

**Proactive Prophylaxis: Multidisciplinary Prevention of Pulmonary Embolism and  
Deep Vein Thrombosis  
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**Direct Thrombin Inhibitors  
John Fanikos, RPh, MBA**

Arterial and venous thrombi are major causes of morbidity and mortality. While arterial thrombi are largely composed of platelet aggregates that are held together by small amounts fibrin, venous thrombi consist mainly of fibrin and red blood cells. Spontaneous or mechanical rupture of atherosclerotic plaque initiates arterial thrombosis by exposing thrombogenic material in the lipid rich plaque core to blood flow. Venous thrombosis occurs when excessive activation of coagulation overpowers the body's natural protective mechanisms and includes vessel wall damage, blood stasis or thrombophilic abnormalities.

Once the initiation of coagulation is triggered, a series of enzymatic produces thrombosis. The key step in this process is the activation of Factor X which converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin monomer. Fibrin monomers polymerize generating a fibrin mesh that is further stabilized through cross linking facilitated by Factor XIII. Thrombin further accelerates its own formation by stimulating platelet activation and aggregation and promoting activation of Factors V, VIII, and IX (1-2).

Heparin, low molecular weight heparins, and pentasaccharide exert their anticoagulant activity indirectly by binding to and activating antithrombin. Antithrombin naturally inhibits thrombin and other clotting factors, but through heparin binding the rate of inhibition is accelerated approximately 1,000 fold (3-4). A greater understanding of the thrombus formation coupled with limitations of existing oral and parenteral anticoagulants have prompted the search for novel agents.

The development of agents that bind directly to thrombin and block its interactions occurred in the 1990s. Direct thrombin inhibitors (DTIs) have properties that given them advantages over the indirect agents. DTIs do not bind to plasma proteins and therefore produce a more predictable anticoagulant response. Unlike heparin products they do not bind to platelet factor-4 and produce thrombocytopenia. Finally, DTIs inactivate both fibrin bound thrombin and circulating thrombin (5). Four parenteral DTIs are FDA approved for limited indications.

There are three binding sites on the thrombin molecule, a catalytic site and two exosites. Bivalent DTIs (bivalirudin, desirudin and lepirudin) block thrombin at the catalytic site and exosite 1. Univalent DTIs (argatroban, melagatran and dabigatran) bind to the catalytic site. Melagatran, dabigatran and lepirudin are primarily eliminated via renal clearance. Bivalirudin is only partially excreted by the kidney. All of these agents require dose adjustments with severe renal impairment. Argatroban is predominantly cleared through hepatic metabolism and dose adjustments are required in patients with hepatic dysfunction (6).

Lepirudin and argatroban are approved for the treatment of patients with heparin induced thrombocytopenia (HIT). Both bivalirudin and argatroban are approved as an alternative to heparin in patients undergoing percutaneous coronary interventions. Desirudin, pending U.S. launch in 2006, is approved for VTE prevention in elective hip replacement surgery. While oral DTIs offer a promising option to existing oral and injectable anticoagulants, none are available in the U.S.

Because of the high morbidity and mortality in patients with HIT and associated thrombosis, the pivotal clinical trials for both lepirudin and argatroban were historically controlled for ethical reasons. In the HAT-1 study the safety and efficacy of lepirudin was prospectively evaluated in 82 patients with confirmed HIT. Patients were treated with 4 different doses of lepirudin based on the presence of HIT with: thrombosis, thrombosis with thrombolytic therapy, no thrombosis, and the need for cardiopulmonary bypass surgery. All patients were evaluated for increases in platelet count. A subset of patients who met predefined inclusion criteria were matched to a historical control group for the combined endpoint of death, amputation, new thromboembolic complications, and incidence of bleeding. Lepirudin treated patients experienced platelet recovery, similar bleeding rates, and the incidence of the combined endpoint was significantly reduced when compared to historical controls (7).

In HAT-2, 122 patients with confirmed HIT were prospectively evaluated. Lepirudin was initiated for treatment of thrombosis alone, in conjunction with thrombolysis, and for prophylaxis. Fewer lepirudin treated patients experienced greater than 1 endpoint (death, limb amputation or recurrent thromboembolic) than historical controls, with a relative risk reduction of 29% at 35 days (8). Bleeding events, however, were more frequent in lepirudin than controls ( $p=0.0001$ ).

