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Myocardial Infarction with Limb Arterial and Venous Thrombosis in a Patient with Enoxaparin-Induced Thrombocytopenia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEF 1 Navdeep Singh
DEF 2 Sandeep Singh Lubana
EF 2 Han-mou Tsai

1 Department of Medicine, Division of Hospice and Palliative Care, North Shore University Hospital, Manhasset, NY, U.S.A.
2 Department of Medicine, Division of Hematology and Oncology, State University New York (SUNY) Downstate Medical Center, Brooklyn, NY, U.S.A.

Corresponding Author: Navdeep Singh, e-mail: imedsingh@gmail.com
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Patient: Female, 67-year-old
Final Diagnosis: Enoxaparin induced thrombocytopenia with life threatening thrombosis
Symptoms: Chest discomfort
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Educational purpose

Background: Heparin, often used as an anticoagulant, acts by binding to antithrombin III. Indeed, heparin binds to a variety of proteins other than antithrombin III. Among them, platelet factor 4 can bind and neutralize the anticoagulant activity of heparin. Upon binding with heparin, platelet factor 4 undergoes a conformational change and expresses immunogenic neo-epitopes that induce the generation of antibodies of the platelet factor 4 heparin complex. This immune reaction may lead to thrombocytopenia and venous, arterial, or microvascular thrombosis. However, the risk of such complications is quite variable, as it is affected not only by the source and dose of heparin and the clinical condition (e.g., cardiovascular surgery and orthopedic surgery) of the patient, but also the molecular size of the heparin formulation. Venous, arterial, and small-vessel thrombosis can lead to leg swelling, pulmonary embolism, stroke, skin necrosis, or gangrene requiring limb amputation or intestinal resection. Myocardial infarction due to coronary thrombosis also occurs, although it is less common and can be readily recognized.

Case Report: Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication of heparin therapy. We report the case of a 67-year-old woman who developed ST-segment elevation myocardial infarction and thrombocytopenia within 10 days of prophylactic enoxaparin therapy after undergoing bilateral total knee replacement surgery. She also had peripheral arterial and venous thrombosis. With thrombolysis and argatroban anticoagulation therapy, she recovered without residual sequelae.

Conclusions: Thrombocytopenia with coronary and other vascular thrombosis is a potentially serious complication of heparin therapy. A trend of decreased platelet count, decreased platelet count by 30% or more, and/or occurrence of any type of thrombosis should raise the suspicion of HIT. This case demonstrates that early recognition and prompt treatment of HIT can be life-saving.

MeSH Keywords: Enoxaparin • Platelet Factor 4 • Thrombocytopenia • Thrombosis

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Background

Heparin, a naturally occurring, highly sulfated, and iduronic acid-rich form of heparan sulfate, is often used as an anticoagulant to stop or prevent thrombosis in the circulation. Heparin acts by binding via a sulfated pentasaccharide sequence to antithrombin III (AT3, encoded by *SerpinC1*), a plasma serine protease inhibitor (serpin). This binding induces conformational transformation of the AT3 reactive site for interaction with coagulation proteases such as factors IIa (thrombin), IXa, and Xa. For inhibition of thrombin but not factor Xa, an additional 13 monomeric units of the heparin molecule are required [1]. Due to this size difference, low-molecular-weight heparins (LMWH) are more effective in inhibiting factor Xa than is thrombin.

Heparin is highly conserved evolutionarily, being synthesized in a variety of animal species, including those without a blood coagulation system [2], indicating that it possesses biological functions other than anticoagulation.

Indeed, heparin binds to a variety of proteins other than AT3 [3]. Among them, platelet factor 4 (PF4), a positively-charged chemokine derived from the alpha granules of platelets, can bind and neutralize the anticoagulant activity of heparin. Upon binding with heparin, PF4 undergoes a conformational change and expresses immunogenic neo-epitopes that induce the generation of anti-PF4-heparin antibodies [4]. This conformational change of PF4 also occurs upon its binding to other poly-anions such as polyphosphates. Occasionally, autoimmune anti-PF4 antibodies occur spontaneously to cause thrombosis without prior exposure to heparin [5,6].

