figure 1. Approach to thrombocytopenia (DIC: Disseminated intravascular coagulation; HIT: Heparin-induced thrombocytopenia; ITP: Immune thrombocytopenia; IVIG: Intravenous immunoglobulin; LDH: Lactate dehydrogenase; TTP: Thrombotic thrombocytopenic purpura).

consultation was requested due to severe thrombocytopenia.

In a peripheral smear, aggregated thrombocytes were seen. A citrate tube hemogram test revealed a WBC of 9.6x10^9/L, a Neu of 5.1x10^9/L, an Hb of 14.8 g/dL, a MCV of 85 fl, and a Plt of 135x10^9/L. Pseudothrombocytopenia (PTCP) was the final diagnosis and the patient was transferred to the catheterization laboratory. Three hundred mg of acetyl salicylic acid (ASA) and 300 mg of clopidogrel were administered, along with 100 IU/kg unfractionated heparin intravenously (IV). An everolimus-eluting stent was placed over the 25-mm, 90% eccentric lesion in the left anterior descending artery. The maintenance treatment consisted of 100 mg ASA, 75 mg clopidogrel, 10 mg rosuvastatin, 50 mg metoprolol, and 40 mg pantoprazole. Postprocedural follow-up was uneventful and the patient was discharged with the aforementioned medication. PTCP is a laboratory finding defined by in vitro thrombocyte aggregation in blood collected in an ethylenediaminetetraacetic acid (EDTA) collection tube. It is seen in 0.1% of hospitalized patients.[7] This proportion is much higher in patients presenting with isolated thrombocytopenia. The diagnosis of PTCP is made by identification of thrombocyte accumulation observed in a peripheral smear. In emergency situations where door-to-balloon time is important, the absence of findings compatible with thrombocytopenia in a patient's history and the lack of mucocutaneous bleeding findings on a physical examination can affect an urgent treatment plan. The collection of blood in citrate tubes will prevent EDTA-induced platelet clumping and will reveal an accurate platelet count.[8] In patients with PTCP, thrombocyte count and function are normal and the usual care can be undertaken without safety concerns. In the follow-up of these patients, thrombocyte counts should be performed with citrate or heparin tubes and/or a peripheral smear. Also, some drugs, like abcimixab, may cause PTCP.[9] Abcimaxib-induced PTCP neither increases bleeding-risk and cardiac side effects nor necessitates early discontinuation of the drug.

Case 2

A 50-year-old female patient presented at the emergency department with a complaint of chest pain. The chest pain resolved upon the patient's arrival to the emergency department. The patient was on clopidogrel treatment due to a previous history of ischemic heart disease without documented coronary angiography. There was an ST-segment depression of 1.5 mm in the inferior and lateral precordial leads (DII, DIII, aVF, V5, and V6) of the ECG. A high-sensitivity troponin assay revealed a significantly elevated level of 250 ng/L. There was a marked segmental wall motion abnormality in the inferior and inferolateral walls with a left ventricular ejection fraction of 51% observed on echocardiography. Her medical history was noteworthy for a diagnosis of immune thrombocytopenic purpura (ITP) that was previously treated with steroids. She reported previous episodes of mucocutaneous bleeding. Petechia and ecchymosis on the trunk and extremities were observed on a physical examination. The patient was diagnosed with acute myocardial infarction (AMI). The complete blood count and coagulation parameters were a WBC of 9.5x10^9/L, a Neu count of 5x10^9/L, a Hb value of 15 g/dL, a MCV of 85 fl, a Plt count of 15x10^9/L, a aPTT of 28 seconds, a PT of 15 seconds, and a lactate dehydrogenase (LDH) value of 155 IU. A peripheral smear revealed a reduced number of thrombocytes. No schistocytes or atypical cells were detected.

