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REVIEW ARTICLE / DERLEME

Heparin induced thrombocytopenia

Heparine bağlı trombositopeni

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a rare but serious prothrombotic adverse effect of heparin treatment. It is induced by platelet-activating antibodies against complexes of platelet factor 4 and heparin. Diagnosis rests on a clinical assessment of disease probability and laboratory testing. Prompt diagnosis of HIT, discontinuation of heparin use, and subsequent treatment with alternative anticoagulant drugs are essential steps to prevent serious complications such as thrombus formation, limb amputation, and death. In this review, we describe the clinical features of HIT and to summarize the data available for its management. *J Clin Exp Invest 2014; 5 (1): 137-144*

Key words: Heparin, thrombocytopenia, cardiac surgery.

ÖZET

Heparine bağlı trombositopeni (HBT) heparin tedavisinin nadir fakat ciddi bir protrombotik yan etkisidir. Bu durum platelet faktör 4 ve heparin komplekslerine karşı trombosit aktive edici antikorlar tarafından indüklenir. Tanı hastalık olasılığının klinik değerlendirmesi ve laboratuvar testlerine dayanmaktadır. Erken tanı, heparin kullanımının kesilmesi ve müteakiben alternatif antikoagülan ilaçlar ile tedavi trombüs oluşumu, ekstremite amputasyonu ve ölüm gibi ciddi komplikasyonların önlenmesi için önemli adımlardır. Bu derlemede, HBT'nin klinik özelliklerini tanımlamak ve onun yönetimi için mevcut verileri özetlemeyi amaçladık.

Anahtar sözcükler: Heparin, trombositopeni, kardiyak cerrahi.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a clinicopathologic disorder initiated by heparin exposure and characterized by thrombocytopenia and paradoxical thrombotic events. This disorder may be classified into 2 categories: type I and type II (Table 1).

Table 1. Distinguishing characteristics of the 2 types of heparin-induced thrombocytopenia

	Type I	Type II
Frequency (%)	10-20	1-3
Timing of onset (day)	1-4	5-10
Nadir platelet count	100.000/microL (mild)	Generally >20,000/microL; median nadir 60,000/microL
Antibody mediated	No	Yes
Thromboembolic sequelae	None	30 to 80%
Hemorrhagic sequelae	None	Rare
Management	Observation	Stopping of heparin, anticoagulation alternatively to heparin for preventing thrombosis

Type I [HIT-I]. The most common form of thrombocytopenia, of no clinical consequence, is typically characterized by a mild decrease in platelet count that consists within the first 2 days after heparin initiation and frequently returns to normal with continued heparin administration. The mechanism of the

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thrombocytopenia is non-immune and appears to be due to a direct effect of heparin on platelet activation.

Type II [HIT-II]. The less common and more severe form is an immune-mediated disorder characterized by the formation of antibodies against the heparin-platelet factor 4 (H-PF) complexes. It has also been called heparin induced thrombocytopenia and thrombosis (HITT), heparin-associated immune thrombocytopenia, and white clot syndrome. White clot syndrome means to platelet-rich arterial thrombosis (rather than fibrin-rich venous thrombosis), which consists with high frequency in patients who develop this disorder [1-4].

PATHOPHYSIOLOGY

Heparin binds to platelets in the absence of an antibody and releases small amounts of platelet factor (PF) 4 (as occurs in heparin-associated thrombocytopenia). PF4 heatedly binds heparin to form H-PF4 complex, which is antigenic in some people. In these people IgG antibodies to the H-PF4 complex are occurred within 5 to 15 days after exposure to heparin and continue to circulate in the absence of more heparin for approximately 3 to 6 months. Anti-H-PF4 IgG antibodies plus H-PF4 complexes form HIT complexes, which unite IgG Fc terminals to platelet Fc receptors (Figure 1). This binding vigorously stimulates platelets to release more PF4. A self-perpetuating, accelerating cascade of platelet activation, release, and aggregation ensues. Since platelet granules comprise several procoagulatory proteins (e.g., thrombin, factor V, fibrinogen, and von Willebrand factor), release also activates coagulation proteins to generate thrombin [1,2,4,5].

