

BLOOD BULLETIN

SEPTEMBER 2013

PROVIDED BY YOUR INDEPENDENT,
NONPROFIT COMMUNITY BLOOD CENTER
in conjunction with America's Blood Centers[®]



Overview of Direct Thrombin Inhibitors: With an Emphasis on Monitoring and Urgent Reversal Strategies

By Chris Gresens, MD, BloodSource, and the Scientific Publications Committee, America's Blood Centers

For many decades, the heparins and vitamin K antagonists (VKAs, e.g., warfarin) have served as the primary pharmacologic means for preventing thromboembolism in at-risk patients. However, the use of drugs within these two traditional anticoagulant classes is being partially superseded by medications that possess more specific mechanisms of action. One of the most important classes of these new drugs is known as the direct thrombin inhibitors (DTIs).

DTIs bind reversibly and directly to one or two domains on the thrombin molecule. Thus, they interfere with thrombin's two primary roles: (1) to generate fibrin clots and (2) to activate platelets. These new agents offer similar, and in some cases better, efficacy than other antithrombotic drugs. Moreover, they are associated with comparable-to-reduced hemorrhage risk, fewer food and drug interactions, and no need for therapeutic monitoring in most situations.¹

The first four DTIs to be approved by the Food and Drug Administration – argatroban, bivalirudin, desirudin, and lepirudin (note: lepirudin was removed from the US market in 2012) – are administered intravenously (IV) and/or subcutaneously (SC) and possess relatively short half-lives ($t_{1/2}$). The use of these parenteral drugs is limited to relatively few indications involving hospitalized patients.^{1,2} Therefore, while they have played a meaningful role in improving anticoagulation safety, their overall scope of use has remained restricted compared to that of the orally administered VKAs. In 2010, however, this changed when dabigatran was approved by FDA as the first oral DTI.

Key Details About Each of the DTIs.
DABIGATRAN (PRADAXA[®]) – This oral DTI was approved by FDA in 2010 for reducing the risk of stroke and systemic embolism in patients with non-valvular

Key Points

- Unlike the heparins and VKAs:
 - DTIs achieve their antithrombotic effect by binding thrombin directly and specifically; and
 - A patient's renal status should be considered when selecting DTIs.
- The use of DTIs is increasingly being applied to indications previously treated exclusively by the heparins and VKAs.
- Three of the four DTIs currently available in North America are administered parenterally, whereas the fourth (dabigatran) is given orally.
- Monitoring options, when needed, are varied.
- None of the DTIs have well-defined antidotes, making their rapid reversal (i.e., in the event of bleeding or impending surgery) problematic.

atrial fibrillation (A-fib). The authors of the RE-LY study found that dabigatran, when “administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.”³ Unlike the VKAs, however, for which vitamin K and 4-factor prothrombin complex concentrates (PCCs) serve as effective reversal agents, no well-defined antidote for bleeding associated with dabigatran (or other DTIs) currently exists.⁴ Dabigatran has a plasma $t_{1/2}$ of approximately 12-14 hours and is cleared by both the kidneys (80%) and liver (20%).¹ A key advantage of this drug is that monitoring is typically not needed other

than during active bleeding. In such instances, testing options include the activated partial thromboplastin time (aPTT), Ecarin clotting time (ECT), and thrombin time (TT). As noted above, the most effective means for urgent reversal have not been well delineated, though differing experts have suggested the use of hemodialysis, diuresis, activated charcoal (if given soon after drug ingestion), 4-factor PCCs, recombinant factor VIIa (rFVIIa), and/or plasma transfusions.^{1,4-7}

