

Direct Thrombin Inhibitors for the Treatment of Type II Heparin-Induced Thrombocytopenia

by Jennifer Namba, Pharm.D.

Heparin-induced thrombocytopenia (HIT) affects up to 20% of patients receiving heparin.¹ The majority of cases result from a non-immune mediated process known as HIT type I, in which heparin stimulates platelet activation.¹ Thrombocytopenia occurs within 1 to 4 days of heparin initiation. Platelet counts typically remain $>100 \times 10^9/L$ and often normalize without intervention. In contrast, HIT type II is estimated to occur in only 2–5% of patients but presents with a more dramatic fall in platelet count within 5–14 days of heparin initiation.¹ Thrombocytopenia associated with HIT type II is caused by an immune-mediated process that can be quantified as a reduction in platelet count of $>50\%$ from baseline.² HIT type II (referred to as HIT for the purposes of this article) is triggered by the formation of IgG antibodies that bind to complexes of heparin molecules and platelet factor 4 (PF4). Antibody binding to the heparin-PF4 complex stimulates platelets to release microparticles that increase thrombin generation.³ The ensuing cascade of platelet activation and aggregation effectively diminishes the platelet count, resulting in thrombocytopenia as well as an increased risk of thrombosis.⁴ Thrombosis therefore represents a significant clinical concern and affects up to 40–75% of patients diagnosed with HIT, also referred to as HIT with thrombosis syndrome or HITTS.⁵ The management of patients with HIT has significantly improved with the advent of direct thrombin inhibitors (DTIs) such as argatroban and lepirudin. However, without an effective antidote available, the use of DTIs becomes increasingly complex in patients with compromised organ function. This article will explore the current evidence behind direct thrombin inhibitors, particularly the role for bivalirudin as a cost-effective alternative for the treatment of HIT.

The clinical consequences and treatment considerations that accompany HIT reinforce the importance of making a correct diagnosis. The presence of HIT should therefore be based upon clinical and serologic evidence, more specifically, the presence of both thrombocytopenia and HIT antibody seroconversion within 5–14 days of heparin initiation. In addition to thrombocytopenia, other clinical sequelae such as thrombosis or localized skin lesions may be suggestive of HIT in patients with antibody seroconversion.² If other potential causes of thrombocytopenia cannot be identified, serological testing should be considered when clinical suspicion for HIT is high.

Two types of laboratory studies may be used to confirm a diagnosis of HIT. Antigen tests such as the ELISA detect antibodies that bind to the heparin-PF4 (H-PF4) complex. The H-PF4 ELISA test is typically preferred for initial evaluation due to lower cost and a turnaround time of <24 hours. Each test costs \$216.50 and results are available in as little as 5 hours. The H-PF4 ELISA tests have a high negative predictive value. However, false positive results occur in 20–50% of cases, particularly following cardiac surgery.⁶ Positive H-PF4 ELISA results should therefore be correlated with a high clinical suspicion for HIT. Functional tests such as the platelet C-serotonin release assay (SRA) may also be useful

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Thrombotic events occur in 23–52% of patients with HIT who do not receive alternative anticoagulants after heparin is discontinued.²

Anticoagulation with direct thrombin inhibitors is recommended for all HIT patients during the initial period following heparin discontinuation.²

Direct thrombin inhibitors do not cross-react with HIT antibodies and are recommended for all patients with HIT.

Low molecular weight heparins are associated with a high rate of cross-reactivity with HIT antibodies and are absolutely contraindicated in acute HIT.

Heparin re-exposure should be avoided until HIT antibodies are no longer detected (~100 days). Once HIT antibody titers fall to undetectable levels, heparin re-exposure may be considered with careful monitoring.

Due to the risk of venous limb gangrene in patients with HIT, warfarin should be avoided until thrombocytopenia resolves.²

for confirming a diagnosis of HIT. The SRA assay provides a higher rate of sensitivity and specificity by evaluating the degree of platelet aggregation and release of intracellular products following antibody binding. However, the SRA assay is typically reserved as a confirmatory test due to its higher cost and slower processing time.

