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Whatever Happened to the PT and PTT?

How to Monitor the New Antithrombotics

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The Fritsma Factor, Your interactive Hemostasis Resource
Sponsored by Precision BioLogic, Dartmouth, Nova Scotia
www.fritsmafactor.com

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Whatever Happened?

What's new in antithrombotics? Everything. We now monitor antiplatelet drugs aspirin, clopidogrel, and in 2009, prasugrel. What do we do about fondaparinux, the 2010 oral anticoagulant dabigatran and in 2011, rivaroxaban, apixiban, edoxaban, betrixaban, and tecarfarin? Meanwhile, we still don't know how to monitor direct thrombin inhibitors. Are ecarin time, thrombin time, chromogenic X and chromogenic anti-Xa the answer?

Objectives:

1. Current anticoagulants: warfarin, unfractionated heparin, low molecular weight heparin, fondaparinux
2. Antiplatelet antithrombotics: eptifibatide, abciximab, tirofiban, aspirin, clopidogrel, prasugrel
3. Current direct thrombin inhibitors argatroban, lepirudin, bivalirudin
4. The 2010–2011 anticoagulants dabigatran, rivaroxaban

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71 YO Female, Atrial Fibrillation 30 Years of 7.5 mg/day Warfarin

- Monday: INR 11, *no bleeding symptoms*
  - Target range 2–3
  - Hx: she noticed bruising, bleeding gums, epistaxis when INR > 5:
  - Had just started on statin therapy
    - Total cholesterol: 263 mg/dL
    - Triglycerides: 319 mg/dL
- Tuesday repeat: INR 11
  - Her PCP gave vitamin K 10 mg IV push, D/C warfarin
  - She contacted ASCLS consumer web forum

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What Happened?

- Dietary change, increased vitamin K?
- Do statins, other drugs interfere with metabolism?
  - Lovastatin and fluvastatin metabolized by CYP450
- Age-related change in warfarin sensitivity?
- Optical coagulometer, lipemia?

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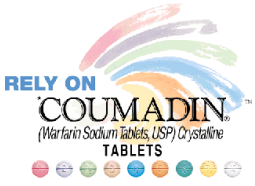
71 YO Female, Atrial Fibrillation 30 Years of 7.5 mg/day Warfarin

- Thursday: fasting INR 1.5
  - Lipemia or vitamin K?
  - Resumed warfarin 7.5 mg/day
- Following Monday: INR 2.5
  - No further follow-up



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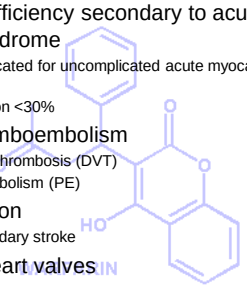
Warfarin Indications
4.2 Million Patients in North America

- Cardiac insufficiency secondary to acute coronary syndrome
  - No longer indicated for uncomplicated acute myocardial infarction
  - Ejection fraction <30%
- Venous thromboembolism
  - Deep venous thrombosis (DVT)
  - Pulmonary embolism (PE)
- Atrial fibrillation
  - Prevent secondary stroke
- Prosthetic heart valves



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Warfarin Dose & Pharmacodynamics

- Start 5 mg/d, adjust to PT-based international normalized ratio (INR) 2–3
  - When over 70 years of age, start at 2 mg/day
  - Screen for high risk polymorphisms CYP2C9*2 and *3 and VKORC1 to start at lower dosage
- Onset of action 8 to12 hours
- Requires 4 to 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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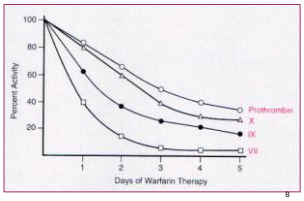
Is the PT/INR All it Could Be?

- Optical coagulometers affected by lipemia
- PT prolonged by lupus anticoagulant
- PT invalid in coagulopathies
- INR invalid during transition from direct thrombin inhibitors (argatroban) to warfarin
- INR invalid in first five days of therapy

Rosborough TK, Jacobsen JM, Shepherd MF. Relationship between chromogenic factor X and INR differs during early warfarin initiation compared with chronic warfarin administration. Blood Coagul Fibrinolysis 2009 20:433-5.



