

# Heparin-Induced Thrombocytopenia

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**Abstract:** Heparin-induced thrombocytopenia (HIT) is a growing complication of a common medication used to prevent deep vein thrombosis (DVT) in hospitalized patients. The purpose of this article is to review the mechanism that causes paradoxical thrombus formation in HIT and ways to recognize this important complication with various testing modalities and to discuss the approaches to treatment once a diagnosis has been made. HIT is a clinical diagnosis that can be further supported by utilizing the “4 Ts”: thrombocytopenia, timing of platelet count fall, thrombosis or other complications, and other causes for thrombocytopenia. Diagnosis of HIT can be established using an HIT antibody test. Once a drop in platelet count is observed in a patient, it is important to rule out HIT. When HIT is first suspected, it is important to discontinue all heparin products. The gold standard in diagnosing HIT is the 14C-serotonin release assay (14C-SRA) assay, which has high sensitivity and specificity but is technically demanding and more time consuming than other antibody-detecting immunoassays. Anticoagulation in HIT patients is essential due to the increased risk of thrombosis. Treatment consists of utilizing alternative, nonheparin anticoagulants like lepirudin, argatroban, bivalirudin, or fondaparinux (although fondaparinux is not formally approved by the US Food and Drug Administration for this condition). Each of these agents should be individually formulated based on the patient and the presence/absence of liver or renal failure. Treatment duration has yet to be determined. However, in patients requiring long-term anticoagulation (pulmonary embolism, DVT, stroke), the transition to warfarin can be made once the platelet count recovers and there has been at least 5 days of overlap with a nonheparin anticoagulant.

## Introduction

Heparin-induced thrombocytopenia (HIT) is described as a drop in platelet count greater than 50%, or a decrease to less than  $150 \times 10^9/L$  in the setting of heparin use, typically 5–10 days after its initiation.<sup>1</sup> In the 1970s, it was noted that a small number of patients being treated with heparin developed life-threatening

### Keywords

Heparin-induced thrombocytopenia, deep vein thrombosis, anticoagulation

venous and arterial thromboemboli.<sup>2</sup> Therefore, it is imperative to recognize HIT, given its possible complication of paradoxical life-threatening thromboemboli formation. There are 2 types of HIT: type I and type II. Type I is a benign condition where there is a mild transient decrease in platelet count, which is not associated with immune formation or increased risk of thrombosis. HIT type II is the focus of this review, as it is an immune-mediated phenomenon that causes a drop in platelets and puts patients at risk for developing significant thrombosis. Examples of complications secondary to HIT type II include deep vein thrombosis (DVT), adrenal vein thrombosis, myocardial infarction (MI), stroke, pulmonary embolus (PE), limb gangrene or acute limb ischemia, organ infarction, and cerebral sinus thrombus. Up to 70% of orthopedic patients diagnosed with HIT can develop DVT, compared to an incidence of 20–30% in patients who receive prophylactic heparin.<sup>3</sup> A study examining a 6-month follow-up of patients with HIT showed an incidence of 11.7% for MI, 2.9% for stroke, and 4.3% for DVT.<sup>4</sup> Those with HIT and central venous catheters have been found to have a higher incidence of upper extremity venous thrombosis.<sup>5</sup>

### Unfractionated Heparin Versus Low-Molecular-Weight Heparin

HIT develops in up to 3% of patients treated with unfractionated heparin (UFH).<sup>6</sup> A prospective cohort follow-up study in hospitalized medical patients receiving subcutaneous UFH showed that the incidence of HIT was lower than previously observed in other settings (ie, IV heparin).<sup>6</sup> Although the incidence of HIT was lower, there was a comparable high rate of thromboembolic events.<sup>6</sup> A meta-analysis in post-operative patients favored the use of low-molecular-weight heparin (LMWH) over UFH—with absolute risk for HIT being 0.2% for LMWH and 2.6% with UFH—but did not enable a reliable estimate of HIT risk.<sup>1</sup> In a prospective cohort follow-up study, it was observed that the cases of HIT that developed were in patients who were given prophylactic heparin beyond 1 week, not those receiving a shorter period of heparin for treatment purposes.<sup>1</sup> This leads to the concern of developing life-threatening thromboembolus in patients with prolonged duration of prophylaxis with UFH. Because it is common to use prophylactic UFH for longer than 1 week, recommendations have arisen to closely monitor patients both clinically and with laboratory values (ie, complete blood count) and to replace UFH with LMWH,<sup>1</sup> which has a lower incidence of paradoxical thromboembolus formation (shown in surgical patients).<sup>3</sup> In a retrospective analysis, LMWH was found to be associated with a lower incidence of HIT than UFH in