Past management of HIT consisted of heparin discontinuation, with or without warfarin therapy. However, despite the resolution of thrombocytopenia within 7–10 days of heparin discontinuation, the risk for thrombosis persists until HIT antibodies become negative (~100 days).² As a result, thrombotic events occur in 23–52% of patients with HIT who do not receive alternative anticoagulants following heparin discontinuation.² The risk of thrombosis is highest within the first month and 5% of events have fatal outcomes.⁷ Both venous and arterial thrombosis can occur, although venous thrombi are 2–4 times more common.⁸ Limb amputation and death subsequently affect 10–30% of patients with thrombotic events.¹

Although thrombosis does not always occur in HIT (isolated HIT), anticoagulation with direct thrombin inhibitors is recommended for all patients during the initial period following heparin discontinuation.² Continued anticoagulation is required not only to treat the underlying condition for which heparin was being used, but also to treat and prevent HIT-associated thrombi.¹ Although low molecular weight heparins (LMWH) are associated with a lower rate of HIT antibody formation, reports of cross-reactivity approach 100% in some *in vitro* studies.³ The use of LMWH in HIT-positive patients has therefore been associated with delayed platelet count recovery and a 47% incidence of new thrombosis.⁹ Consequently, LMWH is absolutely contraindicated in patients with acute HIT.²

Treatment Options for Heparin-Induced Thrombocytopenia

Classifying the clinical course of HIT can be helpful when designing appropriate management for patients.¹⁰ Active or acute HIT refers to the concomitant presence of thrombocytopenia and HIT antibodies. If possible, all exposure to heparin should be avoided and alternative anticoagulants such as direct thrombin inhibitors (DTIs) initiated in patients with suspected HIT. Warfarin should be avoided until thrombocytopenia resolves due to the risk of venous limb gangrene.² Patients remaining HIT antibody-positive but who recover platelet counts can be categorized as having subacute HIT. Although the thrombocytopenia has resolved, the risk of thrombosis persists for several weeks and warfarin becomes a reasonable option for long-term anticoagulation.¹⁰ Ideally, re-exposure to heparin should continue to be avoided until HIT antibodies are no longer detectable, or ~100 days.¹¹ Once HIT antibody titers fall to undetectable levels, heparin re-exposure may be considered with careful monitoring. For example, short-term heparin has been successfully used in patients with a history of HIT requiring cardiac angioplasty or surgery.¹²

Alternative anticoagulants useful in HIT inhibit thrombin directly and bind at one or two sites on the molecule.⁴ Direct thrombin inhibitors are therefore potent inhibitors of coagulation that do not cross-react with HIT antibodies.⁵ Unlike heparin, DTIs bind to both soluble and fibrin-bound forms of thrombin. As a result, the pharmacologic properties of DTIs have stimulated interest in these agents as alternatives to heparin for treatment of HIT, percutaneous coronary intervention (PCI), and cardiac surgery.¹³

Lepirudin (Refludan[®])

Lepirudin was the first direct thrombin inhibitor approved for the treatment of HIT. The evidence supporting the use of lepirudin in HIT is based on two prospective studies known as the HAT trials.^{14, 15} Eligible patients had confirmed HIT antibodies and 65%

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Compared to historical controls, lepirudin significantly reduces the combined incidence of thromboembolic events, limb amputation and death in patients with HITTS.^{16,17}

Studies in isolated HIT indicate that lepirudin also reduces events in patients without baseline thrombosis.¹⁷

Lepirudin antibodies are frequent in patients treated for >5 days. Rather than being “neutralizing,” lepirudin antibodies represent the first example of a drug-induced immune response causing enhanced pharmacological activity.²² Therefore, during prolonged treatment, anticoagulatory activity should be monitored daily to minimize bleeding complications from lepirudin.

presented with baseline thrombosis. Study patients were compared to a historical control group positive for HIT antibodies that received standard treatment (heparin discontinuation and/or oral anticoagulation) without direct thrombin inhibitors. A meta-analysis of the HAT trials evaluated the efficacy of lepirudin in patients with baseline thrombosis.¹⁶ Most patients (93%) received an initial lepirudin bolus of 0.4mg/kg followed by an intravenous infusion of 0.15mg/kg/h. Lower doses of lepirudin were given to patients who received thrombolytics (0.2mg/kg loading dose and 0.1 mg/kg/h infusion). Lepirudin

Table I: Results from Lepirudin Trials in HITTS¹⁶

Endpoints	Historical control (n=75)	Meta-analysis (n=113)	P value
Combined endpoint at day 35*	47.8%	21.3%	p=0.004
New thrombosis	27.2%	10.1%	p=0.005
Death	17.6%	8.9%	p>0.05
Bleeding events	23.6%	42.0%	p=0.001
Severe bleeding (transfusion)	7.1%	18.8%	p=0.02

*Combined endpoint (new thromboembolic complications, limb amputation, and death)