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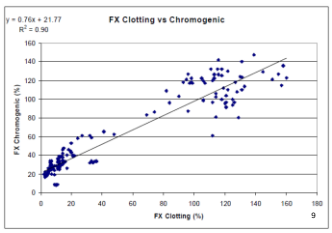
Chromogenic Factor X Assay

Factor X → (Russell viper venom + Ca^{++}) → Factor Xa

Xa digests colorless S-2765 N-a-Z-D-Arg-Gly-Arg-pNA → Releases yellow pNA, measure at 405 nm

diaPharma



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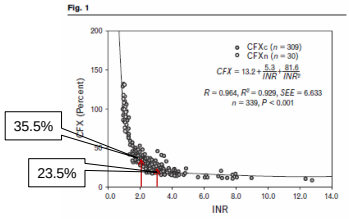
Chromogenic X In Place of PT?



A good model fit between INR and CFX when expressed as a second order inverse function ($n = 339$, $R^2 = 0.929$; $P < 0.001$). Open circles represent samples from normal control group (CFXn) and closed circles from patients receiving Coumadin therapy (CFXc). CFX, chromogenic factor X; INR, international normalized ratio.

McGlasson DL, Romick BG, Rubal BJ. Comparison of a chromogenic factor X assay with INR for monitoring oral anticoagulation therapy. Blood Coag Fibrinolys 2008;19:513–7.

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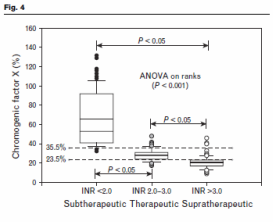
Chromogenic X in place of PT?



Box plots (median: solid line, mean: dotted line, whiskers: 10th and 90th percentile) for CFX values categorized by INR therapeutic ranges. Significant differences were noted between all groups. Dashed lines indicate the CFX range (23.5–35.5%) is equivalent to the INR therapeutic range (INR 2.0–3.0). ANOVA, analysis of variance; INR, international normalized ratio.

"The data suggest the CFX can be a useful tool for monitoring oral anticoagulation in patients in which INR confounders are present."

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Warfarin Limitations

- These supply 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

Dosage Anomalies

- Polymorphisms
  - CYP2C9*2 and CYP2C9*3
  - VKORC1
  - Increased warfarin sensitivity
  - 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 (Feb 08)

Caldwell MD, Awad T, Johnson JA. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111: 4106-12.

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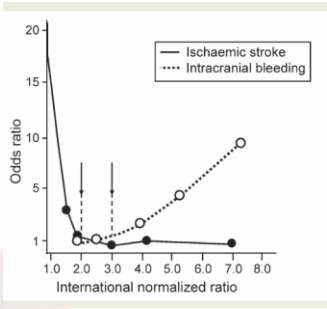
Warfarin Therapeutic Window



Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008;29:155–165

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Warfarin Overdose

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

- 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.

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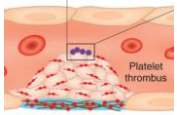
66 YO Male
Acute Myocardial Infection

- Crushing substernal pain upon retiring
- 325 mg ASA PO at home
  - Reduce platelet activation and white clot formation
- Transported to cardiac catherization lab within 90 minutes for percutaneous intervention (PCI, angioplasty and stent)
  - If >3 hours in transport, start thrombolytic therapy
    - Tissue plasminogen activator (TPA, Alteplase)



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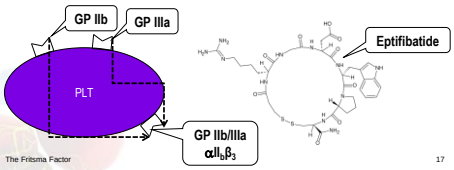
Platelet Membrane Glycoprotein IIb/IIIa Inhibitors (GPIs)

- GP IIb/IIIa is a membrane *arginine-glycine-aspartate* (RGD) sequence receptor
  - Binds fibrinogen and VWF; supports aggregation
- Eptifibatide (Integrilin®) RGD mimetic
  - Use with aspirin or clopidogrel (Plavix®) and heparin
  - IV loading dose of 180 mcg/kg over 1 to 2 minutes
  - Continuous infusion of 2 mcg/kg/m up to 72 h