patients. The incidence of HIT was lower, at 0.084%, in those receiving LMWH compared to those patients receiving UFH (0.51%).<sup>7</sup> LMWH is shorter in molecular length, binds less weakly to platelet factor-4 (PF4), and is less antigenic, therefore causing HIT less frequently.<sup>5</sup>

### Pathophysiology

Immune mediated HIT type II is caused by heparin-dependent platelet-activating immunoglobulin G (IgG). This immune response is triggered by the antibodies that form between heparin and PF4. PF4 is located on the surface of the platelets and signifies the binding site for heparin.<sup>8</sup> The target antigen for this antibody is the heparin/PF4 complex. The immune complexes consist of HIT IgG and heparin/PF4, which form on the platelet surfaces, permitting the Fc region on IgG to activate platelets.<sup>8</sup> Antibodies to the PF4/heparin complex activate platelets in vitro via the platelet Fc receptor for IgG.<sup>9</sup> Newman and colleagues found that HIT IgG was nonreactive with heparin alone, but when platelet releasate was added, binding of heparin to the HIT IgG was observed.<sup>10</sup> This was also supported by an experiment done by Kelton and associates, where they used HIT IgG bound to protein A-Sepharose beads. The immobilized IgG did not react with heparin, but there was an increase in the binding of heparin and IgG once platelet releasate was added, further confirming that the heparin/PF4 complex is the targeted antigen of HIT IgG.<sup>8</sup> This binding with the Fc receptors on the surfaces of platelets provokes intracellular signaling and platelet activation, which eventually leads to platelet aggregation<sup>5</sup> and causes thrombocytopenia.

The activation of platelets causes release of PF4 from the alpha granules located within the platelets, resulting in immense thrombin generation. In turn, PF4 causes platelet aggregation and activates monocytes, which activate tissue factor, thus causing a prothrombotic state.<sup>9</sup> PF4 also is able to attach to endothelial cells,<sup>10</sup> further enhancing the prothrombotic state of HIT.

### Diagnosis

HIT is first suspected within 5–10 days after initial heparin exposure, when there is a drop in platelet count of more than 50%, or a decrease to less than  $150 \times 10^9/L$ . The 4 Ts—which include thrombocytopenia, timing of platelet count fall, thrombosis or other complications, and other causes for thrombocytopenia—is a pretest clinical scoring system that may be utilized in determining probability of HIT when it is suspected in a patient (Table 1). Combining the 4 Ts with a diagnostic test is recommended to help reduce inappropriate switches from heparin to

**Table 1.** The 4 Ts Scoring System in Heparin-Induced Thrombocytopenia

The 4Ts	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and nadir >20 × 10 <sup>9</sup> /L	Platelet count fall 30–50% or nadir 10–19 × 10 <sup>9</sup> /L	Platelet count fall <30% or nadir <10 × 10 <sup>9</sup> /L
Timing of platelet count fall	At day 5–10 or fall at <1 day if heparin used within 30 days	Not clear about timing between 5–10 days or after 10 days or <1 day with prior heparin exposure within 30–100 days	Platelet count fall <4 days without recent exposure
Thrombosis/other complications	Confirmed thrombosis, skin necrosis	Progressive/recurrent thrombosis, erythematous skin lesions, or suspected thrombosis not yet proven	None
Presence of alternative diagnosis	None	Possible	Definite

Adapted from Harenberg J et al. *Br J Haematol.* 2000;109:182-186.