Heparin-induced immune reaction can lead to thrombocytopenia (type II HIT, or simply HIT) that is not easily distinguished from mild thrombocytopenia that is benign and self-limited (type I HIT) [7]. The thrombocytopenia of HIT is rarely severe enough to cause spontaneous bleeding complications, even in the presence of heparin anticoagulation therapy; instead, the immune reaction may lead to venous or arterial thrombosis. However, the risk of such complications is quite variable, as it is affected not only by the source and dose of heparin, the clinical condition (e.g., cardiovascular surgery and orthopedic surgery) of the patient, but also the molecular size of the heparin formulation – the risk is much lower with LMWH than with unfractionated heparin (UFH) [8]. Venous, arterial, and small-vessel thrombosis can lead to leg swelling, pulmonary embolism, stroke, skin necrosis, or gangrene requiring limb amputation or intestinal resection. Myocardial infarction due to coronary thrombosis also occurs, although it is less common and is not widely known.

We report a case of ST-segment elevation myocardial infarction (STEMI) with peripheral arterial and venous thrombosis in a patient receiving prophylactic enoxaparin therapy after undergoing bilateral knee replacement surgery, which was successfully treated with thrombolysis, argatroban, and apixaban.

Case Report

A 67-year-old woman with a past medical history of hyperlipidemia but no known history of coronary artery disease or myocardial infarction was transferred to our facility with STEMI 10 days after undergoing bilateral total knee arthroplasty at an outside hospital.

The patient's preoperative evaluation revealed an abnormal electrocardiogram (EKG) with right bundle branch block (RBBB) and age-indeterminate inferior myocardial infarction. An echocardiogram showed normal left ventricular wall motions with an ejection fraction of 60%. Myocardial imaging did not detect any perfusion defects. The preoperative laboratory tests were unremarkable. The platelet count was 209 000/microliter. The knee replacement surgery was uneventful. Prophylactic subcutaneous enoxaparin at 40 mg daily was started 1 day after the operation, before the patient was discharged on the next day. On day 9 of her enoxaparin therapy, she started to have retrosternal chest pain with diaphoresis and lightheadedness, prompting evaluation at her local emergency room (ER).

In the ER, her physical examination was unremarkable other than the surgical incision wounds of her recent knee surgery. The EKG was notable for ST-segment elevation in leads II, III, and aVF along with old RBBB. Laboratory studies were significant for elevated troponin level (7.27 ng/mL), thrombocytopenia (39 000/microliter), and elevated D-dimer (20 microgram/L). The patient was treated with oral aspirin 325 mg, 1 inch of 2% nitroglycerin paste, tenecteplase 50 mg intravenously as a single bolus, and heparin 4000 units as a bolus followed by infusion at 12 U/kg/h before transfer to our institution.

Upon arrival at our institution, a repeat laboratory test confirmed thrombocytopenia with a platelet count of 36 000/microliter. An echocardiogram demonstrated left ventricular ejection fraction of 55% to 60% with mild inferior wall hypokinesis. The troponins had increased to 238 ng/ml. Heparin-induced thrombocytopenia (HIT) with thrombosis was suspected. Her heparin infusion was discontinued and replaced with argatroban infusion at 2 microgram/kg/min after blood samples were obtained for anti-heparin-platelet factor 4 (anti-heparin-PF4) antibody test (GTI Elisa) and serotonin release assay (SRA), both of which later came back positive.

A computerized tomography angiogram (CTA) of the chest was negative for pulmonary embolism. However, a Doppler ultrasound examination detected an acute thrombosis of the left

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posterior tibial vein. In addition to argatroban infusion, she was treated with aspirin 81 mg daily, metoprolol 25 mg twice daily, and atorvastatin 80 mg daily. The troponin level rapidly trended downward to 14 ng/mL within 3 days. Serial EKG showed resolution of the ST-segment elevations. However, the patient's hospital course was complicated by extreme pain of the left foot, with toe discoloration on the 5th day. Run-off CTA of the abdominal aorta and lower extremities demonstrated bilateral non-occlusive thrombi of femoral and popliteal arteries. The pain improved with analgesics hydromorphone as needed and continued argatroban anticoagulation therapy. Her platelet count was at its nadir of 36 000/microliter at admission and returned to normal on the 9th hospital day. The patient was discharged on hospital day 13 with apixaban 10 mg twice daily.