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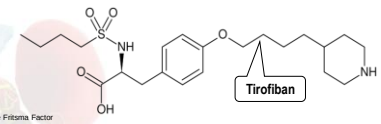
Two More Platelet Membrane GPIs

- Abciximab (ReoPro®) anti-IIb/IIIa antibody
  - 0.25 mcg/kg/1 min, then 0.125 mcg/kg/min to 10 mcg/min
  - Plasma half life 30 minutes
- Tirofiban (Aggrastat®) peptide inhibitor
  - Analogue of *Echinus carinatus* venom component
  - Use with aspirin or clopidogrel (Plavix®) and heparin
  - IV 0.4 mcg/kg/min for 30 minutes
  - Then 0.1 mcg/kg/min up to 48 hours



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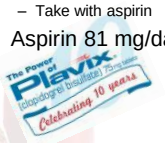
GPI Monitoring

- Weight-adjusted GPI dose without lab monitoring is ineffective
  - Poor platelet suppression risks thrombosis
  - Monitor with platelet aggregometry using thrombin receptor activation peptide (TRAP)
  - POC: Accumetrics Ultegra IIb/IIIa assay using TRAP:fibrinogen-coated microbead technology
  - POC (new): automated Multiplate analyzer from Diapharma
- Thrombocytopenia risk
  - Daily platelet counts

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;9:479–488.
Coons JC, Barcelona RA, Freedy T, Hagerty MF. Eptifibatide-associated acute, profound thrombocytopenia. Ann Pharmacother 2005;39:368–372.

66-YO Male Discharge Day 4

- Clopidogrel, Plavix®
  - 300 loading dose, 75 mg once daily 1–2 years
  - Take with aspirin 81–325 mg/day
- Prasugrel, Effient®
  - Cleared 2009
  - Loading dose, 60 mg
  - Continue 10 mg/day; 5 mg/day if <60 mg 1–2 years
  - Take with aspirin
- Aspirin 81 mg/day: lifelong



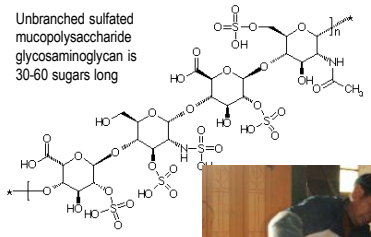
Monitor for Anti-platelet Resistance

- Whole blood impedance aggregometry
  - Reference method
  - Use arachidonic acid agonist to detect aspirin response
  - Use ADP to detect Clopidogrel response
  - Unnecessary for prasugrel—not a prodrug
- Whole Blood Accumetrics VerifyNow®
  - Arachidonic acid cartridge detects aspirin response
  - ADP detects Clopidogrel response
- Whole Blood Siemens PFA-100®
  - Closure time detects aspirin response
- Random Urine AspirinWorks®
  - Urinary 11-dehydrothromboxane B_2 (UDHT) immunoassay

McGlasson D, Fritsma G. Comparison of four laboratory methods to assess aspirin sensitivity. Bld Coag Fibrinolys 2008;19: 120-3.

Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopolysaccharide glycosaminoglycan is 30-60 sugars long



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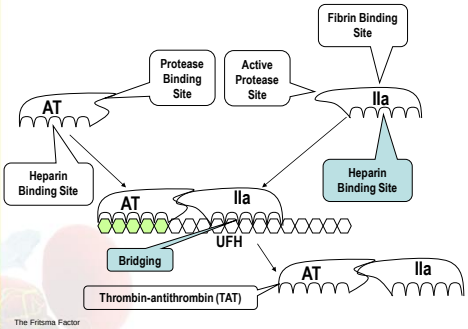
Unfractionated Heparin Binds Antithrombin To Thrombin