more expensive medications caused by false positives in diagnosing HIT. A score of 0–3 points gives a low pretest probability of HIT, 4–5 points is intermediate, and 6–8 points gives a high probability of HIT.<sup>11</sup> A study by Lo and coworkers concluded that the clinical score is valuable in predicting which patients are least likely to have a serologic profile demonstrating the existence of HIT due to the high negative predictive value of the HIT score (HIT frequency in low probability group, <2%).<sup>12</sup>

Further diagnosis can be established by ordering various tests. Commonly used diagnostic tests include the serotonin release assay and antibody detecting assays. The gold standard in diagnosing HIT is the [14C]-serotonin release assay (14C-SRA) because of its high sensitivity and specificity. In the 1980s, a study by Sheridan and coauthors looked at 14C-SRA to diagnose HIT in patients with thrombocytopenia 2 days following heparin administration; the controls were from healthy laboratory staff. They found that the test was sensitive in diagnosing HIT; it was 99% specific, and out of 4 patients without HIT, none had a positive test.<sup>13</sup> The authors showed that those with the highest probability of having HIT clinically also had the highest rate of positivity in the assay.<sup>13</sup> There are limitations to the 14C-SRA test: it is expensive, technically demanding, and it requires the use of a radioactive labeled substance. A study comparing the 14C-SRA test to an enzyme immunoassay (EIA-SRA) that does not utilize radioactive serotonin showed EIA-SRA sensitivity and specificity of 100% and 97.4%, respectively, compared to 100% and 92.9% with the 14C-SRA test in HIT patients,<sup>14</sup> resulting in higher specificity of the EIA. This EIA-SRA method provides a dependable way to diagnose HIT without exposing patients to radioactive serotonin.

PF-4-dependent antigen assays are an additional modality in detecting HIT antibodies. These assays detect IgG/A/M to identify HIT antibodies. A more recent study by Legnani and associates evaluated newer and more rapid automated panel assays for diagnosing patients with HIT. The researchers looked at an assay that is specific for IgG antibodies against the PF-4/heparin complex (HIT-IgG), and another assay that detects IgG, IgM, and IgA anti-PF-4/heparin antibodies (HIT-Ab). They used the clinical 4 Ts score to determine the probability of HIT along with the immunoassays. No false negatives were detected; therefore, both assays had sensitivity and negative predictive values of 100%.<sup>15</sup> These results support the use of these immunoassays in ruling out HIT when used with the 4 Ts clinical scoring method. The specificity differed between the 2 assays, with a specificity of 96.5% in the IgG assay and 81.2% in HIT-Ab. The researchers attribute this to the fact that nonfunctional antibodies are also detected and are usually IgM or IgA, which can be detected by the HIT-Ab assay.<sup>15</sup> Legnani and associates concluded that both the HIT-IgG and HIT-Ab assays can be used dependably to rule out HIT (with the HIT-IgG assay having a greater specificity), both can be performed in a short period of time (approximately 30 minutes), and are highly reproducible.<sup>15</sup> A study by Poupard and colleagues also looked at new immunoassays, one specific for IgG against PF-4/heparin complex and the other for IgG/A/M. The investigators concluded that an immunoassay that detects only IgG antibodies (HIA IgG) is more efficient.<sup>16</sup> They also showed that sensitivities were comparable between HIA IgG/A/M and HIA IgG, with 97.7% sensitivity in both assays, but a higher specificity in the HIA IgG (90%) compared to the HIA IgG/A/M (77%). This further demonstrates the large

**Table 2.** Drugs Used in Heparin-Induced Thrombocytopenia<sup>19-27</sup>

Drug	Mechanism of Action	Usual Dosage	Monitoring	Metabolism	Half-Life	Adverse Effects
Lepirudin	Direct thrombin inhibitor	0.11 mg/kg/hr	aPTT (goal 1.5–2.5 × control)	Renal	1.3 hours	Bleeding, anemia
Bivalirudin	Direct thrombin inhibitor	0.15–0.2 mg/kg/hr	aPTT (goal 1.5–2.5 × control)	Renal	10–24 min	Bleeding, hypotension, nausea
Argatroban	Direct thrombin inhibitor	2 µg/kg/min	aPTT (goal 1.5–3 × control)	Hepatobiliary	39–51 min	Bleeding, hypotension
Fondaparinux	Anti-Xa inhibitor	Not established for HIT (5–10 mg SC daily in DVT/PE)	Anti-Xa activity of fondaparinux	Renal	17–21 hours	Bleeding, fever, nausea, anemia

aPTT=activated partial thromboplastin time; DVT=deep vein thrombosis; HIT=heparin-induced thrombocytopenia; PE=pulmonary embolism.

role IgG antibodies play in HIT pathogenesis,<sup>16</sup> and that IgG antibody detection is effective in diagnosing HIT.

