Monitoring Antithrombotic Therapy

Monitoring Antithrombotic Therapy

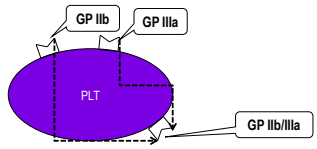
- Platelet Receptor Antagonists
- Standard Unfractionated Heparin
- Aspirin and Clopidogrel
- Pentasaccharide
- Rivaroxaban
- Direct Thrombin Inhibitors

64 YO Male
Acute Myocardial Infection

- Crushing substernal pain
- 325 mg ASA PO at home to disable platelets
- Transported to cardiac catherization lab within 90 minutes for percutaneous intervention (PCI, angioplasty and stent)
  - If >3 h, start thrombolytic therapy
    - Tissue plasminogen activator (TPA, Alteplase)

Platelet Membrane Glycoprotein IIb/IIIa Inhibitor (GPI)

- GP IIb/IIIa is a membrane receptor
- Abciximab (ReoPro®) anti-IIb/IIIa antibody
  - 0.25 mg/kg/1 minute, then 0.125 ug/kg/m to 10 ug/m max
- May cause thrombocytopenia

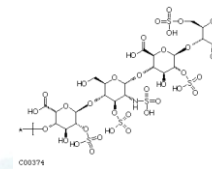


van Werkum JW, Harmsze AM, Elsenberg EH, et al. The use of the VerifyNow system to monitor antiplatelet therapy: a review of the current evidence. Platelets 2008;19: 479-88.

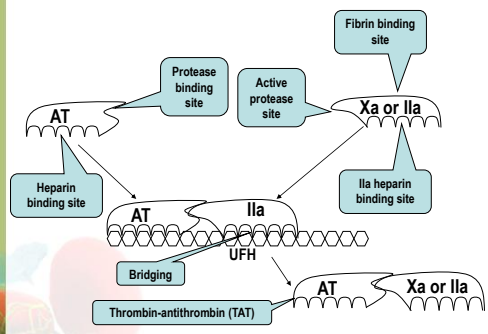
Coons JC, Barcelona RA, Freedy T, Hagerty MF. Eptifibatide-associated acute, profound thrombocytopenia. Ann Pharmacother 2005;39:368-72.

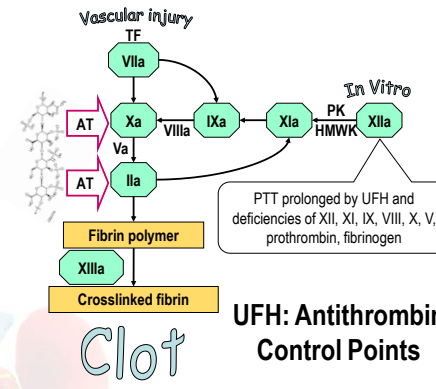
Coronary Bypass Graft Unfractionated Heparin (UFH)

- UFH bolus: 5000–10,000 IUs
- Maintenance dosage: 1600 IUs/hour



Unfractionated Heparin Binds Antithrombin With Xa &Thrombin





UFH: Antithrombin Control Points

Monitoring Antithrombotic Therapy

Monitoring UFH Therapy Standard Schedule

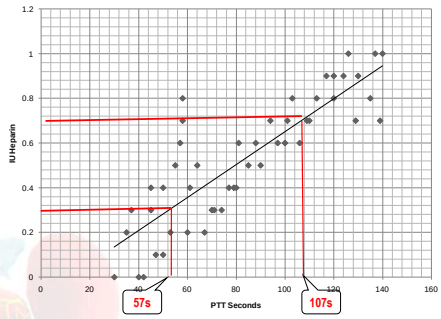
- Perform “baseline” PTT to r/o factor deficiency, inhibitors, lupus anticoagulant
- Start therapy
- 4–6 h after start, perform second PTT
- Adjust dose to maintain PTT therapeutic range
  - *Never use* 1.5–2.5 x mean of normal range
  - Use laboratory-published range
    - Laboratory generates range using Brill-Edwards *ex vivo* curve

Establishing The *Ex Vivo* PTT Heparin Therapeutic Range

- Collect at least 50 patient specimens
  - All UFH dosage ranges
  - No oral anticoagulant (Warfarin), PT normal
- Collect at least 20 normals
  - Representative demographics, 10♂, 10♀
- Perform PTT & chromogenic anti-Xa heparin assay
- Prepare graph of paired results
- Correlate PTT range to the anti-Xa range
  - Therapeutic: 0.3-0.7 heparin anti-Xa units
  - Prophylactic: 0.2-0.4 heparin anti-Xa units

Brill-Edwards P, et al. Establishing a therapeutic range for heparin therapy. Ann Intern Med 1993;119: 104-9.