Timeline:

Day 0 – Preoperative evaluation;
Day 8 – Patient underwent bilateral knee replacement;
Day 9 – Prophylactic enoxaparin started;
Day 10 – Discharged on subcutaneous enoxaparin;
Day 17 – Patient started to have retrosternal chest pain;
Day 18 (Outside ER) – Diagnosed with STEMI, Tenecteplase was administered, Platelets 39000/microliter;
Day 18 (Our hospital) – Heparin discontinued (HIT suspected), argatroban infusion started, heparin-PF4 antibody positive, positive deep vein thrombosis;
Day 20 – SRA came back positive, confirming the diagnosis of HIT;
Day 25 – CTA detected lower-extremities arterial thrombosis;
Day 26 – Platelets returned normal;
Day 28 – Argatroban switched to apixaban;
Day 30 – Patient was discharged.

Discussion

Heparin-induced thrombocytopenia (HIT) is a potentially serious adverse event of heparin anticoagulation therapy. It typically presents with thrombocytopenia or a decrease of the platelet count by more than 30–50% on days 5–15 of heparin therapy, accompanied with venous or arterial thrombosis in approximately 50% of patients. Although this complication occurs less frequently with low-molecular-weight heparin (LMWH) than with unfractionated heparin (UFH) [4], the risk is not negligible, being 0.5–5% for individuals treated with enoxaparin for at least 5 days [9].

Laboratory investigations have demonstrated that HIT antibodies are formed against the heparin- platelet factor 4 (PF4) complex [10–13]. PF4 [14], also known as CXCL4, is a 70-amino acid positively-charged protein that is released from the alpha granules of activated platelets. It binds to negatively-charged heparin and heparin-like molecules via electrostatic interactions on the surface of vascular endothelium. This binding keeps heparin from binding to antithrombin 3 (AT3), thereby preventing activation of AT3 by heparin for controlling the activity of factors IIa (thrombin), IXa, and Xa. As a consequence, PF4 is pro-coagulation and may be pro-thrombosis. PF4 may also be involved in the regulation of megakaryopoiesis [15] and is a chemokine for various cell types, including neutrophils and fibroblasts.

The binding of PF4 with heparin exposes neo-epitopes on PF4 that trigger the formation of anti-heparin-PF4 antibodies in approximately 8–50% of patients treated with UFH, 1–8% with LMWH, and 1–3% with fondaparinux [8,16,17]. The heparin-PF4 complex is most stable for the trigger of an immune reaction when PF4 and heparin are at stoichiometric molar ratios (~1 for UFH and ~0.5 for LMWH) of electrostatic neutralization [18,19]. Thus, heparin formulation, dosage, and clinical conditions of the patients contribute to the wide variation of the incidence rate of immune reactions to heparin-PF4.

Only a small fraction of patients with heparin-PF4 antibodies develop thrombocytopenia with or without thrombosis. This variation likely reflects the difference in the molecular size of the heparin formulations and the heterogeneity of antibodies produced. In laboratory studies, the higher affinity of the antibodies for heparin-PF4 complex or for PF4 alone correlates with greater platelet-activating ability [20]. In addition to the type of heparin used, clinical conditions such as cardiac transplant and neurosurgery are associated with a higher risk of HIT.

The mechanism of thrombocytopenia and thrombosis in HIT is complex and not fully established. In laboratory studies, Heparin-PF4 complex is deposited on the platelet surface. This deposition is suppressed by high concentrations of heparin, suggesting that the heparin-PF4 complex binds to platelets via its heparin component [21]. HIT IgG binds via its Fab sequences to the PF4 component of heparin-PF4 complex on the platelet surface. The IgG molecule then binds via its Fc sequences to the Fcg receptor IIa of platelets, resulting in activation of the platelet and generation of pro-coagulant platelet microparticles. *In vivo*, P-selectin is expressed on circulating platelets, and platelet-derived microparticles are increased, confirming that platelets are activated in HIT [22,23]. Nevertheless, platelet activation alone is insufficient to cause thrombosis. Other studies further show that HIT sera cause IgG and C3 to deposit on endothelial cells [24] and HIT IgG induces monocytes to express pro-coagulant tissue factor activity [25]. These alterations create a prothrombotic state that can lead to thrombosis, especially in vessels with pre-existing injury. Attraction of neutrophils, possibly by PF4, and formation of neutrophil extracellular trap (NET) may contribute to the propagation of thrombus [26,27].