Table II: Results from Lepirudin Trials in Isolated HIT¹⁷

Endpoints	Historical control (n=47)	Meta-analysis (n=91)	P Value
Combined endpoint at day 35*	29.8%	19.8%	p=0.028
New thrombosis	14.9%	4.4%	p=0.02
Death	21.3%	14.3%	p=0.094

*Combined endpoint (new thromboembolic complications, limb amputation, and death)

significantly reduced the combined incidence of new thromboembolic complications, limb amputation and death when compared to historical controls (see Table I). Platelet counts recovered to >100 x 10⁹/L in 75% of patients after 3–4 days of therapy. The incidence of new thrombosis alone was significantly lower with lepirudin therapy, but there were non-significant trends toward reduced mortality and fewer limb amputations. Similar efficacy was demonstrated in a meta-analysis of patients with isolated HIT, suggesting the beneficial role of lepirudin for reducing thromboembolic events in patients without baseline thrombosis (see Table II).¹⁷ The incidence of bleeding secondary to lepirudin therapy was consistently greater in all trials versus historical controls.

Table III: Initial Lepirudin Dosing in HIT²⁰

Clcr (mL/min)	Bolus	Infusion
>60	0.4 mg/kg	0.15 mg/kg/hr
45-60	0.2 mg/kg	0.075 mg/kg/hr
30-44	0.2 mg/kg	0.045 mg/kg/hr
15-29	0.2 mg/kg	0.0225 mg/kg/hr
<15	0.1 mg/kg	None – give 0.05 mg/kg bolus prn for aPTT <60 sec

Lepirudin Dose Titration Based on aPTT²¹

aPTT <60 sec	↑ by 20%
aPTT 60-80 sec	No change
aPTT >80 sec	Hold for 2 h then ↓ by 50%

Monitoring of lepirudin therapy should be based on a target aPTT of 60–80 seconds. Following initiation of lepirudin, an aPTT should be obtained in 4 hours, and daily thereafter. More frequent monitoring is recommended for patients with renal insufficiency and suspected thromboembolism or hemorrhage. Lepirudin is primarily cleared by the kidneys and the presence of renal impairment requires dose adjustment (see Table III). Normally, the half-life of lepirudin is ~80 minutes and the effects on aPTT persist for 2–8 hours following discontinuation.¹⁸ However, the half-life may be prolonged for up to 2 days in patients with marked renal insufficiency.¹⁹

Bleeding remains the most common adverse effect of lepirudin, occurring in 18–20% of patients treated for HIT.^{14, 15} Lepirudin has also been observed to induce antibody formation in 44–74% of patients.¹⁰ The clinical significance of antibody formation differs from patient to patient, but most often delays clearance of lepirudin and

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Patients who require decreasing doses of lepirudin over time should be considered for the formation of anti-lepirudin antibodies.

Argatroban is the only direct thrombin inhibitor approved for both the treatment and prophylaxis of HIT-associated thrombosis.

The half-life of argatroban is intermediate among the DTIs (39–51 minutes), and effects on the aPTT typically persist for 2–8 hours following drug discontinuation.

Dose reduction of argatroban is not required in renal insufficiency, but use of argatroban is not recommended in severe hepatic impairment.

INR prolongation from argatroban is not associated with the same bleeding risk as warfarin. However, the prolonged INR complicates the transition from argatroban to warfarin.

**Table VI:
Argatroban Dosing for HIT²⁵**

Initial dose	2 mcg/kg/min
aPTT <60 sec	↑ by 20%
aPTT 60-80 sec	No change
aPTT >80 sec	Hold for 2 h then ↓ by 50%

increases the aPTT.²² Patients who require decreasing doses of lepirudin over time should be considered for the formation of anti-lepirudin antibodies. Re-exposure is generally well tolerated, but cases of anaphylaxis have been rarely reported.¹⁰ There is a positive correlation between risk of death secondary to anaphylactic reactions and re-exposure. Therefore, lepirudin should be avoided in patients who received the agent within the prior 3 months.⁴ Lepirudin may also falsely elevate the INR making it difficult to accurately bridge to warfarin therapy.¹