ARGATROBAN (ARGATROBAN) – This IV drug was initially approved by FDA in 2000 for the prophylaxis or treatment of thromboses in patients with heparin-induced thrombocytopenia (HIT). In 2002, FDA expanded its approval to include patients undergoing percutaneous coronary intervention (PCI), who are experiencing or at risk for HIT. Its plasma $t_{1/2}$ is approximately 45 minutes and it is cleared via the liver.¹ Monitoring options include the aPTT (the first choice for guiding dosage adjustments) and activated clotting time (ACT) tests.^{1,2} No specific antidotes exist, though rFVIIa, hemodialysis, and/or hemoperfusion have been used. Currently, discontinuation of the drug plus the application of locally directed hemostasis serve as the primary “counter-agent” until drug concentrations fall to sufficiently low levels for spontaneous bleeding to resolve.^{1,2}

BIVALIRUDIN (ANGIOMAX[®]) – This IV drug, approved by FDA in 2000, is indicated for patients: (1) with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA); (2) undergoing PCI with provisional use of glycoprotein IIb/IIIa inhibitor; and (3) with, or at risk of, HIT, undergoing PCI. It should be used in conjunction with low-dose aspirin. Its plasma $t_{1/2}$ is approximately 25 minutes and it is cleared primarily via the liver.¹ Monitoring options include the ACT (the first choice as an indicator for when to make dosing adjustments), aPTT, and ECT tests.^{1,2} See “Argatroban” for discussion on drug reversal.

DESIRUDIN (IPRIVASK[®]) – This IV/SC drug was approved by FDA in 2003 for prevention of deep venous thromboses (DVTs) in patients undergoing elective hip replacement surgery. Its plasma $t_{1/2}$ is approximately 60 minutes when given IV (vs. 120 minutes when given SC), and it is cleared via the kidneys.¹ Generally, no monitoring is necessary, except in the event of severe kidney failure and/or during significant bleeding episodes. In these situations, the aPTT is believed to be the best option.^{1,2} See “Argatroban” for discussion on drug reversal (though hemodialysis and hemoperfusion do not apply for this DTI). Also, keep in mind that the relatively short plasma $t_{1/2}$ can be prolonged considerably in the presence of renal failure.¹

Direct Thrombin Inhibitor Comparisons			
Drug			
Dabigatran (Pradaxa [®])	Argatroban (Argatroban [®])	Bivalirudin (Angiomax [®])	Desirudin (Iprivask [®])
Half Life			
12-14 hrs	45 min.	25 min.	60 min. (IV) 120 min. (SC)
Metabolism			
Kidneys (80%); liver (20%)	Liver	Liver	Kidneys
Indications			
● Non-valvular A-fib: Reduce stroke and systemic embolism risk	● HIT: Prophylaxis and treatment, including patients undergoing PCI	● PCTA with unstable angina ● PCI with glycoprotein IIb/IIIa inhibitor ● HIT.	● DVT prophylaxis for elective hip replacement

References

- Lee CJ and Ansell JE. Direct thrombin inhibitors. *BJCP*. 2011; 72:581-92.
- Garcia DA et al. Parenteral anticoagulants. *Chest*. 2012; 141 (suppl): e24S-43S
- Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. *NEJM*. 2009;361:1139-51.
- Bracey A et al. How do we manage patients treated with antithrombotic therapy in the perioperative interval? *Transfusion*. 2011;51:2166-77
- Cushman M et al. 2011 clinical practice guide on anticoagulant dosing and management of anticoagulation-associated bleeding complications in adults. American Society of Hematology. Accessed via ASH website [www.hematology.org/practiceguidelines] on July 16, 2013.
- Kaatz S et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol* 2012; 87:S141-45.
- Van Ryn J et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103:1116-27.



Blood Bulletin is issued periodically by America's Blood Centers. Publication Committee Chair: Julie Cruz, MD. The opinions expressed herein are opinions only and should not be construed as recommendations or standards of ABC, ABC SMT Committee, or its board of trustees. Publication Office: 725 15th St., NW, Suite 700, Washington, DC 20005. Tel: (202) 393-5725; Fax: (202) 393-1282; E-mail: abc@americasblood.org. Copyright America's Blood Centers, 2013. Reproduction is forbidden unless permission is granted by the publisher. (ABC members need not obtain prior permission if proper credit is given.