Brill-Edwards Curve Therapeutic Range



PTT Limitations

- Falsely prolonged by coagulopathy, lupus anticoagulant, or inhibitor (anti-FVIII)
  - Unreliable for heparin assay
- Insensitive (resistant) to heparin when…
  - Reduced antithrombin
  - Elevated FVIII (acute phase reactant)
- Substitute chromogenic anti-Xa heparin assay: should have used it anyway!

Eikelboom, JW, Hirsh J. Monitoring unfractionated heparin with the APTT; time for a fresh look. Thromb Haemost 2006; 96: 547–52.

64-YO Male Discharge Day 4

- Clopidogrel, Plavix®
  - 300–600 mg bolus, 75 mg once daily 1-2 years
- Aspirin 81 mg/day: lifelong

Monitor for Variable Dosage Effect

- Platelet aggregometry
- Whole blood Accumetrics VerifyNow®
- Whole Blood Siemens PFA-100®
- Random Urine AspirinWorks®
  - 11-dehydrothromboxane B_2 (UDHT) immunoassay

Monitoring Antithrombotic Therapy

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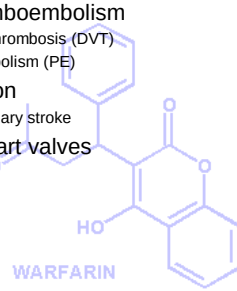
Warfarin (Coumadin) Indications

- Cardiac insufficiency
- Venous thromboembolism
  - Deep venous thrombosis (DVT)
  - Pulmonary embolism (PE)
- Atrial fibrillation
  - Prevent secondary stroke
- Prosthetic heart valves
  - St. Jude valve



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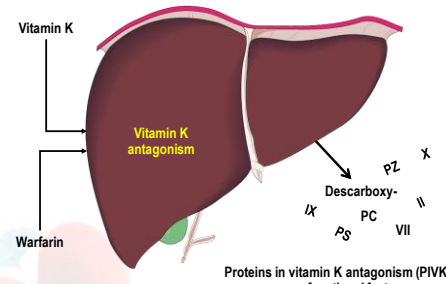
Warfarin Products: PIVKA



Proteins in vitamin K antagonism (PIVKA): non-functional factors

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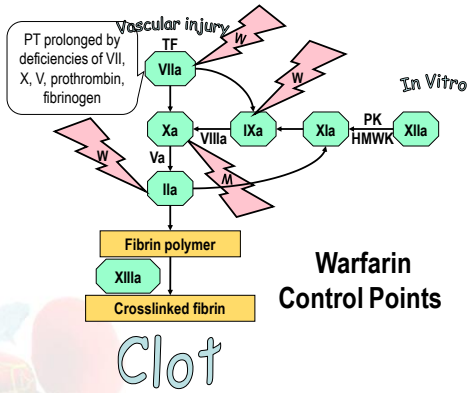

Warfarin Control Points

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Warfarin Dose & Pharmacodynamics

- Start at 5 mg/d, adjust PT to international normalized ratio (INR) 2.0 to 3.0
- When >70, start at 2 mg/d
- Onset of action 8–12 hours
- Requires 4–5 days to achieve stability
- Daily INRs until two match in Rx range
- Observe two INRs/week for first two weeks
  - Confirm stability
- Then every four weeks for duration

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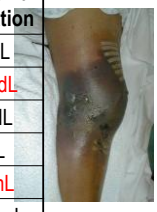
Risk of Thrombosis First Five Days of Therapy