Though the thrombocyte level is low in ITP, arterial and venous thromboses are more common than bleeding complications.[10,11] Unfortunately, there is no high quality evidence regarding the management of these patients. A randomized study investigating ASA safety in thrombocytopenic patients with ACS was initiated at the MD Anderson Cancer Center but terminated prematurely due to slow recruitment (ClinicalTrials.gov identifier: NCT00501345). During the early period of treatment, a fast thrombocyte response is expected with intravenous immunoglobulin (Ig) (1g/kg for 2 days) or IV – anti-D in Rh (+) patients along with steroids. Thrombopoietin inhibitors have been approved by the US Food and Drug Administration for treatment of ITP. However, there is not sufficient evidence regarding the use of these agents in ITP patients with ACS.[12] Although guidelines for the management of ITP are available, no particular recommendation regarding the use of antiplatelet and anticoagulant agents is provided. Many patients with AMI and thrombocytopenia undergo uneventful percutaneous coronary intervention with adjunctive antiplatelet and anticoagulant therapy, as has been previously reported.[13,14] In the latest relevant guidelines pertaining to the use of antiplatelet therapies,

ASA is not recommended in patients with thrombocyte counts of less than $50x10^9$/L.[15] In a recent study, mortality was found to be higher in thrombocytopenic (thrombocyte $<50x10^9$/L) cancer patients with ACS. Paradoxically, in the same patient group, mortality was higher in non-ASA treated patients compared with an ASA-treated group.[16] Furthermore, bleeding complications did not increase in the ASA group with severe thrombocytopenia. Likewise, other high-risk patient groups should have a risk-benefit ratio analysis for ASA use. In the relevant guidelines, while a full dose of low-molecular-weight heparin (LMWH) is recommended in patients with a thrombocyte count of $>50x10^9$/L, it should be lowered to a half-dose in patients with a thrombocyte count between 25 and $50x10^9$/L. Although there is a lack of high quality evidence, discontinuation of anticoagulant treatment is recommended in patients with ACS and a thrombocyte count of $<25x10^9$/L.[17,18] This patient was treated with IV immunoglobulin (IVIG) (1 g/kg for 2 days) and methylprednisolone (0.8 mg/kg for 3 weeks and tapered). Thrombocyte suspension was transfused and ASA (100 mg) treatment was administered until the thrombocyte count was elevated to $>25x10^9$/L, 4 days after IVIG.

In this case, thrombotic thrombocytopenic purpura (TTP) could be considered in the differential diagnosis of thrombocytopenia, since the patient was on clopidogrel treatment. Although TTP is more common with ticlopidine, it can also be seen with clopidogrel use.[19] Findings generally appear in the first 2 weeks. The classic pentad is rarely observed with early diagnosis (Table 1).[20]

TTP should be kept in mind in cases demonstrating hemolysis (increased LDH, reticulocyte count, indirect bilirubin level, decreased haptoglobulin), microangiopathy (schistocytes in peripheral smear), renal failure, and neurological findings (headache, convulsion, or stroke). Treatment consists of discontinuation of the responsible drug and plasma exchange therapy.[21]

Table 1. Thrombotic thrombocytopenic purpura-associated pentad[20]

1.	Microangiopathic hemolytic anemia (schistocyte, LDH>N, reticulocytosis)
2.	Thrombocytopenia ($<150x10^9$/L)
3.	Renal failure (>1.5 mg/dL)
4.	Neurological findings (confusion, headache, seizures, stroke)
5.	High fever (>38°C)