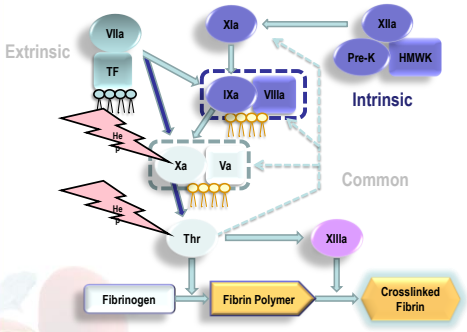


Figure courtesy of Margaret G. Fritsma

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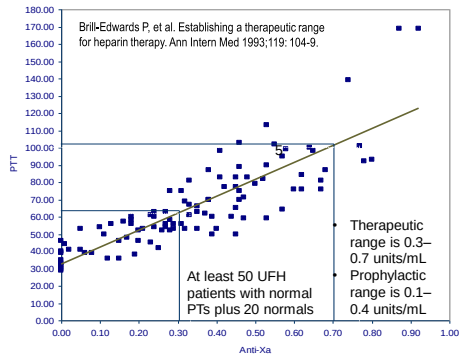
Monitoring UFH Therapy Standard Schedule

- Perform "baseline" PTT to r/o factor deficiency, inhibitors, lupus anticoagulant
- Initiate therapy: bolus + continuous infusion
- At least 4–6h after bolus, not >24h, perform second PTT
- Adjust dose to 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

Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. Ann Intern Med 1993;119:104-109.

Computing the UFH Therapeutic Range Using the Brill-Edwards Curve Comparing the PTT to the Chromogenic Anti-Xa Heparin Assay



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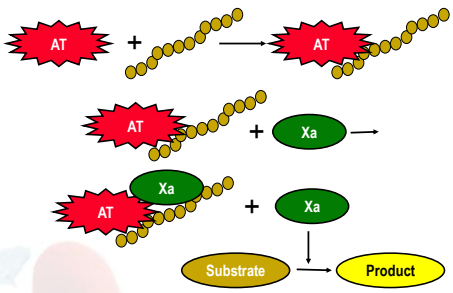
Chromogenic Anti-Xa Heparin Assay



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Limitations of PTT in UFH Monitoring

- Lupus anticoagulant, present in 1-2% of unselected individuals, prolongs PTT
- Coagulopathy prolongs PTT
- Coagulation factor inhibitor prolongs PTT
- Elevated FVIII renders PTT insensitive to heparin
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot
  - Brill-Edwards curve
- Antithrombin deficiency or consumption renders PTT non-responsive, "heparin resistance"

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

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A 56-YO Athletic Female with Total Knee Replacement

- 50% risk of DVT if no anticoagulant
- Start low molecular weight heparin six hours after surgery
  - Enoxiparin (Lovenox®) 30 mg/300 uL SC BID 7-10 days
- Prothrombin (IIa):Xa reduction 1:4

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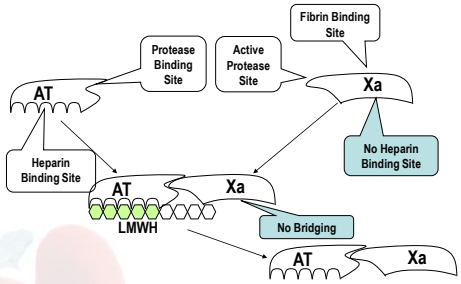
Low Molecular Weight Heparin Binds Xa



LMWH Advantages over UFH

- Achieves therapeutic level 30” after injection
- Half-life 4 hours
- Fixed dose-response relationship reduces need for laboratory monitoring
- Rate of HIT in de-novo therapy 10% of UFH rate

Moll S, Roberts HR. Overview of anticoagulant drugs for the future. Semin Hematol 2002; 39: 147-147

When to Monitor LMWH

- Renal disease with inadequate excretion
  - Monitor when serum creatinine > 2.0 mg/dL
  - Or creatinine clearance < 30 mL/min
- Obesity: relatively reduced fluid compartment
- Pediatric: relatively increased fluid compartment
- Pregnancy, malignancy, DIC
  - Unstable coagulation system
- These rules now apply to fondaparinux, rivaroxaban, and dabigatran

How to Monitor LMWH

- Collect blood 4 hours after injection
- Chromogenic anti-Xa heparin assay
- Standard target for therapy
  - Chromogenic anti-Xa 0.5 to 1.0 U/mL
- Standard target for prophylaxis
  - Chromogenic anti-Xa 0.1 to 0.4 U/mL

Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326

Chromogenic Anti-Xa Heparin Curve

- Separate curves for UFH and LMWH?
- Hybrid curve: one curve fits all
- Numerous LMWH formulations
  - Aventis lost Lovenox patent 5/1/09
- Separate curve for fondaparinux?
  - Synthetic pentasaccharide
  - Marilyn Johnston, McMaster: uses same curve as LMWH

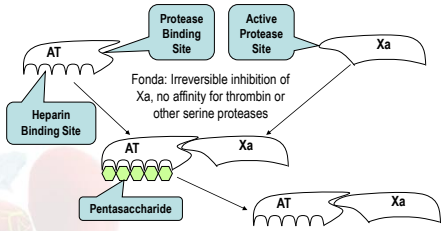
McGlasson DL, Kaczor DA, Krasuski RA, et al. Effects of pre-analytical variables on the anti activated factor X chromogenic assay when monitoring unfractionated heparin and low molecular weight heparin. Blood Coagul Fibrinolysis 2005;16:173–6.

Synthetic Pentasaccharide, Fondaparinux (Fonda)

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

Fonda and Antithrombin

- Sulfate residues critical to high-affinity AT binding
- Conformational change in AT raises Xa affinity 300X



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Monitoring Fondaparinux

- Chromogenic anti-Xa calibrated with pentasaccharide in mg/L
  - No international standard
  - Standards available from Beckman-Coulter and Aniara for their kits
- SC (never IM) injection; 2.5 mg
  - Peak plasma level at 3 h: 0.4–0.5 mg/L
  - Minimum steady state 0.14–0.19
- No current therapeutic range

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Fonda Comments

- Efficacy: 50% reduction in DVTs
  - Frequency of repeat DVT 11 days after surgery 6.8%
    - Compared to 13.7% for LMWH ($p=10^{-17}$)
  - Fatal PE events 1% at day 49, same as LMWH
- Half-life 17 h; single 2.5 mg SC/24 h
  - Overdose: no direct reversal
- Risk of major bleed 2.7%, LMWH 1.7%
- Cost exceeds LMWH by 50%
  - Offset by reduced adverse events

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: 1833–40
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: 1806–8

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Fonda Contraindications

- Renal disease: kidney only excretion route
  - Creatinine clearance < 30 mL/min
- Weight less than 50 kg
- Over 75 years old; not included in studies
- Bleeding Hx
  - Congenital or acquired coagulopathies
  - Ulcerative gastrointestinal disease
  - Hemorrhagic stroke

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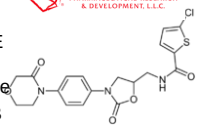
Rivaroxaban (Xarelto®)

- An oxazolidinone derivative direct anti-Xa
- Safety and efficacy exceed Lovenox in three out of four phase III trials
- Cleared 2009 for DVT & PE prophylaxis in orthopedic surgery in Canada & Europe
- Application at FDA for AFIB

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



Xarelto® rivaroxaban

Bauer KA, Homering M, Berkowitz SD. Effects of age, weight, gender and renal function in a pooled analysis of four phase III studies of rivaroxaban for prevention of venous thromboembolism after major orthopedic surgery. Blood 2008; 112: Abstract 436

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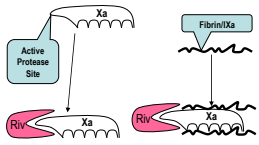
Rivaroxaban

- Oral dose: 10 mg/day: steady state at 4 hours
- Neutralizes free, fibrin-bound, and IXa-bound Xa
- Excretion: 66% renal, 28% fecal
- Monitoring; none required?
  - Doubles PT interval at 230 nM
  - Doubles PTT interval at 690 nM
  - Neutralizes Xa
- Binds Xa only



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;33:5115–5123.

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Rivaroxaban Interactions

- No food interactions
- P-glycoprotein inhibitors
  - PGPs are enteric pathways that protect from toxins
  - Inhibitors include azole antimycotics (ketoconazole)
- P450 3A4 inhibitors
  - HIV protease inhibitors (ritonavir)
- NSAIDS, aspirin, and clopidogrel
- OTC supplements such as St. John's Wort, platelet inhibitors

Walenga JM, Adiguzel C. Drug and dietary interactions of the new and emerging oral anticoagulants. Int J Clin Pract. 2010;64:956–967.