Factor	Half-life	Mean Plasma Concentration
Prothrombin	60 h	10 mg/dL
VII	6 h	0.05 mg/dL
IX	24 h	0.3 mg/dL
X	50 h	1 mg/dL
Protein C	8 h	2-6 μg/mL
Protein S		20-25 μg/mL



Fritsma GA. Monitoring Anticoagulant Therapy. In Rodak B., Fritsma G, Doig K. Hematology: Clinical Principles and Applications 3nd Ed 2007 Elsevier

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Warfarin Dosage Anomalies

- Warfarin sensitivity
  - Cytochrome: CYP2C9*2 and CYP2C9*3
  - Vitamin K epoxy reductase: VKORC1
  - Screen and start with 2 mg/d
- Warfarin receptor insufficiency
  - Hereditary warfarin resistance
  - Require dosages of 25 mg/d or more
  - CYP4F2 variant raises dosage 1 mg/d
  - Five more reported

Caldwell MD, Awad T, Johnson JA. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111: 4106-12.
International Warfarin Pharmacogenetics Consortium: Estimation of the warfarin dose with clinical and pharmacogenetic data. NEJM 2009; 60:753-64.

Monitoring Antithrombotic Therapy

Warfarin Limitations

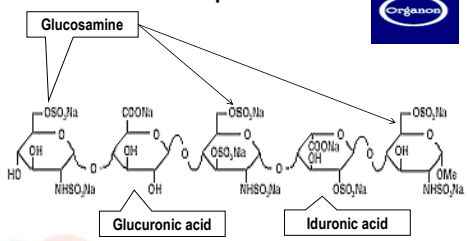
- These provide vitamin K and reduce Warfarin efficacy:
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba, parenteral nutrition formulations
- Over 80 drugs unpredictably influence CYP2C9 cytochrome oxidase pathway
- Warfarin allergy with anaphylaxis

Warfarin Overdose

- Most common cause of ER hemorrhage
- 10 mg oral, IM, or IV vitamin K provides 6-hour reversal (overdose: thrombosis)
- Frozen plasma, prothrombin complex concentrate, NovoSeven® (VIIa) provide immediate reversal of hemorrhage

- Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: 204S-33S.
- Sugg RM, Gonzales NR, Matherne DE, et al. Myocardial injury in patients with intracerebral hemorrhage treated with recombinant factor VIIa. Neurology 2006;67:1053-5.

Synthetic Pentasaccharide, Fondaparinux

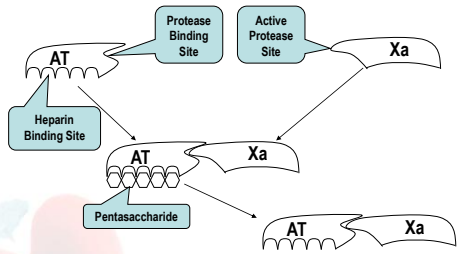


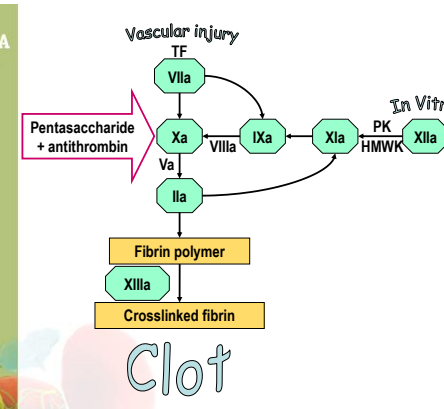
Turpie AGG. Pentasaccharides. Semin Hematol 2002; 39: 158-171

Pentasaccharide and Antithrombin

- Conformational change in AT increases affinity for Xa 300-fold
- Irreversible inhibition of Xa, no affinity for thrombin nor other serine proteases

Pentasaccharide Binds Xa to Antithrombin





Monitoring Antithrombotic Therapy

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Monitoring Pentasaccharides

- Chromogenic anti-Xa calibrated with pentasaccharide in mg/L
  - No international standard
  - Standards available from Beckman-Coulter and Aniara for their kit
- Injection of 2.5 mg
  - Peak plasma level at 3 h: 0.4-0.5 mg/L
  - Minimum steady state 0.14-0.19

