# Argatroban in heparin-induced thrombocytopenia: rationale for use and place in therapy

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***Abstract:*** Heparin-induced thrombocytopenia (HIT) is a recognized complication of heparin and requires urgent detection and treatment. HIT can be divided into two types, type I and type II, with type I being a transient decrease in platelet count without clinical consequence. For the purpose of this review, the term HIT refers to the immune-mediated type II that causes paradoxical thrombo-emboli. The aim of this review is to familiarize clinicians with a specific direct thrombin inhibitor, argatroban, in the treatment of HIT. Argatroban has been successfully employed in treating HIT in many different subsets of patients, including those with endstage renal disease on hemodialysis and in patients undergoing percutaneous coronary intervention and those with multiorgan dysfunction syndrome.

***Keywords:*** argatroban, heparin, heparin-induced thrombocytopenia

## Introduction

Heparin-induced thrombocytopenia (HIT) is suspected when the platelet count decreases more than 50% or decreases to < 150 × $10^9$/l, most commonly 5–10 days after the initiation of heparin [Martel *et al.* 2005]. HIT type II is the immune-mediated type and is crucial to recognize due to the known complication of life-threatening venous and arterial thrombo-emboli [Evan Sadler and Mortimer, 2010]. The first step in treating HIT is discontinuing all heparin products, including removal of heparin-coated central lines if present. HIT leads to a hypercoagulable state and paradoxical thrombus formation; therefore alternate anticoagulation is essential to decrease this risk. Without alternate anticoagulation, the risk of thromboembolic complications can be seen in 30–75% of cases [Saugel *et al.* 2010]. The life-threatening complications of HIT include deep vein thrombosis (DVT), myocardial infarction, cerebral sinus thrombus, pulmonary embolus, stroke, adrenal vein thrombosis, limb gangrene and acute limb ischemia. Several direct thrombin inhibitors (DTIs) have been studied in the management of HIT, including lepirudin, bivalirudin and argatroban. This review focuses on the use of argatroban in treating HIT.

## Pathophysiology of HIT

HIT can develop in up to 3% of patients treated with unfractionated heparin (UFH) [Girolami *et al.* 2002]. It is an immune-mediated phenomenon caused by heparin-dependent platelet activating immunoglobulin G (IgG) that is triggered by antibodies formed between heparin and platelet factor 4 (PF4) [Kelton *et al.* 1994]. This forms an immune complex consisting of a heparin/PF4 core and is the target antigen for the antibody. These immune complexes develop onto platelet surfaces, thus allowing the Fc receptor region on IgG to activate platelets [Kelton *et al.* 1994] and eventually leading to platelet aggregation, causing thrombocytopenia. Activation of platelets also leads to release of PF4 from granules that are located within the platelets and this in turn results in a vast generation of thrombin, leading to a prothrombotic state [Thachil, 2010]. HIT can be diagnosed *via* various assays that have been developed, namely the serotonin release assay that detects the specific antibody. There are also PF4-dependent antigen assays that detect IgG/A/M HIT antibodies and, when combined with clinical features, are very sensitive [Legnani *et al.* 2010].

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## Argatroban

Argatroban is a small molecule DTI that acts by reversibly binding to the catalytic thrombin active site, thus inhibiting activation of factors V, VIII and XIII (the coagulant factors), as well as preventing fibrin formation and platelet aggregation [Hursting *et al.* 1997]. It is eliminated *via* the hepatobiliary system; therefore precaution is needed in patients with hepatic impairment due to decreased clearance. It is not absolutely contraindicated but dose adjustment is recommended. It is given *via* the intravenous (IV) route and usual initial dosing is 2 μg/kg/min continuous IV infusion adjusted to steady-state activated partial thromboplastin (aPTT) 1.5–3 times initial baseline value but cannot surpass 100 seconds. No initial bolus is needed and lower doses can be used in patients with multiorgan failure or severe anasarca at 0.5–1.2 μg/kg/min [Warkentin *et al.* 2008]. Maximum dose is 10 μg/kg/min [Micromedex 2.0]. The half-life of argatroban is 39–51 minutes and adverse effects that are common for all DTIs include bleeding and hypotension [Warkentin *et al.* 2008]. Argatroban has specific molecular properties that allow this agent to have less risk of systemic anticoagulant effects. It is a small molecule with a shorter half-life compared with lepirudin or fondaparinux and has selective reversible binding to the thrombin catalytic site [Hursting *et al.* 1997]. Given these properties, argatroban offers the capacity to have a substantial anticoagulant effect with fewer chances of systemic toxicity and adverse events.

