# Pharmacotherapy of heparin-induced thrombocytopenia: Therapeutic options and challenges in the clinical practices

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*Heparin-induced thrombocytopenia (HIT) is an immune response to heparin associated with significant morbidity and mortality in hospitalized patients if unidentified as soon as possible, owing to thromboembolic complications involving both arterial and venous systems. Early diagnoses based on a comprehensive interpretation of clinical and laboratory information improves clinical outcomes. Management principles of strongly suspected HIT should not be delayed for laboratory result confirmation. Treatment strategies have been introduced including new, safe, and effective agents. This review summarizes the clinical therapeutic options for HIT addressing the use of parenteral direct thrombin inhibitors and indirect factor Xa inhibitors as well as the potential non-vitamin K antagonist oral anticoagulants.* (J Vasc Nurs 2015;33:10-20)

Unfractionated heparin (UFH) or related molecules such as low-molecular weight heparin (LMWH) are widely used in both outpatient and inpatient settings for many thromboembolic events. Paradoxically, patients exposed to UFH or LMWH are at risk for thrombotic complications that may include deep vein thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, cerebral vein thrombosis, and disseminated intravascular coagulation. These thrombotic complications are owing to a serious adverse reaction called heparin-induced thrombocytopenia (HIT).[1-5]

HIT is defined as a drop in platelet count during or after heparin administration.[4-6] The nonimmune heparin-associated thrombocytopenia, traditionally called type I HIT, is mediated by direct interaction between heparin and circulating platelets, causing platelet clumping or sequestration. Heparin-associated thrombocytopenia is a self-limiting thrombocytopenia that affects ≤10% of patients receiving heparin formulations, usually develops within the first 72 hours after heparin administration, and platelet counts do not drop below 100,000/mm$^3$; it often normalizes once the heparin is ceased.[7,8] The immune-mediated HIT, known as HIT type II,[8-10] is a prothrombotic and potentially lethal disorder caused by platelet, endothelial, and monocyte-activating antibodies that target multimolecular complexes of platelet factor 4 (PF4) and heparin.[11] The immune-mediated HIT is reported to occur in 0.2%–5% of heparin-treated patients and the platelet count begins to fall between 5 and 10 days after the initiation heparin formulation.[4,5,12-14]

The devastating clinical consequences of the immune-mediated HIT, which may include amputation and death, should alert clinicians to identify patients with HIT and those with increased risk of development of immune-mediated HIT as soon as possible to initiate early management and prevent serious complications. For the purpose of this review, the term HIT refers to the immune-mediated type II that causes paradoxical thromboemboli.

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## RISK FACTORS

Patients' exposure to heparin is the main risk factor and a critical step in the development of HIT (Table 1). A heparin source such as bovine lung is more immunogenic than those produced from porcine intestine,[15] and the risk of HIT rises with the length and volume of exposure to heparin as well as the route of administration,[16] and more likely with intravenous heparin than subcutaneous administration.[17-19] Nevertheless, HIT can develop from any heparin exposure, including incidental amounts from heparin flushes or heparin-coated devices.[20,21] Although HIT is more common in patients receiving UFH than in those treated with LMWH,[22,23] it is very important to note that HIT that is developing in patients receiving UFH frequently cross-reacts with the use of LMWH.[24] HIT antibodies are more likely to occur in trauma and postoperative patients receiving heparin than in patients for medical reasons.[25,26]

## PATHOPHYSIOLOGY

HIT is an autoimmune response caused by the formation of antibodies that activate platelets after heparin administration.[27,28] This response leads to an interaction with PF4, which is normally found on endothelial cells and platelets, and formation of immunogenic heparin–PF4 complexes that cause