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In a typical case, there is no history of exposure to heparin within the preceding 3 months, thrombocytopenia occurs after 4 but usually within 15 days of heparin treatment, and there is no other potential cause of the thrombocytopenia. For such cases, the diagnosis of HIT is straightforward, especially when it is accompanied with evidence of new thrombosis and when the thrombocytopenia quickly resolves in a few days after heparin is discontinued, with or without starting alternative anticoagulation therapy. Our patient did not have prior exposure to heparin, her symptoms of myocardial infarction and thrombocytopenia were noted on day 9 of enoxaparin treatment, there were no other plausible causes of her thrombocytopenia, and she had myocardial infarction as well as arterial and venous thrombosis.

Diagnosis of HIT

The diagnosis of HIT can be quite challenging at the time of presentation. Several instruments have been designed to stratify the risk of HIT based on clinical features, including the 4T score and HIT Expert Probability (HEP) score [28,29]. However, the information necessary for determining clinical scores may be inaccurate or unavailable. Hence, incorrect assignment of scores may occur. In a study of more than 500 cases of suspected HIT, the sensitivity of an intermediate [30,31] or high [32–34] 4T score was 81.3% for patients with HIT, while the specificity of a low 4T score (≤3) was 63.8% for exclusion of HIT. Consequently, the positive predictive value for HIT was 1.9%, 6.7%, and 36.6% for low, intermediate, and high 4T scores, respectively, according to one study [35]. The performance of HEP score is similarly problematic [30]. Overall, clinical scores alone are insufficient for diagnosis or exclusion of HIT, although a low score helps increase the negative predictive value of a negative HIT diagnostic test to nearly 100%.

There are 2 types of laboratory tests for the diagnosis of HIT: those that detect antibodies of PF4 neo-epitopes (HIT antibodies [HIT Ab] or HIT IgG), and functional assays that detect the aggregation [36] or serotonin release [37] of platelets after incubation with patient serum or plasma samples in the presence of heparin. The specificity of the functional tests is increased by showing that platelet aggregation or serotonin release in the presence of heparin in the range of therapeutic concentrations is suppressed by high (10× to 100×) concentrations of heparin. The serotonin release assay (SRA) is used as the ultimate test for the diagnosis of HIT. SRA is technically demanding and requires the use of a radioisotope (^{14}C serotonin). The test is only performed in a few reference laboratories and the turnaround time may be several days.

Among the commercially available tests for detection of HIT Ab [38,39], the sensitivity ranges from ~70% to ~100%; the specificity ranges from ~80% to ~99%, and the turnaround time ranges from less than 20 minutes to hours or even days. In general, tests that only detect IgG are more specific but tend to be less sensitive than tests that detect all 3 classes of immunoglobulins (IgG, IgM, and IgA). In interpreting a test result, the performance of the test method used and the estimated pre-test probability (e.g., the patient's 4T score) should be taken into consideration. Specifically, among patients with a high pre-test probability, a negative test result may not completely exclude the diagnosis of HIT [40]. Occasionally, even a negative test result in a patient with low 4T-score does not exclude the diagnosis of HIT [41].

Functional flow cytometry that detects annexin V (also referred to as annexin A5) binding or P-selectin (also known as CD62P) expression as an indicator of platelet activation may replace SRA if its preliminary promising performance is validated [42,43].

Thrombosis

HIT was first described in a patient presenting with arterial thrombosis [44]. However, thrombosis may occur in any vascular bed, including arteries of the extremities, brain, aorta, heart, and other visceral organs; veins of the extremities, with or without pulmonary embolism; cerebral vein sinuses; jugular veins; cardiac chambers; and skin or venous gangrene, presumably due to microvascular thrombosis. The risk of thrombosis is 8- to 9-fold higher for patients with a platelet count decreased by more than 70% [45]. Nevertheless, normal or mildly decreased platelet counts do not exclude the risk of thrombosis due to HIT. Thus, HIT should be suspected in all patients presenting with new thrombosis during heparin therapy or with heparin exposures via a vascular device.