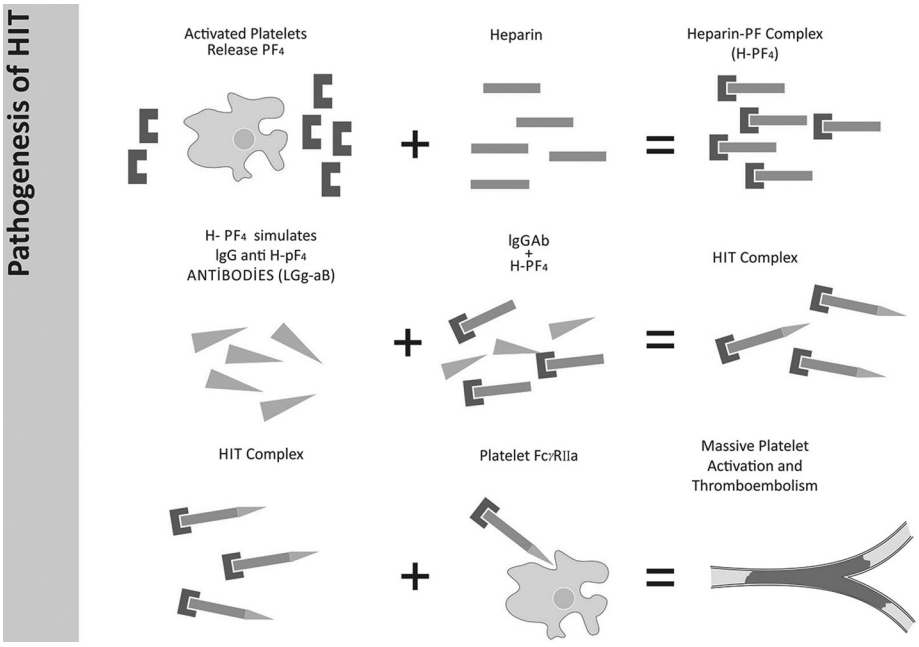

Figure 1. The generation of HIT complexes. Read each horizontal group of three left to right beginning at top left.

INCIDENCE AND RISK FACTORS

A critical evaluation of immune-mediated HIT suggests a frequency of 0.2 to 5.0% in patients exposed to heparin for more than 4 days. There are three factors in addition to longer duration of treatment that are most vigorously associated with the development of HIT (Table 2,3).

1. Use of unfractionated heparin (UFH) rather than low molecular weight heparin (LMWH)

2. Surgical rather than medical patients

3. Female rather than male patients update

Antibodies are more likely to form in patients undergoing open heart surgery than in orthopedic patients. But, among those in whom antibodies do form, orthopedic patients are more likely to develop HIT than undergoing open heart surgery.

HIT is unusual among patients < 40 years of age as well as in women following delivery. Occasional patients have developed this disorder after exposure to as little as 250 units from a heparin flush or after the use of heparin-coated catheters [3,4,6-8].

Table 2. Risk factors for HIT

Risk factors
Heparin exposure > 4 days
Recent heparin (past 100 day)
Exposure to unfractionated heparin (versus low molecular weight heparin)
Postoperative patients (orthopedic > cardiac and vascular surgery)
Intravenous heparin administration (versus subcutaneous)
Dose of heparin (therapeutic > prophylaxis > flushes)
Female sex, female > male
Age > 40 years

Table 3. Incidence of HIT according to patient population and heparin exposure-risk ratios

Examples of patient groups with risk estimated to be > 1%
Postoperative patients taking prophylactic dose UFH > 4 day
Postoperative patients taking therapeutic dose UFH > 4 day
Examples of patient groups with risk estimated to be 0.1-1%
Medical/obstetric patients taking prophylactic or therapeutic dose UFH > 4 day
Postsurgery patients taking LMWH > 4 day
Postsurgery patients taking UFH "flushes" > 4 day
Medical/obstetric patients taking LMWH after first taking UFH
Examples of patients groups with risk estimated to be < 0.1%
Medical/obstetric patients taking LMWH > 4 day
Medical/obstetric patients taking only heparin flushes
Any patient taking UFH or LMWH < 4 day