## Treatment

Due to the risk of life-threatening thromboembolus formation, it is imperative to treat HIT once it has been diagnosed. The first step is to discontinue all exposure to heparin-containing products, including catheters coated with heparin. Aside from stopping heparin use, treatment with a direct thrombin inhibitor such as lepirudin, bivalirudin, or argatroban is necessary, as there is an increased risk of developing thrombosis (Table 2).

Lepirudin is a recombinant hirudin that has been approved by the FDA for HIT complicated by thrombosis.<sup>11</sup> This drug is a direct thrombin inhibitor that is not activated by PF-4, and thus does not cross-react with HIT antibodies.<sup>17</sup> Several prospective studies evaluated lepirudin and its efficacy and safety in treating HIT. Greinacher and coworkers compared the clinical outcomes of patients treated with lepirudin to those in a historical control group (historical due to the high risk of thrombus complications; placebo group was not utilized). In this comparison, lepirudin prolonged activated partial thromboplastin time (aPTT) and caused rapid normalization of platelet counts.<sup>17</sup> The primary adverse event associated with lepirudin is bleeding, which was more common in invasive sites, but did not differ in serious bleeding occurrences or spontaneous bleeding when compared to the control.<sup>17</sup> There is no antidote available for lepirudin. Its use in HIT has been further supported

by the HAT-3 (Heparin-Associated Thrombocytopenia) trial, which also demonstrated that treatment for HIT should not be delayed. In this study, the risk for a new thromboembolic complication was decreased by 92.9% during active treatment.<sup>18</sup> Lepirudin is eliminated renally, so it is strongly recommended that dosing is adjusted and consecutive aPTT levels are monitored every 4 hours until a steady state is achieved.<sup>18</sup> The HAT-3 study also utilized a mean dose that was approximately 30% lower than previous recommended doses. The investigators avoided the initial bolus and decreased the maintenance dose to 0.11 mg/kg/hr (adjusted for aPTT), hence decreasing the risk of major bleeding.<sup>18</sup> Warkentin and coworkers recommended that the initial bolus be given only if the patient is experiencing life- or limb-threatening thrombosis.<sup>19</sup> The preferable aPTT is 1.5–2.5 × control.<sup>20</sup> Rare anaphylactic reactions have been reported<sup>21</sup>; it is advised to begin treatment in a monitored setting.

Although bivalirudin is another direct thrombin inhibitor that has been shown to successfully treat HIT, it has only been FDA-approved for treatment in patients who are undergoing percutaneous coronary intervention (PCI). Several case studies have reported successful treatment of HIT in patients following PCI, with prevention of life-threatening thromboembolic complications.<sup>22</sup> Bivalirudin has been shown to be safe, and has provided adequate anticoagulation during PCI.<sup>23</sup> Daily aPTT monitoring should be done in patients who are treated with bivalirudin for more than 5 days in order to avoid bleeding complications.<sup>11</sup> The infusion rate of bivalirudin is 0.15–0.2 mg/kg/hr.<sup>19</sup> A study showed that patients with