Coronary thrombosis with myocardial infarction is an uncommon complication of HIT, occurring in 2–3% of patients with HIT and thrombosis [45,46]. Our review of the literature identified 9 case reports of coronary thrombosis [32,47]. Among these, only 2 cases occurred in patients without recent coronary intervention or bypass surgery. Although selective reporting of extraordinary events might have been a factor, the data along with the case series cited above support the common clinical impressions that myocardial infarction is an uncommon complication of HIT, especially in the absence of recent coronary intervention or bypass surgery.

Screening for HIT

HIT can lead to 20%–30% mortality if it is not recognized early and treated appropriately [48]. To minimize adverse effects of HIT, monitoring of the platelet count and high index of suspicion are critical (Table 1). To detect HIT early before serious complications occur, the baseline platelet count should be determined before heparin treatment is initiated. The platelet

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Table 1. Prevention and management of heparin-induced thrombocytopenia (HIT).

- Avoid use of UFH or LMWH when alternative anticoagulants are available.
- If heparin has to be used.
  - obtain the baseline platelet count before it is initiated.
  - monitor the platelet count daily to twice weekly during the course of treatment, at least between days 4–15, depending on the type of heparin and its dosage.
- HIT is suspected when the platelet count trends downward, decreases by more than 30%, or new thrombosis occurs.
- Determine the clinical HIT score (4T or HEP); check the D-dimer level; and venous ultrasound and other imaging studies as clinically indicated.
- Diagnostic tests for HIT: HIT Ab tests with reflex for serotonin release assay.
- Discontinued all heparin administration and exposure and institute anticoagulation therapy with a non-heparin alternative when HIT is suspected.
  - To minimize the risk of bleeding, prophylactic doses may be used for patients with thrombocytopenia but a low risk score (e.g., 4T ≤3) and no other indication of anticoagulation therapy.
- Alternative non-heparin anticoagulants include.
  - Direct thrombin or factor Xa inhibitors.
    - Intravenous: argatroban[1], lepirudin[1,2], bivalirudin[3].
    - Oral[4]: dabigatran, rivaroxaban, apixaban, edoxaban.
  - Chemically related to heparin (AT3 dependent): danaparoid[1,2], fondaparinux[5].
- Duration of anticoagulation therapy.
  - Patients without thrombosis and no indication of anticoagulation therapy otherwise.
    - Treatment at least until the platelet count is normalized, preferably for 4 weeks to prevent delayed HIT thrombosis.
  - Patients with thrombosis and otherwise no indication of anticoagulation therapy.
    - At least 3 months, until maximal clot resolution is achieved.
  - Patients with an indication of anticoagulation therapy other than HIT.
    - Continue anticoagulation therapy for at least 3 months or longer as clinically indicated.

[1] FDA-approved for the treatment of HIT; [2] No longer available in the USA; [3] FDA-approved for anticoagulation during percutaneous coronary intervention; [4] These direct oral anticoagulants are increasingly used, with favorable efficacy and safety, but have not been rigorously investigated in large trials or are not FDA-approved for this indication; [5] Chemically related to heparin but not associated with platelet activation.

count is monitored during the course of treatment, at least between day 4 and 15, daily to twice weekly, depending on the type and dose of heparin used. Another recommendation is to monitor the platelet count only when the estimated risk of HIT is more than minimal (e.g., >0.1%) [49]. Nevertheless, risk estimation for HIT is not consistently reliable. Our case demonstrates the risk of not screening for HIT in patients being treated with LMWH.

HIT should be suspected when the platelet count shows a downward trend, decreases by more than 30%, or there is evidence of new venous and/or arterial thrombosis, or atypical presentations such as skin necrosis, adrenal hemorrhage, or venous limb gangrene [50,51].

In practice, possibly due to the perceived lower risk of HIT, the platelet count is often not monitored for patients receiving prophylactic or therapeutic LMWH therapy. Furthermore, since HIT is not a widely known cause of myocardial infarction, its diagnosis was not immediately suspected in our case and the patient was treated with intravenous heparin when she presented with myocardial infarction. Fortunately, heparin was discontinued within a few hours before it caused further damage.