Argatroban

Argatroban is FDA approved for both the treatment and prophylaxis of HIT-associated thrombosis. It is also approved as an alternative to heparin in patients with HIT who require PCI. The evidence supporting the use of argatroban in HIT is derived from two large prospective studies in which the agent was compared to historical controls.^{23,24} Patients with isolated HIT (thrombocytopenia alone) and baseline thrombotic events (HIT with thrombosis syndrome, or HITTS) were included in the trials (see Tables IV and V). In contrast to the lepirudin trials, laboratory confirmation of HIT antibodies was not required. Rather, study patients were compared against historical controls with thrombocytopenia or positive HIT antibody results. The control group received standard treatment with heparin discontinuation and/or oral anticoagulation. Upon initiation of argatroban, platelet counts recovered in 70–80% of patients at a faster rate versus historical controls.^{23,24} The composite endpoint of death, amputation, and new thromboembolic events was less in patients with isolated thrombocytopenia, but the trend was not statistically significant in patients with baseline thrombosis. Argatroban significantly reduced the incidence of new thrombosis in both patient groups. Severe bleeding events were not significantly different versus historical controls.

Table IV: Results from Argatroban Trials in HITTS^{23,24}

Endpoint	Historical control (n=46)	Argatroban-1 (n=144) ²³	Argatroban-2 (n=229) ²⁴
Combined endpoint*	56.5%	43.8% p=0.131	41.5% p=0.07
New thrombosis	34.8%	19.4% p=0.044	13.1% p<0.001
Mortality	28.3%	18.1% p=0.146	23.1% p=0.45
Severe bleeding	2.2%	11.1% p=0.077	6.1% p=0.48

*Combined endpoint (new thromboembolic complications, limb amputation, and death)

Table V: Results from Argatroban Trials in Isolated HIT^{23,24}

Endpoint	Historical control (n=147)	Argatroban-1 (n=160) ²³	Argatroban-2 (n=189) ²⁴
Combined endpoint*	38.8%	25.6% p=0.014	28.0% p=0.04
New thrombosis	22.4%	8.1% p<0.001	5.8% p<0.001
Mortality	21.8%	16.9% p=0.311	19.0% p=0.78
Severe bleeding	8.2%	3.1% p=0.078	5.3% p=0.27

*Combined endpoint (new thromboembolic complications, limb amputation, and death)

Argatroban is unique among the direct thrombin inhibitors due to its primary route of metabolism via the liver. As a result, the agent is not recommended in patients with severe hepatic impairment, but no dose reduction is required in renal insufficiency. Argatroban should be initiated as an IV infusion of 2mcg/kg/min and titrated to an aPTT goal of 60–80 seconds (see Table VI). The half-life of argatroban is intermediate among the DTIs (39–51 minutes), and effects on the aPTT typically persist for 2–8 hours following discontinuation.²⁵ A major disadvantage of argatroban is that it falsely elevates the INR. INR prolongation secondary to argatroban is not associated with the same bleeding risk as warfarin therapy. However, it can be difficult to accurately assess the INR in patients who

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Two different strategies for monitoring INR have been recommended for patients transitioning between argatroban and warfarin.

Bivalirudin does not significantly affect the INR and can be used in patients with both renal and hepatic insufficiency.

Table VII:
Bivalirudin Dosing for HIT²⁹

Initial dose	0.15 mg/kg/hr
Clcr <60	↓ by 20%
Clcr <30	↓ by 60%
Clcr <10	↓ by 90%

Fondaparinux (Arixtra^R) is a subcutaneous anticoagulant that selectively inhibits factor Xa and does not cross-react with HIT antibodies *in vitro*. There is currently minimal data for efficacy in HIT, but it may represent a safe alternative for completing HIT therapy in the outpatient setting.

must be bridged to warfarin.¹ In order to determine the actual INR in patients receiving argatroban, the INR should be rechecked after the infusion has been stopped for 4–6 hours. Alternatively, a therapeutic INR of 2–3 on warfarin alone can be roughly equated to an INR >4 on concurrent argatroban therapy. Using this method, argatroban can be discontinued once an INR >4 is achieved for at least 2 days while on warfarin.²⁶

Bivalirudin (Angiomax^R)

Bivalirudin is the only direct thrombin inhibitor that does not carry FDA approval for the treatment of HIT. Its FDA approved use is limited to PCI in patients with unstable angina. Evidence supporting a role for the use of bivalirudin in HIT is based on the promising preliminary data from one retrospective trial.²⁷ Fifty-two patients with HIT based on clinical suspicion (thrombocytopenia and/or thrombosis) received bivalirudin infusions adjusted to a target aPTT of 1.5–2.5X baseline. Eighty-three percent of patients had confirmed HIT antibodies and 42% had baseline thrombosis. Bivalirudin was continued for an average of 8 days with platelet counts on average recovering by day 3. No cases of major bleeding, amputation, or death were reported and 85% of patients were successfully transitioned to warfarin therapy. Further analysis of these preliminary findings is pending full publication of the trial results.