UFH: Unfractionated heparin, LMWH: low-molecular-weight heparin

CLINICAL MANIFESTATIONS

Onset time

Immune-mediated HIT consists 5 to 10 days after the initiation of heparin treatment. Onset after 2 weeks is rare, an observation that correlates with serologic tests showing that heparin-dependent antibodies generally develop between days five to eight after exposure to heparin, but rarely later. Earlier onset of HIT can be seen if the patient had been treated with heparin in the prior 1 to 3 months and still has circulating HIT antibodies.

a. Early onset HIT: It (median time of platelet fall 10 hours after the start of heparin administration) can be occurred in about 30 percent of patients with persistent antibodies due to heparin treatment within the prior 1 to 3 months.

b. Delayed onset HIT: It, in which thrombocytopenia and thrombosis, occur after heparin has been withdrawn (average of 9 days, 5 to 19 days).

Degree of thrombocytopenia

Thrombocytopenia and/or a decrease in the platelet count greater than 50 percent, due to immune-mediated HIT is uncommonly serious, with platelet counts typically >20,000/microL and a median platelet count of about 60,000/microL. As a result, spontaneous hemorrhage is rare [4,8].

Cardiac surgery patients

A major fall in the platelet count of approximately 40 to 50 percent occurs universally during the first 72 hours following open heart surgery, due at least in part to prolonged contact of platelets with the artificial surface of the extracorporeal circuit. These patients generally take large amounts of unfractionated heparin, a setting in which the incidence of HIT antibodies is as high as 25 to 70 percent by immunoassay and 4 to 20 percent by platelet activation assay. Since several other potential causes of thrombocytopenia are frequently present, it is difficult to determine whether or not HIT is present in these patients.

While this question has not been satisfactorily settled, the presence of a secondary decrease in the platelet count ≥ 50 percent that begins between the 5th and 10th postoperative day appears to be highly predictive of HIT [3,4].

Thrombosis

The major clinical problem associated with HIT is thrombosis/thromboembolism, venous, arterial, and

intracardiac. The certain mechanism of this hypercoagulable state are the release of procoagulants from activated platelets, the generation of platelet microparticles, fragments of the platelet membrane. Since HIT antibodies also bind to heparan sulfate on the surface of endothelial cells, thrombosis can be based on endothelial cell activation and/or increased tissue factor and thrombin generation due to endothelial cell injury.

Among patients taking heparin for thromboprophylaxis or treatment, the first sign of HIT generally is the development of thrombocytopenia. If such a patient develops an initial or recurrent thrombotic event, the presence of thrombocytopenia suggests that it is due to HIT rather than failure of anticoagulation. The major manifestations of venous thrombosis are deep vein thrombosis (DVT) and pulmonary thromboembolism. Pulmonary thromboembolism is the most common life-threatening event, occurring in 25 percent of patients. Other manifestations of venous thrombosis involve venous limb gangrene (distal ischemic necrosis after DVT) and cerebral sinus thrombosis. Upper extremity DVT has also been reported in HIT, but is less common than lower extremity DVT.

Arterial thrombosis, although less common, may lead to a variety of clinical manifestations involving stroke, myocardial infarction, acute limb ischemia from peripheral arterial occlusion, or organ infarction (mesentery, kidney) [4].

Skin necrosis

Affected areas are usually fat-rich, such as the abdomen, as in warfarin-induced necrosis. However, the distal extremities and the nose may also be included. The appearance of erythema is followed by purpura and hemorrhage leading to necrosis. Although the lesions appear similar to warfarin-induced skin necrosis, deficiencies of the natural anticoagulants are not present.