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Pentasaccharide Advantages

- Efficacy
  - 50% reduction in venographic DVT compared to low molecular weight heparin (LMWH)
  - Repeat DVT 11 days after surgery 6.8%
    - Compared to 13.7% for LMWH ($p=10^{-17}$)
  - Fatal thrombotic events 1% at day 49, same as LMWH
- Half-life 17 h; single 2.5 mg SC/24 h

Turpie AGG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux Vs. Enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002; 162: 1833-1840

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Pentasaccharide Disadvantages

- Risk of major bleed 2.7%, LMWH 1.7%
- Overdose: no direct reversal, long half-life
- Cost exceeds LMWH by 50%
  - Offset by reduced adverse events

Heit JA. The potential role of fondaparinux as venous thromboembolism prophylaxis after total hip or knee replacement of hip fracture surgery. Arch Intern Med 2002; 162: 1806-1808

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Rivaroxaban

- Dose: 10 mg/d: steady state at 4 hours
- Neutralizes free and clot-bound Xa
  - Interacts with no other serine proteases
- Doubles PT at 230 nM, PTT at 690 nM and neutralizes Xa
- Excretion: 66% renal, 28% fecal
- No laboratory monitoring necessary and no therapeutic range is developed
- Chromogenic anti-Xa may be modified to measure Rivaroxaban dosage

Laux V, Perzborn E, Kubitza D, Misselwitz F. Preclinical and clinical characteristics of Rivaroxaban: A novel, oral, direct factor Xa inhibitor. Semin Thromb Hemost 2007;33:5115-23.

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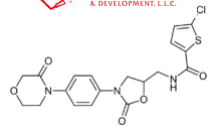
Rivaroxaban (Xarelto®)

- An oxazolininone derivative direct anti-Xa
- First of a family of oral anti-Xa drugs
- FDA study committee recommendation to approve 3/19/09
- US FDA asked J&J for more information May 28, 2009
- Approved in Europe

Bayer

Johnson & Johnson PHARMACEUTICAL RESEARCH & DEVELOPMENT, L.L.C.



Xarelto rivaroxaban

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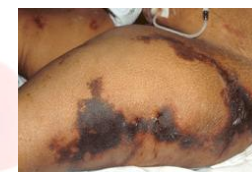
Heparin-Induced Thrombocytopenia (HIT)

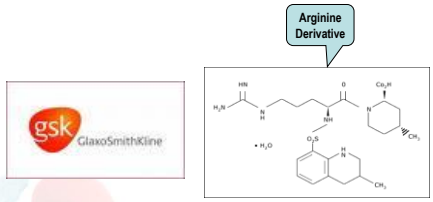
- 30–40% of bypass patients develop heparin-PF4 antibodies after 5 days of UFH
- 1–5% of all patients treated with UFH develop HIT with thrombosis after 5 days
- Antibody to heparin-PF4 complex binds platelet Fc receptors, activates platelets

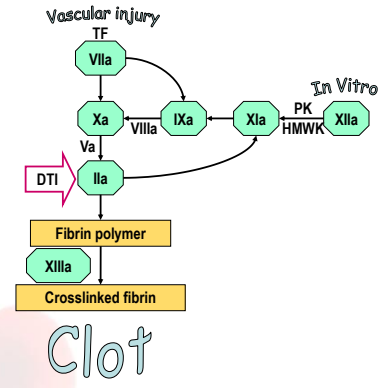


Monitoring Antithrombotic Therapy

Argatroban (Novastan®)

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



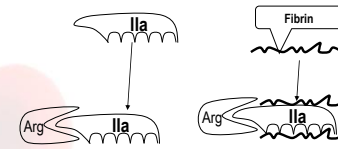


Argatroban Administration and Monitoring

- IV: 2 μg/kg/m: immediate steady state
  - Maintain PTT 1.5–3 x MRI
    - Linear to 40 μg/kg/m
  - Prolongs PT
    - Doubles INR when bridging to Warfarin
- During percutaneous intervention
  - Bolus 350 ug/kg
  - Continuous infusion 15–40 ug/kg/m
  - Maintain ACT 300–450 seconds

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



Dabigatran (Pradaxa®)

- Oral direct thrombin inhibitor 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