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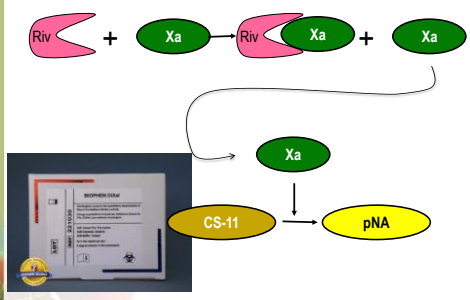
Direct Xa Chromogenic Inhibitor Assay BIOPHEN DiXal® (RUO)



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Direct Xa Chromogenic Inhibitor Assay BIOPHEN DiXal®

- Lyophilized reagent lacks antithrombin
  - Purified human factor Xa in measured excess
  - Chromogenic substrate CS 11 with pNA chromophore
- Intensity of yellow product inversely proportional to Rivaroxaban plasma concentration
- Additional direct factor Xa inhibitors
  - Apixiban; Bristol-Myers-Squibb and Pfizer
  - Edoxaban: Daiicho-Sankyo
  - Betrixaban: Portola (D/C and sold by Merck 3/24/11)

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Direct Thrombin Inhibitors (DTIs)

- Indication: antithrombotic in heparin-induced thrombocytopenia (HIT)
- DTIs 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
  - Fondaparinux OK

- Kaplan KL, Francis CW. Direct thrombin inhibitors. Semin Hematol 2002;39:187–196.
- 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.

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

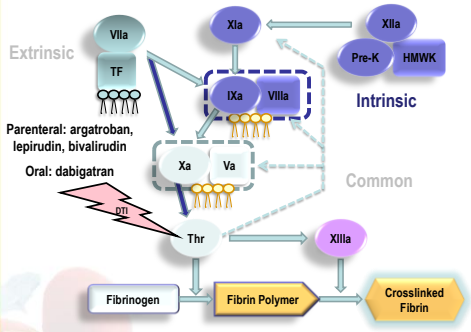
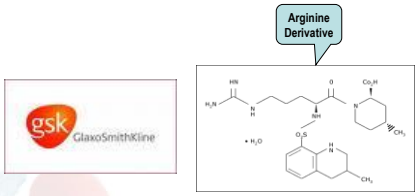


Figure courtesy of Margaret G. Fritsma

THE FRITSMA FACTOR Your Interactive Hemostasis Resource

Argatroban (Novastan®)

- Raises nitric oxide, causing vasodilatation
- Metabolized and excreted by liver CYP450



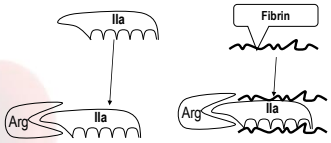
THE FRITSMA FACTOR Your Interactive Hemostasis Resource

Argatroban Administration and Monitoring

- IV: 2 mcg/kg/m: immediate steady state
  - 5–7 d
  - Maintain PTT 1.5–3 x MRI
    - Linear to 40 mcg/kg/m
  - Ecarin clotting time
  - Prolongs PT
    - Doubles INR when bridging to warfarin
- During cardiac catheterization or coronary artery bypass graft surgery
  - Bolus 350 mcg/kg
  - Continuous infusion 15–40 mcg/kg/m
  - Maintain ACT 300–450 seconds

Argatroban Comments

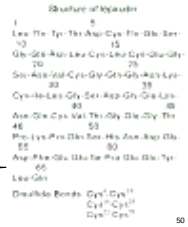
- Safe to use in renal disease
- Liver disease
  - Reduce to 0.5 μg/kg/h and monitor with PTT
- Major bleeds 5.3%, minor 14.4%
- No antidote, but half-life is 40 minutes
- Inhibits free and fibrin-bound thrombin



Hirudin: Lepirudin

- Inhibits free, not bound thrombin
- Metabolized and excreted by kidney only
  - Monitor in kidney disease
- Danger: peptide causes immune response