Case 3

A 68-year-old male patient presented at the emergency department with chest pain, nausea, and vomiting. The ECG was remarkable for a 3-mm ST-segment elevation in the precordial leads V1-V4 and reciprocal ST depressions in the inferior leads. The diagnosis of anterior AMI was made based on the ECG results. The left ventricle ejection fraction was 42% with severe hypokinesis in the anterior wall in all segments. The laboratory results were a WBC of $9.5x10^9$/L, a Neu count of $5x10^9$/L, a Hb value of 15 g/dL, a MCV of 85 fl, a Plt count of $255x10^9$/L, a aPTT of 28 seconds, and a PT of 15 seconds. On the fifth day of intensive care unit follow-up after the initiation of ASA 300 mg, clopidogrel 300 mg, and enoxaparin 1 mg/kg therapy following a percutaneous transluminal coronary angioplasty, the laboratory values were a WBC of $6.5x10^9$/L, a Neu count of $3x10^9$/L, a Hb value of 14 g/dL, a MCV of 84 fl, a aPTT of 29 seconds, and a PT of 14 seconds. The thrombocyte count was $100x10^9$/L. Following an episode of sudden dyspnea accompanied by sinus tachycardia, a repeat echocardiogram was performed, which demonstrated right ventricular dilatation with moderate tricuspid regurgitation and an estimated systolic pulmonary artery pressure of 47 mm Hg. The patient was normotensive. Computerized tomographic pulmonary angiography with IV contrast was ordered, and a pulmonary embolism was detected in the right upper lobe pulmonary artery. Lower extremity duplex ultrasonography ruled out deep venous thrombosis.

After hematological assessment, a diagnosis of heparin-induced thrombotic thrombocytopenia (HIT) was made, due to 50% reduction in thrombocytes, the timing of thrombocytopenia, new onset thrombosis, and the lack of other secondary causes of thrombocytopenia. The patient was treated with 7.5 mg fondaparinux, and after 5 days, a $>150x10^9$/L thrombocyte count was achieved. Warfarin therapy was initiated and anticoagulation was continued for 3 months.

Although unfractionated heparin (UFH) and LMWH are commonly used agents in the treatment of thrombosis, HIT, a prothrombotic situation, can

develop, depending on the drugs used. HIT is seen approximately 10 times more frequently with UFH, compared with LMWH.[22] HIT is an antibody-dependent drug reaction. It is secondary to IgG antibodies formed against platelet factor 4 (PF4)-heparin complexes, and these complexes activate thrombocytes.[23] The risk is increased in patients with UFH usage, of advanced age, of female sex, those who are surgical patients, and those who are receiving the drug for more than 6 days.[22] This condition typically occurs 5 to 10 days following the initiation of anticoagulation.[24] The only exception is patients who were given heparin within the last 90 days. HIT may develop quickly in these patients, since they will already have circulating antibodies against the PF-4/heparin complex, and readministration of heparin can cause an amnestic reaction. Anaphylactic allergic reactions due to heparin can also develop in some of these patients.[25] When UFH is administered more than 90 days after the previous exposure and the PF4/heparin antibodies have already disappeared, an amnestic reaction does not occur, and the development of HIT requires at least 5 days.[26] Even 1 dose of heparin can be enough for HIT to develop. A HIT diagnosis is made based on clinical findings. Immunoassay and laboratory findings are supportive, and may be required in uncertain cases. The thrombocyte count is typically found to be 40 to 80x10^9/L. Lower thrombocyte counts necessitate investigation of other etiologies.[27] Sometimes the thrombocyte count may be in the normal range. A 50% decrease in the baseline thrombocyte count of the patient is an important finding (e.g., 400x10^9/L to 150x10^9 /L).[28] The 4T scoring system may be helpful in the diagnosis of HIT (Table 2).[29] A low 4T score (0–3 points) has a high negative predictive value and in a broad spectrum meta-analysis, the negative predictive value of a low 4T score was found to be ≥98%.[30] In this meta-analysis, it was recommended that heparin be continued if the 4T score <4 (Fig. 2).[30] In contrast, the positive predictive value of a 4T score is 10% to 20% for 4 to 5 points, and 40% to 80% for 6 to 8 points.[31] The 4T is a pretest scoring system and laboratory tests should be performed in patients who have high scores. Laboratory tests should be used to exclude HIT, rather than confirm it. Functional tests aside from an anti-PF4-heparin enzyme immunoassay should be used to make an accurate diagnosis.[28] Thrombocyte activation tests (serotonin release assay and heparin-induced activation test) are much more specific than an enzyme immunoassay. A negative functional test can exclude HIT.[28]

Two things to do in HIT treatment are discontinuing heparin administration of any type and switching to an alternative anticoagulant. Two things not to do are administering warfarin in the early period and thrombocyte replacement, unless there is a vital indication.[32] Early initiation of warfarin and thrombocyte transfusions can increase thrombosis. Direct thrombin inhibitors (argatroban, lepirudin, bivaluridin) and direct Factor Xa inhibitors (danaparoid, fondaparinux) can be used as anticoagulants.