## Argatroban in HIT

Argatroban has been effectively utilized in critically ill intensive care unit patients with multiorgan dysfunction diagnosed with HIT [Saugel *et al*. 2010]. This agent has been approved for both HIT prevention and treatment; it does increase the international normalized ratio (INR) when overlapping it with warfarin for anticoagulation and therefore the therapeutic INR range may need to be increased [Warkentin *et al.* 2008]. Due to the fact that it is eliminated *via* the liver, it is commonly used in patients undergoing renal replacement therapy (RRT). A retrospective study was recently done comparing the three DTIs approved for HIT management in patients receiving RRT, comparing primary endpoints of thrombosis, hemorrhage and in-hospital mortality. There was no statistically significant difference in rates of hemorrhage or mortality when comparing lepirudin, argatroban and bivalirudin [Abel *et al.* 2012]. Argatroban is an accepted and effective treatment of HIT in patients receiving RRT.

Argatroban has also been successfully employed in patients with HIT undergoing percutaneous coronary intervention (PCI). Anticoagulation in patients with HIT having PCI is critical and was examined in this specific subset of patients by Lewis and colleagues. Argatroban was safely used with acceptable outcomes post-PCI and provided sufficient anticoagulation [Lewis *et al.* 2002].

With regard to dosing of argatroban, the reported maximum dose is 10 μg/kg/min. A case report has described using high-dose argatroban for treatment of HIT with thrombosis, with initial dose starting at 2 μg/kg/min and target aPTT of 40–80 seconds. This patient had continued worsening of swelling at the site of thrombosis, and therefore the goal aPTT was increased eventually to >75 seconds and the infusion rate was increased to 15.5 μg/kg/min [Hellwig *et al.* 2012]. Higher doses of argatroban can be considered in patients with HIT plus thrombosis which is not responding to initial doses of infusion and may need the goal aPTT increased. This patient did not have significant adverse events but this is hard to predict with such high doses. Optimally, it would be beneficial if laboratories were able to measure actual argatroban concentration in patient's serum but this is not currently available. High doses of argatroban are an option, if needed, with close in-hospital monitoring.

Argatroban can also be considered in patients with hepatic dysfunction even though it is cleared by the hepatobiliary system. In these instances, aPTT needs to be monitored closely and frequently, and dose reduction is required. Initial dose recommendation in hepatic impairment is 2 μg/kg/min [Hursting and Murray, 2008] and some patients may even require lower doses, especially those considered to be high risk, i.e. postcardiac surgery or severe anasarca [Hursting and Murray, 2008]. Argatroban dose can be successfully reduced to 0.5 μg/kg/min in a patient with moderate liver disease without major bleeding risks, although dosing has not been specifically examined in patients with severe liver disease [Yarbrough *et al.* 2012]. Although argatroban is eliminated *via* the hepatobiliary route, it can still be considered in patients with mild-to-moderate liver dysfunction who have been diagnosed with HIT. Anticoagulant values return to baseline value usually within 2–4 hours of stopping argatroban but may take longer in

patient with impaired hepatic function [Hursting and Murray, 2008].

Critically ill patients with multiple organ dysfunction syndrome as well as patients undergoing PCI can be successfully anticoagulated with argatroban, but due to their critical illness, initial dose reduction is needed [Saugel *et al.* 2010]. One of the additional benefits of argatroban is that no initial bolus is required, thus facilitating ease of administration. Argatroban is rapidly acting and has been shown to significantly reduce the risk of death or new thrombosis [Lewis *et al.* 2001]. Treatment of HIT with argatroban successfully lowers mortality rates from thrombosis without increased bleeding risk [Lewis *et al.* 2001].

Given this information, argatroban is a DTI that clinicians need to be aware of and this agent can be effectively utilized in treating HIT with monitoring of the aPTT.

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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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