Other complications

Other unusual complications of HIT include adrenal hemorrhage secondary to adrenal vein thrombosis, and transient global amnesia [4,6,7].

DIAGNOSIS

Suspecting HIT

The first step in establishing a diagnosis of HIT is suspecting the presence of this disorder. Any one of the following scenarios could raise the possibility of HIT in a patient begun on heparin treatment within the preceding 5 to 10 days, or in a patient taking prolonged therapy with LMWH;

1) Onset of else unexplained thrombocytopenia,

2) Arterial or venous thrombosis associated with thrombocytopenia,

3) A platelet count which has fallen 50% or more from a previous value, even if absolute thrombocytopenia is not present,

4) Necrotic skin lesions at heparin injection sites,

5) Acute systemic (anaphylactoid) reactions (eg, fever/chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest) occurring after IV heparin bolus administration.

The diagnosis of HIT is firstly made on clinical grounds, because the assays with the highest sensitivity and specificity cannot be readily available and have a slow return time. The most specific diagnostic laboratory tests for HIT involve serotonin release assays, heparin-induced platelet aggregation assays, and solid phase immunoassays (Figure 2).

To aid in the diagnosis of HIT, a pretest clinical score called the "4Ts" was developed and validated. A score is calculated based on the following 4 categories (Table 4):

1. Degree of thrombocytopenia,

2. Timing of platelet count fall,

3. Clinical sequelae such as thrombosis, and

4. Presence of other etiologies of thrombocytopenia

Laboratory tests

Various laboratory tests are available to diagnose HIT and are broadly classified into functional and antigen-based assays. Two standard reference functional assays are the serotonin release assay (SRA), which has high sensitivity and specificity (both 95%) when performed at experienced centers, and the heparin-induced platelet aggregation (HIPA) assay, which is specific (90 %) but not sensitive. Due to limited ability of many clinical laboratories to perform these functional tests, a commercially-available ELISA immunoassay that detects antibodies against the H-PF4 complex is frequently used instead. The ELISA is a sensitive antigen-based assay (90%) and has a high negative predictive value (95%) but low specificity, and hence, may be falsely positive, detecting non-pathogenic antibodies in patients without clinical evidence of HIT (Table 5) [3,6-8].

