

Monitoring Antithrombotic Therapy: Part 4



Monitoring Antithrombotic Therapy

- Part 1: Thrombolytics
- Part 1: Platelet Receptor Antagonists
- Part 1: Unfractionated Heparin
- Part 2: Aspirin and Clopidogrel
- Part 2: Coumarins
- Part 3: Low Molecular Weight Heparin
- Part 3: Pentasaccharide
- Part 4: Direct Thrombin Inhibitors
- Part 4: Laboratory Monitoring

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Direct Thrombin Inhibitors (DTIs)

Argatroban–Novostan[®]

Hirudin–Lepirudin[®]

Bivalirudin–Angiomax[®]

Dabigatran–Pradaxa[®]

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62 YO Male with AMI

- Aspirin
- Thrombolytics
- UFH 5 days
- Platelet counts:
 - Day 0: 353,000/uL
 - Day 1: 257,000/uL
 - Day 2: 240,000/uL
 - Day 3: 125,000/uL
- Day 3: Anti-heparin-PF4 antibodies by EIA



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Heparin-Induced Thrombocytopenia (HIT)

- 30-40% of bypass patients develop heparin-PF4 antibodies after 5 days of UFH
- 1-5% of all patients treated with UFH develop HIT with thrombosis after 5 days
- Antibody to heparin-PF4 complex binds platelet Fc receptors, activates platelets



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Direct Thrombin Inhibitors (DTIs)

- Indicated for HIT
- Do not generate or bind anti-heparin-PF4
 - Platelet counts recover within three days
- Rapidly reduce thrombin production in HIT
 - Warfarin too slow
 - LMWH may cross-react

- Kaplan KL, Francis CW. Direct thrombin inhibitors. *Semin Hematol* 2002;39: 187-96
- Prechel M, Walenga JM. The laboratory diagnosis and clinical management of patients with heparin-induced thrombocytopenia: an update. *Semin Thrombos Hemostas* 2008;34:86-96.

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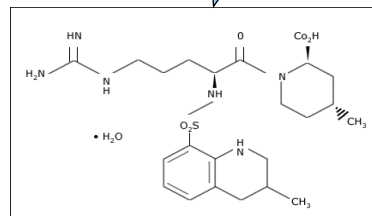
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Argatroban (Novastan[®])

- Raises nitric oxide, causing vasodilatation
- Metabolized and excreted by the liver



Arginine Derivative



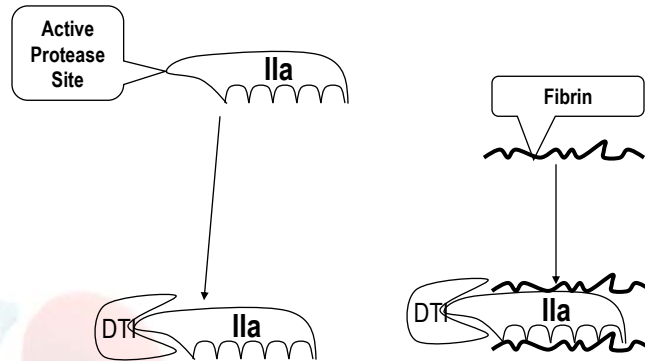
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Argatroban and Bivalirudin Inhibit Fibrin-Bound and Free Thrombin



Argatroban Administration and Monitoring

- IV: 2 $\mu\text{g}/\text{kg}/\text{m}$: immediate steady state
 - 5–7 d
 - Maintain PTT 1.5-3 x MRI
 - Linear to 40 $\mu\text{g}/\text{kg}/\text{m}$
 - Ecarin clotting time
 - Prolongs PT
 - Doubles INR when bridging to Coumadin
- During PCI
 - Bolus 350 $\mu\text{g}/\text{kg}$
 - Continuous infusion 15-40 $\mu\text{g}/\text{kg}/\text{m}$
 - Maintain ACT 300-450 seconds

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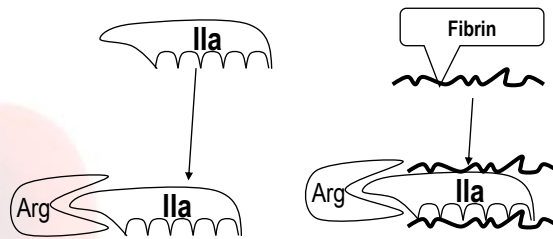
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Argatroban Comments

- Use in renal disease
- Liver disease
 - Reduce to 0.5 µg/kg/h and monitor with PTT
- Major bleeds 5.3%, minor 14.4%
- No antidote, but half-life is 40 minutes
- Inhibits free and fibrin-bound thrombin



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Hirudin: Lepirudin

- Inhibits free, not bound thrombin
- Metabolized and excreted by kidney
 - Monitor in kidney disease



7000 D, 65 aa polypeptide

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Structure of Lepirudin

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1      5
Leu-Phe-Tyr-Thr-Arg-Cys-Phe-Glu-Ser-
10     15
Gly-Glu-Asp-Leu-Cys-Leu-Cys-Glu-Gly-
20     25
Ser-Asp-Val-Cys-Gly-Gly-Gly-Phe-Lys-
30     35
Cys-His-Leu-Gly-Ser-Arg-Glu-Glu-Leu-
40     45
Asp-Glu-Cys-Val-Thr-Gly-Glu-Gly-Thr
48     53
Pro-Lys-Phe-Glu-Ser-His-Asn-Arg-Gly-
55     60
Asp-Phe-Glu-Glu-Ile-Phe-Glu-Glu-Tyr-
65
Leu-Gln
Disulfide Bonds: Cys1-Cys11
                  Cys21-Cys31
                  Cys41-Cys51
    