Bivalirudin offers several theoretical advantages over other available DTIs. The drug exhibits a shorter half-life of 25–35 minutes, which may be desirable in this class of agents without an effective antidote. Bivalirudin has been associated with a lower bleeding risk than lepirudin; however, the two agents have not been compared directly in a head-to-head trial. Additionally, although the half-life increases in renal failure, 80% of drug elimination occurs via non-renal mechanisms.¹³ Therefore, bivalirudin appears to be attractive for use in patients with both hepatic and renal insufficiency. At UW Medicine, monitoring of bivalirudin therapy should target an aPTT of 60–80 seconds. An initial bolus dose is not required and an IV infusion of 0.15mg/kg/h can be used as a starting dose (see Table VII). Coagulation parameters return to baseline 60 minutes following discontinuation.²⁸ Unlike lepirudin, formation of antibodies secondary to bivalirudin therapy has not been observed.⁴ In addition, bivalirudin has only a minor effect on PT/INR, thereby facilitating the transition to warfarin therapy.

Duration of Treatment

Unless negative laboratory tests are confirmed, patients diagnosed with HIT should receive alternative anticoagulation for at least 30 days.¹⁰ Studies in patients without baseline thrombosis suggest that alternative anticoagulation with DTIs significantly reduces the incidence of new thrombosis.^{17, 23, 24} DTIs are therefore recommended for treating isolated HIT until thrombocytopenia has resolved. Patients who develop thrombotic complications associated with HIT should receive 3–6 months of anticoagulation for secondary prophylaxis.³⁰ Immediate anticoagulation with warfarin is not recommended

in patients with acute HIT. Due to the rapid depletion of protein C, warfarin may actually increase the risk of microvascular thrombosis and cause skin necrosis or limb gangrene.² Warfarin monotherapy should therefore be avoided until thrombocytopenia has resolved with platelet counts greater than 100–150 x 10⁹/L.² Direct thrombin inhibitors remain the most efficacious option for initial anticoagulation and are recommended as a bridge to warfarin therapy.⁷ DTIs and low doses of warfarin, typically no greater than 5mg/day, should

Table VIII: Cost of Therapy at UW Medicine

Agent	Dose	Average cost per day*
Argatroban	2 mcg/kg/min	\$523
Bivalirudin	0.15 mg/kg/hr	\$334
Heparin	15 - 18 units/kg/hr	\$3
Lepirudin	0.15 mg/kg/hr	\$738

*Based on dosing for a 70 kg patient with normal renal function.

When HIT is suspected or diagnosed, initiation of alternative anticoagulation with direct thrombin inhibitors remains essential for reducing the risk of thrombosis, amputation, and death.

Patients diagnosed with HIT should receive anticoagulation with DTIs followed by warfarin for at least 30 days.

Patients who develop thrombotic complications associated with HIT (HITTS) should receive 3–6 months of anticoagulation for secondary prophylaxis.

be overlapped for at least 5 days.² DTIs may be discontinued once the INR is >2.0 for at least two consecutive days.²

Conclusion

When HIT is suspected or diagnosed, initiation of alternative anticoagulation with direct thrombin inhibitors remains essential for reducing the risk of thrombosis, amputation, and death. Although the efficacy of DTIs has not been directly compared in clinical trials, considering the pharmacologic properties of each agent can guide the choice of therapy. Lepirudin and argatroban are currently the only FDA-approved agents for the treatment of HIT, but their use is limited in more complex patient populations. Lepirudin can be utilized in patients with hepatic impairment; however, careful dose titration is necessary with renal insufficiency. The formation of anti-lepirudin antibodies can also render therapy less effective. Argatroban offers the benefit of a shorter half-life, which may allow for faster resolution of untoward bleeding events. However, the elevation in INR associated with argatroban use makes it difficult to bridge patients to warfarin therapy. Finally, bivalirudin represents a promising alternative to lepirudin and argatroban in the treatment of HIT. Bivalirudin possesses the shortest half-life of any of the DTIs and its clearance is less dependent on renal function. In addition, bivalirudin is less costly than other DTIs at UW Medicine (see Table VIII). Based on its pharmacologic characteristics and the existing clinical data, bivalirudin offers an attractive safety profile and is emerging as a cost-effective treatment option for HIT.

References available on request or at <http://uw.pnrx.org/therapyTopics.asp>

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