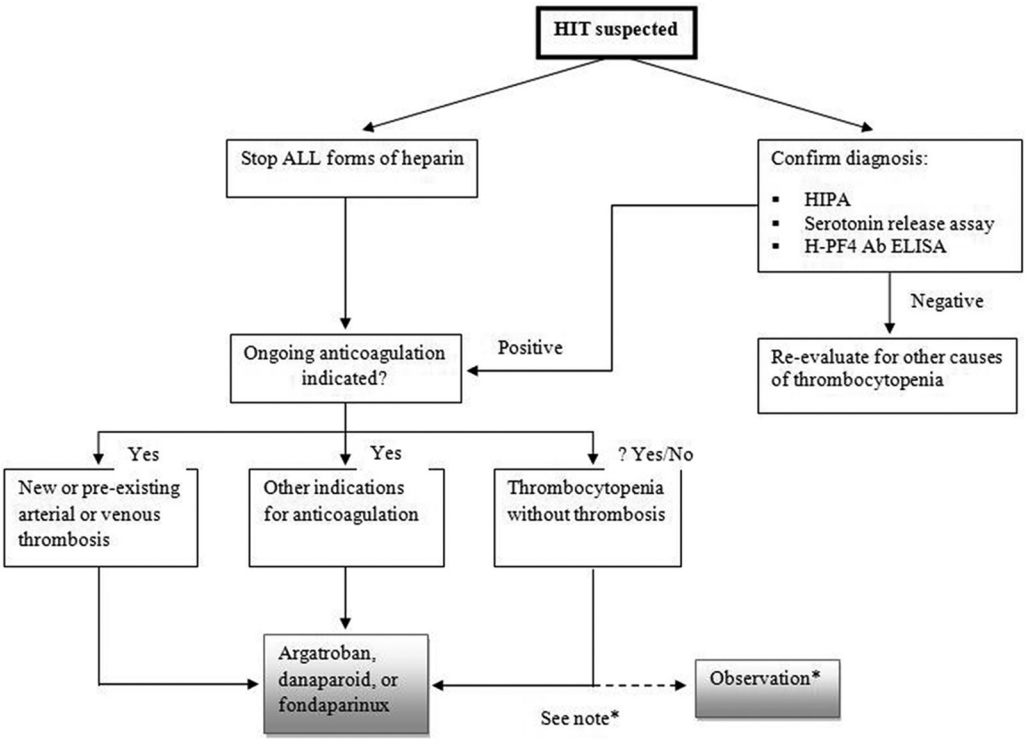

Figure 2. Approach to the patient with suspected heparin induced thrombocytopenia.

* Observation could be chosen only if patient is at high risk for bleeding. Otherwise treatment (anticoagulation with the agents listed) is preferred until the platelet count has returned to normal.
HIPA: Heparin-induced platelet aggregation assay; H-PF4 Ab: Heparin-platelet factor 4 antibody.

Table 4. The 4Ts assessment tool for patients with suspected HIT

Category	2 Point	1 Point	0 Point
Thrombocytopenia	50 % fall and platelet nadir ≥20 x10^9/l	30-50% fall or platelet nadir 10-19 x10^9/l	• < 30% platelet fall • Any platelet fall with nadir <10 x10^9/l
Timing of platelet count fall or other sequelae	• Platelet fall day 5-10 after starting of heparin • Platelet fall within 1 day of starting of heparin AND heparin exposure within past 5-30 days	• Consistent with platelet fall days 5-10 but not clear (e.g., missing counts) • Platelet fall within 1 day of starting of heparin AND exposure to heparin in past 31-100 days • Platelet fall after day 10	Platelet fall day ≤ 4 without exposure to heparin in past 100 days
Thrombosis or other sequelae (e.g. skin lesions)	• Confirmed new thrombosis (venous or arterial) • Skin necrosis at injection site • Anaphylactoid reaction to IV heparin bolus •Adrenal hemorrhage	• Recurrent venous thrombosis in a patient taking therapeutic anticoagulants • Suspected thrombosis (awaiting confirmation with imaging) • Erythematous skin lesions at heparin injection sites	Thrombosis suspected
Other cause for thrombocytopenia not evident	No alternative explanation for platelet fall is evident	Possible other cause is evident: • Sepsis without proven microbial source • Thrombocytopenia associated with initiation of ventilator	Exact other cause is present

Pretest probability score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low.

Table 5. Laboratory tests

Washed-platelet activation assays	SRA (Serotonin release assay)	Sensitivity and specificity, > 95%
	HIPA (Heparin-induced platelet aggregation)	Specificity (> 90%), not sensitivity
Antigen assays	ELISA immunoassay	Sensitivity (90%), not specificity

TREATMENT

The initial intervention in a patient with HIT could be prompt stopping of all exposure to heparin, involving heparin-bonded catheters and heparin flushes (eg, for arterial lines or heparin locks). LMWH could also be avoided since it may crossreact with the heparin-induced antibodies. In the other hand, heparin stopping alone is frequently not sufficient; since these patients remain at risk for subsequent thrombosis (30 day risk of thrombosis is 53 percent).