Thrombosis

Therapeutic options

When HIT is suspected, all heparin administration and exposure should be discontinued. This includes Hep-Lock and heparin-coated vascular devices. With or without evidence of thrombosis, the patients should be treated with an alternative anticoagulant. The treatment options have expanded beyond vitamin K antagonists (e.g., warfarin) in recent years, as they now include 2 intravenous direct thrombin inhibitors, argatroban [52] and bivalirudin [53]; subcutaneous fondaparinux [54], a pentasaccharide that is chemically related to heparin but does not cross-react with HIT antibodies; and direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban. Among these, only argatroban is approved for treatment of HIT. Bivalirudin is approved for use during percutaneous coronary intervention (PCI) in patients with the diagnosis of HIT, although it has been used off-label for the treatment of HIT. Two other FDA-approved anticoagulants – danaparoid and lepirudin – are no longer available in the USA.

Argatroban is contraindicated in patients with impaired liver function. Argatroban treatment requires monitoring of PTT,

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which is often confounded by the levels of other clotting factors. Subcutaneous fondaparinux does not routinely require monitoring. When monitoring is necessary, chromogenic anti-Xa level assay, which is less affected by the levels of other clotting factors, is used to guide dose adjustment. A national, multicenter registry study has shown that the efficacy and safety of fondaparinux are far superior to those of argatroban [54].

Direct oral anticoagulants have also been increasingly used off-label for HIT, generally with favorably efficacy and safety, either as primary treatment or secondary treatment following initial treatment using a parenteral non-heparin anticoagulant [55].

Before the newer alternative anticoagulants became available, warfarin was the only option to provide anticoagulation for the treatment of HIT. Initiation of a vitamin K antagonist prior to platelet count recovery is contraindicated as it is associated with a heightened risk of venous limb gangrene, presumably due to the compounding effects of decreased protein C synthesis by vitamin K antagonists and the inhibition of protein C activation by HIT antibodies [56]. Furthermore, the effect of vitamin K should be reversed if a patient is being treated with a vitamin K antagonist at the time of HIT diagnosis.

In practice, unstable hospitalized patients are often treated with intravenous argatroban or bivalirudin, followed by one of the direct oral anticoagulants when the patients are stabilized or discharged.

Duration of treatment

For patients without thrombosis, the anticoagulation therapy should be continued at least until the platelet count normalizes or returns to its baseline level. The treatment is generally extended to 4 weeks to prevent delayed thrombosis [57].

For patients with thrombosis due to HIT, the anticoagulation therapy is continued for at least 3 months, preferably until the thrombosis has reached its optimal resolution, or longer as clinically indicated if the patients have other indications of long-term anticoagulation therapy.

Thromboembolic events may continue to occur in HIT patients during non-heparin anticoagulation therapy. We speculate that the intense pain of the left foot with toe discoloration on day 5 of our case might have resulted from embolism of the dissolving thrombosis upstream in the femoral and popliteal arteries. We are uncertain whether the thrombosis in the left posterior tibial vein in this case was due to her knee surgery or due to HIT. In a clinical trial that included prophylactic enoxaparin at 40 mg daily after total knee arthroplasty, as was used in our patient, asymptomatic, mostly distal, DVT occurred in nearly one-quarter of the patients [58].

Conclusions

In summary, we report a case of heparin-induced thrombocytopenia (HIT) that caused myocardial infarction on day 9 of prophylactic enoxaparin therapy after bilateral total knee arthroplasty. The patient also had bilateral lower-extremity artery thrombosis and a distal deep venous thrombosis. She was successfully treated with thrombolysis and argatroban followed by apixaban, with good recovery and no adverse events. Considering the seriousness of HIT, we propose that UFH or LMWH should be avoided when alternative options of anticoagulation are available. Among patients being treated with any formulation of heparin, the platelet count should be monitored to detect HIT before it causes serious complications. A trend of decrease of the platelet count, decrease of the platelet count by 30% or more, and/or occurrence of any type of thrombosis should raise the suspicion of HIT and prompt the discontinuation of all heparin exposures and institution of anticoagulation with a non-heparin alternative to prevent or treat thrombosis. The clinical HIT score should be determined. D-dimer measurement may help determine if there is active thrombosis. Further management is guided by the results of HIT diagnostic tests.

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