Argatroban studies similarly reflect “real-life” HIT treatment practices. Patients could be enrolled without thrombocytopenia or laboratory confirmation of HIT. In the ARG-911 study, 160 patients with thrombocytopenia and 144 patients with thrombocytopenia and thrombosis (HITT) were treated with argatroban (9). Mean therapy lasted 6 days and clinical outcomes were compared to historical controls over 37 days. The incidence of the composite endpoint of death, amputation, or new thrombosis was reduced in the argatroban HIT group (25.6% vs 38.8%,  $p=0.014$ ) and the HITT (43.8% vs 56.5%,  $p=0.13$ ). ARG-915 was a prospective study of 189 HIT and 229 HITT patients treated with argatroban for 5-7 days (10). The incidence of the composite endpoint of death, amputation, or new thrombosis was compared historical controls. In the HIT patients, the composite endpoint was reduced (28.0 vs 38.8,  $p=0.04$ ). In the HITT arm, the composite endpoint was reduced (41.5% vs 56.5%,  $p=0.07$ ). In both studies, platelet count recovered more quickly in argatroban treated patients and bleed events were similar to historical controls.

Argatroban has been used successfully in HIT and HITT patients requiring percutaneous coronary intervention (PCI) (11). In a multicenter, opened label trial, 91 patients underwent 112 interventions including angioplasty, stent placement, and atherectomy. All patients received aspirin prior to the procedure. Argatroban was initiated with a loading dose of 350 mcg/kg and an infusion of 25 mcg/kg/minute to achieve an activated clotting time of 300-450 seconds. Procedural success, defined as lack of death, emergent coronary bypass surgery, or Q-wave infarction, was reported in

98.1% of argatroban treated patients compared to 94.3% heparin treated historical controls. Concurrent argatroban and warfarin administration causes in an International Normalized Ratio (INR) prolongation beyond that produced by warfarin alone. INR should be measured daily during co-administration. In patients treated with argatroban up to 2 mcg/kg/min, discontinue the argatroban when the INR is greater than 4, and repeat the INR measurement in 4 to 6 hours. For patients receiving doses greater than 2 mcg/kg/min, the relationship becomes less predictable. In these patients, reduce the argatroban dose to 2mcg/kg/minute and repeat the INR 4 to 6 hours after the dose reduction. When the INR is greater than 4, discontinue the argatroban, and repeat the INR measurement in 4-6 hours (11).

DTIs have been used in clinical trials for treatment of acute coronary syndromes (ACS). The REPLACE-2 trial compared bivalirudin with provisional glycoprotein IIb/IIIa (GPIIb/IIIa) to heparin and planned GPIIb/IIIa blockade in PCI. In this controversial study, the primary endpoint was a composite of the 30 day incidence of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding. The secondary endpoint was a composite of the 30 day incidence of death, myocardial infarction, urgent repeat revascularization. Provisional GPIIb/IIIa was used in only 7.2% of bivalirudin treated patients. The primary endpoint occurred in 9.2% of the bivalirudin patients vs 10.0% of the heparin plus GPIIb/IIIa patients. The secondary composite endpoint occurred in 7.6% of patients in the bivalirudin group vs 7.1% of patients in the heparin plus GPIIb/IIIa group. The authors concluded that bivalirudin plus provisional GPIIb/IIIa blockade was not inferior to heparin plus planned GPIIb/IIIa use in PCI, but is associated with less bleeding (12).

In long term management of coronary artery disease, atrial fibrillation, VTE treatment, and VTE prevention, injectable melagatran and its prodrug oral ximelagatran looked extremely promising. In September 2004, an FDA advisory panel voted that the sponsor failed to demonstrate a favorable risk to benefit ratio, primarily due to safety concerns with liver function. The oral DTI agent, Dabigatran, has been evaluated in Phase II dose ranging studies for VTE prevention in orthopedic surgery. Early results suggest an efficacy and safety profile similar to the LMWHs (5). Several DTI studies are ongoing evaluating their efficacy in infant and pediatric populations, and in the setting of CABG surgery.

In summary, DTIs are firmly established for the treatment of HIT and HITT and offer alternatives to heparin in the setting of PCI. The role of new oral DTIs offer advantages over currently available anticoagulants. Whether they can be safely administered in general patient populations will be determined in future clinical trials.

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