Table 6. Non-heparin anticoagulants for use in HIT

Anticoagulant	Argatroban	Lepirudin	Bivalirudin	Danaparoid	Fondaparinux
Activity	DTI	DTI	DTI	Factor Xa inhibitor	Factor Xa inhibitor
Route of administration	iv	iv, sc	iv	iv, sc	sc
Half-life (minute/hour)	40-50 min	80 min	25 h	18-24 h	17-20 h
Monitoring	aPTT	aPTT	aPTT	Anti factor Xa level	Anti factor Xa level
Effect on INR	+++	+	++	0	0
Dosing in HIT	Initial infusion rate 2 µg/kg/min IV (no initial bolus); a reduced initial infusion rate (0.5-1.2 µg/kg/min) is appropriate in certain patient populations*	Bolus 0.2-0.4 mg/kg IV; maximum initial infusion rate 0.10 mg/kg/h IV (target, 1.5-2.0 x patient's baseline or mean of laboratory normal range)	Initial infusion rate 0.15-0.20 mg/kg/h IV (target, 1.5-2.5 x patient's baseline or mean of laboratory normal range (no initial bolus)	Bolus: 2,250 U IV; infusion, 400 U/h - 4 h, then 300 U/h x 4 h, then 200 U/h IV, subsequently adjusted by anti-Xa levels (target, 0.5-0.8 anti-XaU/mL)	Not established for HIT (<50 kg:5 mg/day 50-100 kg: 7.5 mg/day, >100 kg: 10 mg/day SC)
Crosses placenta	Unclear	Unclear	Unclear	No	Yes
Dialyzable	20%	High-flux dialyzers	25%	Yes	20%
Elimination (half-life)	Hepatobiliary (40-50 min)	Renal (80 min)	Both enzymic (80%) and renal (20%) metabolism (25 min)	Renal (24 h, anti-Xa activity)	Renal (17-20 h)

DTI: Direct thrombin inhibitor *Patients with heart failure, multiple organ system failure, severe anasarca, and during the early post-cardiac surgery period.

There are a number of recommended alternative anticoagulants to heparin in a patient with HIT: a direct thrombin inhibitor such as lepirudin (recombinant hirudin), bivalirudin, argatroban; fondaparinux; or danaparoid (Table 6). Whichever alternative anticoagulant is used, it is important to administer it in suitable therapeutic doses as discussed below, as there is evidence for therapy failure in cases where doses deemed suitable for prophylaxis in other circumstances have been used in active HIT.

For patients with vigorously suspected or confirmed HIT who do not have active hemorrhage, prophylactic platelet transfusions could not be given.

For patients with HIT, whether or not there is clinical evidence of lower extremity DVT, routine ul-

trasound scan of the lower extremity veins are recommended for investigation of DVT.

Women with HIT in pregnancy could be treated with a non-cross reacting anticoagulant. Danaparoid could be used where available and fondaparinux also considered.

If the patient has taken a vitamin K antagonist at the time of diagnosis it could be reversed by administering intravenous vitamin K [3,4,9].

Warfarin and HIT

Warfarin could be initiated in a patient with HIT only when both of the following have been accomplished; [1] The patient has been stably anticoagulated with a thrombin-specific inhibitor, and [2] The platelet count has increased to at least 150,000/microL.

There could be a minimum of 5 days of overlapping treatment before the thrombin inhibitor is discontinued. The initial use of warfarin alone for a patient diagnosed with HIT could be avoided since warfarin treatment may increase the risk of venous limb gangrene in patients with DVT through its rapid lowering of protein C levels.

When the above 2 goals have been reached and warfarin treatment is started, high initial doses (eg, ≥10 mg/day) could be avoided to minimize the transient hypercoagulable state induced by the rapid decline in protein C levels. Accordingly, warfarin could be started at low maintenance doses of ≤5 mg/day (or phenprocoumon ≤6 mg/day). The target range for anticoagulation with warfarin treatment could be an international normalized ratio (INR) in the range of 2.0 to 3.0. [3,4,7].

The length of therapy with warfarin has not been defined in any prospective study, but in view of the high risk of thrombosis within 30 days of the diagnosis of HIT, anticoagulation with warfarin could probably be continued for at least 2 to 3 months, and for at least 3 to 6 months if a thrombotic event has occurred [4].

SPECIAL POPULATION

Cardiac surgery and HIT

1. Patients with previous HIT undergoing open heart or vascular surgery

a) For patients with a history of HIT who are HIT antibody negative and require open heart surgery, we recommend the use of UFH over an anticoagulation without heparin (Grade 1B).

b) For patients with a history of HIT who are antibody positive by PF4-dependent EIA but antibody negative by washed platelet activation assay, we recommend the use of UFH over an anticoagulation without heparin (Grade 2C).