Table 2. The 4T scoring system[29]

4T	2 points	1 point	0 point
Thrombocytopenia	Platelet count decrease of >50% and nadir ≥20x10^9/L	Platelet count decrease of 30–50% or nadir 10–19 x10^9/L	Platelet count decrease <30% or nadir ≤10x10^9/L
Timing of onset	Day 5–10, or day 1 if recent heparin exposure (prior heparin exposure within 30 days)	>day 10 or unclear exposure	Platelet count fall <4 days with recent exposure
Thrombosis	New thrombosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other causes of thrombocytopenia	None	Possible	Definite

The 4T score is the sum of the values for each of the 4 categories. Scores of 0-3, 4-5, and 6-8 are considered to correspond to a low, intermediate, and high probability of heparin-induced thrombocytopenia, respectively.

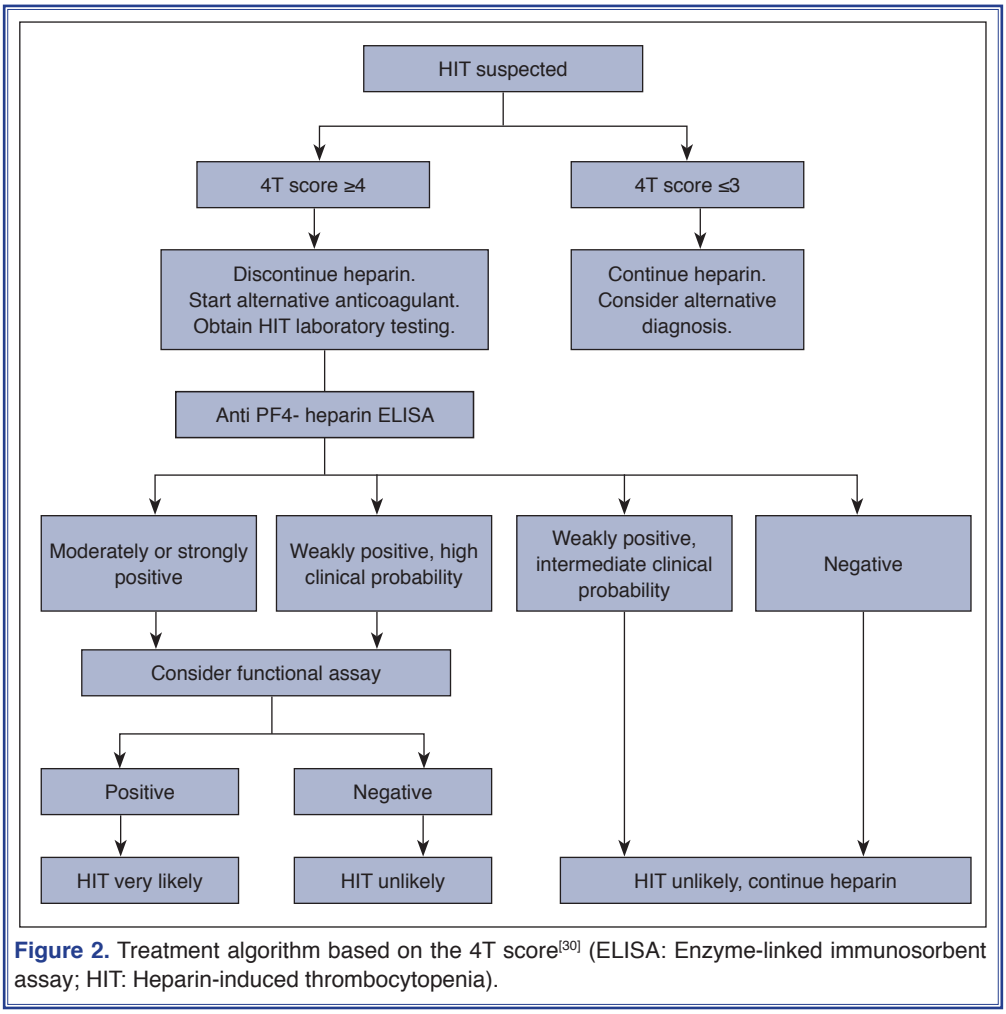

Figure 2. Treatment algorithm based on the 4T score[30] (ELISA: Enzyme-linked immunosorbent assay; HIT: Heparin-induced thrombocytopenia).

Argatroban is an approved agent for HIT treatment. It is provided with a continuous infusion and dose adjustment is performed by targeting a aPTT 1.5 to 3 times the upper reference value. Some guidelines recommend a decreased dose in cases of liver failure, heart failure, anasarca, edema, and recent cardiac surgery, because it is eliminated by the liver.[33] Switching from argatroban to warfarin is challenging, since the international normalized ratio (INR) is influenced by both. The INR should be measured 4 hours after argatroban is interrupted. Lepirudin is a direct antithrombin inhibitor eliminated by the kidneys. As a result, dose adjustment is necessary in cases of renal failure. The dose is adjusted by aiming for a 1.5 to 2 times longer aPTT. The use of another anticoagulant should be considered in patients with previous lepirudin exposure, due to the risk of anaphylaxis.[34]

Bivalirudin has a short half-life as long as it is enzymatically inactivated. Hence, it is well studied and preferred in a certain group of patients with cardiovascular disease.[35,36] Its effectiveness is monitored through the activated clotting time or aPTTx1.5 to 2.5 times. Dose adjustment is required in patients with renal and/or hepatic failure.[37]