severe renal insufficiency required dose adjustments, but current recommendations state that bivalirudin is preferred in the setting of both hepatic and renal impairment.<sup>20</sup> In addition to the lepirudin and bivalirudin, argatroban is another direct thrombin inhibitor that is approved for both HIT prevention and treatment. It is eliminated via the hepatobiliary system, and has been successfully used in critically ill, intensive care HIT patients with multi-organ dysfunction, although dose adjustments need to be made in order to reduce bleeding complications.<sup>24</sup> Argatroban increases the international normalized ratio (INR). When administering it concurrently with warfarin, a higher INR therapeutic range may be needed.<sup>19</sup> The initial infusion rate is 2 µg/kg/min without an initial bolus; a lower dose can be used in patients with heart failure, multiple organ system failure, or severe anasarca (0.5–1.2 µg/kg/min).<sup>19</sup> When transitioning to warfarin, it is recommended that the platelet count be at least  $100 \times 10^9/L$ ; the transition should occur after the patient has been adequately anticoagulated.<sup>25</sup> Treatment with warfarin and argatroban should be overlapped for at least 5 days and continued until target INR is reached for 2 consecutive days with a stabilized platelet count.<sup>25</sup> An analysis by Hursting and associates found that most patients received less than 5 mg/day of warfarin. The research supports previous guidelines that recommended that once the target cotherapy INR is reached, the physician may discontinue argatroban and check the INR level 4–6 hours after discontinuation to make certain the INR is therapeutic.<sup>25</sup> Subtherapeutic INR was defined as less than 1.9, supratherapeutic INR was defined as more than 3.5, and therapeutic INR was defined as 1.9–3.5, with no major bleeding events occurring in any of the groups. Patients with mild to moderate hepatic failure may require dose reduction to 0.5 µg/kg/min.<sup>20</sup>

In 1997, Warkentin observed that warfarin use in patients with acute HIT is associated with a higher incidence of venous thrombosis. This can lead to limb gangrene and/or limb amputations, which is secondary to a reduction in protein C levels, leading to a further hypercoagulable state.<sup>26</sup> A retrospective study in 1999 concluded that modest doses of warfarin were not associated with limb gangrene, death, or thrombosis.<sup>27</sup> Current recommendations are to start warfarin once the platelet count has reached a stable plateau and after the platelet count has increased above  $100 \times 10^9/L$ .<sup>28</sup> Warfarin treatment is initiated in patients who are in need of long-term anticoagulation with a goal INR of 2–3.<sup>20</sup> Situations that may require long-term anticoagulation include patients with a history of HIT and the sustained presence of antibodies,<sup>20</sup> and those at risk of future thrombus formation (ie, patients with a prior history of a hypercoagulable state).

Fondaparinux is an agent to consider, although it has not been formally approved by the FDA for the treatment of HIT. It is approved for prevention of DVT following orthopedic or abdominal surgery and for DVT treatment.<sup>19</sup> It is a synthetic pentasaccharide that binds to antithrombin III and potentiates inhibition of factor Xa.<sup>29</sup> Minimal data show that there is a lack of in vitro cross-reactivity with HIT antibodies<sup>19</sup> and that the structure of fondaparinux is too short to provoke an antibody response.<sup>29</sup> A single-center study examined the use of fondaparinux for HIT and compared it to patients receiving lepirudin. Grouzi and coworkers found that patients who received fondaparinux had complete platelet recovery without suffering additional thromboembolic complications or major bleeding.<sup>29</sup> The same study also showed that both groups had limb gangrene (2 patients in the lepirudin group and 1 patient in the fondaparinux group), which was attributed to a probable delay in diagnosis and treatment initiation.<sup>29</sup> Fondaparinux has been shown to successfully treat HIT-associated venous thrombosis,<sup>30</sup> which suggests that it may be a useful option for anticoagulation in HIT. Since it is not currently approved for HIT, no dosing guidelines have been formally established. Dosing for treating acute DVT/PE is weight based, ranging from 5 mg to 10 mg of daily subcutaneous administration.

Treatment duration with an alternative anticoagulant has not been determined. Some practitioners treat for 30 days due to the concern of a delayed onset of HIT.<sup>20</sup> It was noted in a prospective cohort study that the incidence of thromboembolic events was higher in patients with HIT.<sup>6</sup> Recommendations suggest anticoagulating at minimum during the immediate period in acute HIT. A DTI should be continued until platelet count normalizes. If complications such as DVT, PE, MI, or stroke arise, long-term anticoagulation may be continued for 3–6 months, although no formal guidelines have been established.

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