In open heart surgery, there is a rationale and some data that support the safe use of UFH in patients with prior HIT;

1) HIT antibodies are transient, with the median time to antibody disappearance of 50 to 80 days,

2) In rapid-onset HIT, there is not a strong association with remote (> 100 days) previous heparin exposure,

3) Short term re-exposure to heparin for <4 days, such as for open heart surgery, can be possible without triggering another episode of HIT in patients with a history of HIT but no detectable HIT antibodies,

4) The limited experience with alternative anticoagulants for open heart surgery, and the inability to readily reverse their anticoagulant effects following surgery are important drawbacks,

5) The risk of perioperative complications, particularly major hemorrhage (and, potentially, catastrophic intraoperative cardiopulmonary bypass [CPB] thrombosis), is higher with the non-heparin anticoagulants.

These patients must be avoided UFH before and after open heart surgery, alternative anticoagulants are recommended in this periods.

2. Patients with acute or subacute HIT undergoing cardiac surgery

a) For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require open heart surgery, we recommend one of the following alternative anticoagulant approaches: delaying surgery (if possible) until HIT has resolved and antibodies are negative (see 1a) or weakly positive (see 1b) [Grade 1B]; using bivalirudin for intraoperative anticoagulation during CPB (Grade 1B) or during off-pump open heart surgery [Grade 1B].

b) For patients with subacute HIT (platelet count recovery, but continuing HIT antibody positive), we recommend delaying surgery (if possible) until HIT antibodies (washed platelet activation assay) are negative, then using heparin (see 1) over using a non-heparin anticoagulant [Grade 1C]. If surgery cannot be delayed, we suggest the use of a non-heparin anticoagulant (see 2a) over the use of UFH [Grade 2C] [3,4,6,8,10,11] (Table 7).

Table 7. Anticoagulant protocol example used for cardiac surgery

Preferred (level 1) options	Protocol	Comments
UFH	Standard UFH dosing for CPB	Avoid UFH before and after open heart surgery
Bivalirudin	*Off-pump:* bolus 0.75 mg/kg, then 1.75 mg/kg/h infusion to maintain ACT > 300; *CPB:* 1 mg/kg bolus, 50 mg bolus added to priming solution of CPB, 2.5 mg/kg/h infusion, additional 0.1-0.5 mg boluses to maintain ACT > 2.5-fold baseline ACT	Shorter t1⁄2 (25 min) and minor renal excretion (20%) are advantageous for cardiac surgery; avoid using patient blood for testing graft patency or for cardioplegia solution (as clots can form in stagnant, bivalirudin-anticoagulated blood); special maneuvers needed to prevent stasis and consequent clotting of CPB circuit during or after surgery

UFH: Unfractionated heparin, ACT: Activated coagulation time, CPB: Cardiopulmonary bypass

Percutaneous coronary intervention (PCI)

1. For patients with vigorously suspected (or confirmed) acute HIT who require cardiac catheterization or PCI, we recommend a non-heparin anticoagulant (bivalirudin [Grade 1B]) over UFH or LMWH [Grade 1B].

2. For patients with prior HIT (who are antibody negative) who require cardiac catheterization or PCI, we suggest use of a non-heparin anticoagulant (see 1) over UFH or LMWH [Grade 2C] [3,6,8].

Anticoagulation in patients with a history of HIT

Although recurrence is rare, where a patient with prior HIT requires a period of anticoagulation or anticoagulant prophylaxis an alternative to UFH or LMWH could be prescribed. Fondaparinux and danaparoid can be used [3,6,8].

Hemodialysis

Alternatives (where available) involve saline solution flushing, citrate, danaparoid,

lepirudin, argatroban, and long-term vitamin K antagonist use. But the most often, danaparoid and argatroban have both been used. Guideline (2012) is not made any specific recommendations for anticoagulation of this patient population [3,6,8].

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