7000 D, 65 aa polypeptide



Lepirudin Administration

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

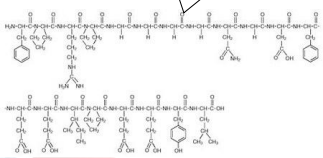
PHARMION

50mg ®
Refludan
Powder for solution for injection or infusion
lepirudin

Bivalirudin

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

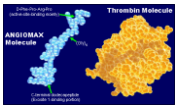
2180 D, dodecapeptide



THE MEDICINES COMPANY®

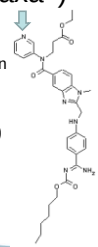
Bivalirudin

- Neutralizes free and bound thrombin
- FDA-cleared spring, 2008
  - Reduced major hemorrhage by 41% to 61%
  - Proven antithrombotic effect
  - Always use with aspirin
- Bolus 0.75 mg/kg plus 1.75 mg/kg/h
- Renal excretion, 25 m half-life
  - Must monitor creatinine, reduce dosage
  - Monitor bivalirudin



Dabigatran Etexilate (Pradaxa®)

- Benzamidine–based prodrug
  - Hydrophobic side chain enables it to be taken orally
  - Etexilate side chain removed upon digestion
- Cleared in Canada & Europe 2009
  - Indication: post-surgical VTE prevention
- Cleared by FDA October 2010
  - Indication: atrial fibrillation
- 150 mg/bid with wide safety range
  - Two hours to steady state
  - No laboratory monitoring when uncomplicated



Dabigatran (Pradaxa®)

- Binds clot-bound and free thrombin
- Renal excretion 80%
  - Reduce dosage and monitor in renal disease
- Half-life 12–17 hours
- No interaction with food
- Not metabolized by CYP450 pathway
- Levels raised by quinidine and verapamil
- Predictable efficacy
- No liver toxicity
- Dyspepsia in 2–3%

Ecarin Clotting Time (ECT)

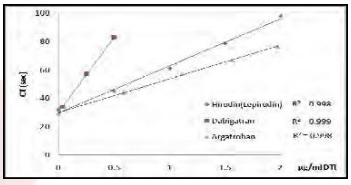
- Thrombin-like venom from *Echinus carinatus*
  - Cleaves prothrombin to produce intermediate activation product meizothrombin, which stimulates fibrin polymerization
- ECT is reliably linear to all DTI plasma concentration, even at prophylactic doses
- ECT is unaffected by heparin or warfarin and cannot be used to monitor these
  - Insensitive to LMWH, fondaparinux
  - Cannot measure direct Xa inhibitor Rivaroxaban

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
- Diagnostica Stago has developed reliable kit (RUO)
- Few North American reference laboratories and no clinical providers offer the ECT assay

Aniara Hemoclot® DTI Assay

- Dilute test plasma 1:8 (1:20 for Lepirudin)
- Mix diluted test plasma 1:2 with normal plasma
- Add human α-thrombin, Ca^{++} reagent
- Record clot interval, compare to reference curve
- Linear relationship with DTI concentration



FDA Advisory Panel 9/20/2010 We're getting ever closer

ARRHYTHMIA/EP

Warfarin, move over: Dabigatran gets unanimous thumbs-up from FDA advisory panel

SEPTEMBER 20, 2010 | Steve Stiles

Silver Spring, MD (updated) – One of cardiology's fondest wishes moved closer to fulfillment as an **FDA** advisory panel unanimously recommended approval of a potential replacement for warfarin in one of the most common heart disorders. Barring any unforeseen damning revelations about the drug, for which the agency had already expressed support, its approval of the oral thrombin inhibitor **dabigatran** (Pradaxa, Boehringer Ingelheim) for stroke prevention in atrial fibrillation (AF) is all but certain.

"I think it's a tremendous advance; people have been looking for a replacement for warfarin for decades," **Dr A Michael Lincoff** (Cleveland Clinic, OH), acting chair of the FDA's Cardiovascular and Renal Drugs Advisory Committee, observed for heartwire after the meeting adjourned. In the key dabigatran clinical trial it considered, the drug came out ahead of warfarin in multiple ways, he said: ease of administration, associated risk of intracranial hemorrhage, "and it's somewhat better at preventing stroke."