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Lepirudin Administration

- IV bolus: 0.4 mg/kg/h
- Infusion 0.1 to 0.15 mg/kg/h 11-14 d
- Steady state within 2.5 hours
- Maintain PTT at 1.5 to 3 x MRI
- ECT may be used to monitor
- Clearance half-life 20 minutes
- Bypass: 0.25 mg/kg/h
 - ACT > 350 s
 - ECT > 250 s



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Hirudin Comments

- 50% develop antibodies that prolong clearance and do not affect activity
 - Bleeding risk
- Nine cases of anaphylaxis with 5 deaths in repeat usage



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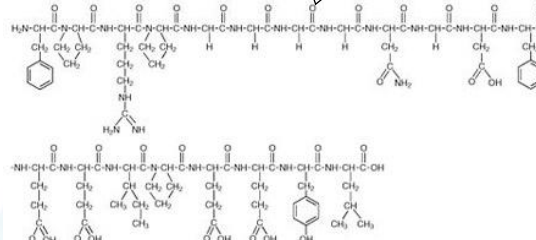
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Bivalirudin

- Thrombin active site-directed peptide, D-Phe-Pro-Arg-Pro, linked to an analogue of the carboxy-terminal of hirudin

2180 D, dodecapeptide



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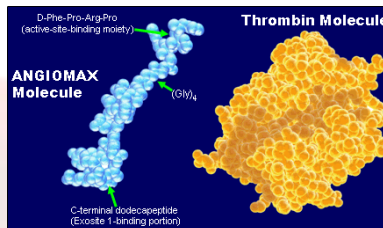


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Bivalirudin

- Neutralizes free and bound thrombin
- FDA-approved spring, 2008
 - Reduced major hemorrhage by 41% to 61%
 - Proven antithrombotic effect
 - Use with aspirin only
- Bolus 0.75 mg/kg plus 1.75 mg/kg/h
- Renal excretion, 25 m half-life



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Bivalirudin in Renal Disease

- If the creatinine clearance is less than 30 mL/minute, reduce infusion to 1 mg/kg/h
 - No reduction in bolus
- If a patient is on hemodialysis, reduce infusion to 0.25 mg/kg/h
- Monitor with PTT, ECT or ACT
 - Therapeutic range not defined

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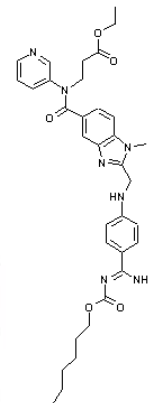
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Dabigatran (Pradaxa®)

- Oral DTI approved in Canada and Europe
 - Application to US FDA 2008
- Indication: post-surgical VTE prevention
- Dose 110 mg/d with wide safety range
 - Immediate steady state
 - No laboratory monitoring



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Limitations of the PTT

- Prolonged by warfarin therapy, LA, and congenital or acquired factor deficiency
 - PTT anticoagulant response is exaggerated
- Conversely, elevated factor VIII and fibrinogen shorten the PTT and underestimate anticoagulant; *in vitro* drug resistance
- No inter-laboratory normalization; a variety of reagent and instrument combinations generate diverse responses

• Adcock D. In "The Fritsma Factor," www.fritsmafactor.com. Accessed 7-27-08

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Ecarin Clotting Time (ECT)

- Thrombin-like venom from *Echinus carinatus*
 - Cleaves prothrombin to produce intermediate activation product meizothrombin, which stimulates fibrin polymerization
- ECT is reliably linear to DTI plasma concentration, even at prophylactic doses
- ECT is unaffected by heparin or warfarin and cannot be used to monitor these
 - Insensitive to low molecular weight heparin (LMWH), Fondaparinux, and direct Xa inhibitors Rivaroxaban and Apixaban

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Ecarin Clotting Time (ECT)

- ECT may be used to monitor DTIs while patients are starting warfarin therapy
- ECT is not sensitive to the presence of lupus anticoagulants
- Current ECT reagents are poorly standardized with lot-to-lot variability, and no international calibrators are available.
- Few North American reference laboratories and no clinical providers offer the ECT assay.

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Chromogenic Anti-Xa Assay

- Rely on either patient or reagent antithrombin and produce a colorimetric result inversely proportional to heparin plasma concentration
- The anti-Xa has been applied successfully to UFH, LMWH and fondaparinux
- Anti-Xa has been enhanced so that UFH and LMWH may be monitored on a single “hybrid” curve
- Anti-Xa could potentially be modified to assay Rivaroxaban and Apixaban

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Thrombin Generation Time

- We wish there were a universal antithrombotic assay with a common standard. The recently reborn thrombin generation time assay (TGT, TGA) may be developed to meet these requirements
- TGT is automatable, clot-based assay and lends itself to numerous modifications designed to detect a variety of anticoagulant effects and coagulopathies.
- TGT development will require a number of careful reagent standardizations and formulations

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Monitoring new Oral Anticoagulants

Clinical trial data for investigational antithrombotics provide little information on therapeutic ranges. This may be by design, as developers prefer to emphasize there is little need for laboratory monitoring. Experience with LMWH and fondaparinux however, teaches that laboratory monitoring becomes necessary under a variety of clinical circumstances.

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Monitoring new Oral Anticoagulants

Laboratory scientists may scramble to develop monitoring protocols that empirically determine therapeutic ranges. Perhaps there could be a concerted effort uniting laboratory scientists and pharmaceutical distributors towards the common goal of good anticoagulant monitoring for current and developmental drugs.

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Questions or Comments

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- Please select the CACMLE link to take a quiz and record CE credit
- Thank you for listening to Monitoring Antithrombotic Therapy



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