Danaparoid is an activated Factor Xa inhibitor and also 1 of the 2 approved drugs for the treatment of HIT. It is administered intravenously. Its effect is followed by the activity of anti-Factor Xa and the target range is 0.5 to 0.8 U/mL. Dose adjustment should be performed in patients with renal failure, since it is eliminated through the kidneys. In rare cases, cross-reactivity with HIT antibodies has been observed in the use of danaparoid.[38]

Fondaparinux is an indirect Factor Xa inhibitor and has an off-label usage in HIT patients. It is administered subcutaneously and is excreted renally. The formation of anti-PF4/heparin antibodies with fondaparinux is similar to LMWH, but these antibod-

ies rarely cause HIT. The advantages of fondaparinux include no need for monitoring, easy accessibility, and once-daily dosing.[39] Use of this agent is growing, and it should be considered in uncomplicated patients.

HIT patients can be switched to oral anticoagulants after achieving stabilization and a thrombocyte level of >150x10^9/L. Parenteral anticoagulants can be discontinued after 5 days of overlapping usage with warfarin, guided by target INR values. While anticoagulation is recommended for 3 months in patients with thrombosis, treatment of 4 weeks of anticoagulation is deemed sufficient for those without thrombosis.[32]

In conclusion, thrombocytopenia is an important disorder encountered in the routine daily practice of in cardiology, where antiplatelets and anticoagulants are commonly used. In these cases where physicians are reluctant to use these agents due to the fear of bleeding, and therefore choose conservative treatments, increasingly, liberal treatment policies are emerging. Treatment should always be performed with consideration for the risk-benefit ratio. According to the current guidelines, avoidance of antiplatelet and anticoagulant treatment should be restricted to patients with very severe thrombocytopenia (i.e., platelet count <25x10^9/L) or bleeding.[17,18] It should be recognized that patients are more likely to die from thrombosis than bleeding.

Conflict-of-interest: None declared.

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Keywords: Anticoagulant; antiplatelet; cardiology; heparin induced thrombotic thrombocytopenia; immune thrombocytopenic purpura; thrombocytopenia.

Anahtar sözcükler: Antikoagülan; antitrombosit; kardiyoloji; heparine bağlı trombotik trombositopeni; immün trombositopenik purpura; trombositopeni.