**TABLE 1**

**FACTORS CONTRIBUTING TO THE DEVELOPMENT OF HEPARIN-INDUCED THROMBOCYTOPENIA**

| *Risk Category* | *Immunogenicity Value (Immunogenic Effects)* |
|---|---|
| Heparin source | Bovine higher than porcine |
| Heparin type | UFH more than LMWH |
| Volume of heparin dose | Therapeutic dose > prophylactic > flush or heparin-coated devices |
| Heparin exposure | |
| First exposure | Platelet fall day 5–10 after heparin initiation |
| Previous exposure (within 90 days) | Platelet fall within 1 day after heparin initiation |
| Patient population | Postoperative more than medical more than obstetric |
| Patient gender | Female more than male |

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

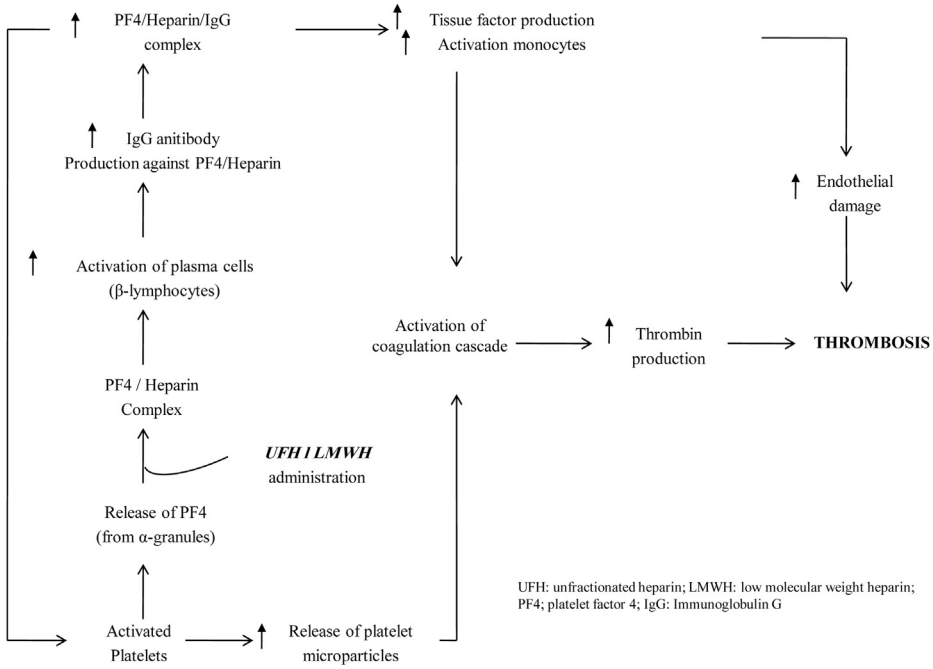


***Figure 1.*** *Pathophysiology of heparin-induced thrombocytopenia and thrombosis.*

an immunologic response. Antibodies are generated resulting in a complex forming among antibodies, heparin, and PF4. This complex leads to further platelet activation, resulting in formation of microparticles and thrombin generation.[29] Antibodies also recognize PF4 bound to heparin on the endothelial surface, and this surface becomes activated, leading to another route of thrombin production.[30] These pathways of thrombin generation may ultimately lead to thrombus formation and possible thromboembolic sequelae (Figure 1). The antibodies that are formed may persist for weeks to months after heparin administration; therefore, if a patient develops HIT and is administered heparin at a later date when circulating antibodies are still present, platelet levels may decrease within hours.[31,32]

## CLINICAL PRESENTATION AND LABORATORY DIAGNOSIS

HIT may occur rapidly or with a delayed onset, depending on the presence of heparin–PF4 antibodies from a previous administration and sensitization of heparin and related molecules may induce rapid-onset HIT.[33] In patients exposed to heparin for the first time, the onset of HIT may occurs 5–10 days after receiving heparin.[4,5,12,34] The thrombocytopenia in HIT is usually moderate in severity, with a median platelet count being between 50 and 80 $\times$ $10^9$/L, although the nadir platelet count can remain at a level considered normal (ie, >150 $\times$ $10^9$/L) but having dropped by $\geq$50% with respect to the preheparin