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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, and the 2011 oral anticoagulants rivaroxaban, apixiban and dabigatran? And we still don't know how to monitor direct thrombin inhibitors. Are ecarin time, chromogenic X and chromogenic anti-Xa the answer?

Objectives:

1. Brief summary of current antithrombotics
2. Monitor antiplatelet drugs, fondaparinux, direct thrombin inhibitors, and 2010 oral anticoagulants
3. Employ chromogenic X and chromogenic anti-Xa to monitor several new anticoagulants

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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: when INR 5–6: bruising, bleeding gums, epistaxis
  - Just started on statin
    - 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
- 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

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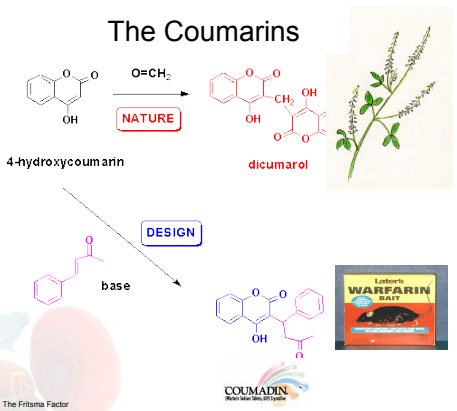
The Coumarins



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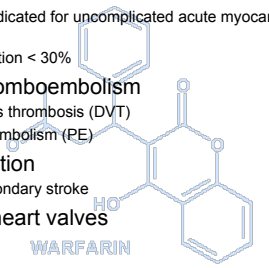
Warfarin Indications

- 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
  - INR 2.5–3.5



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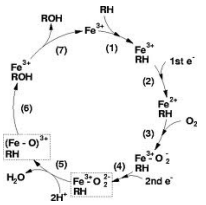
Properties of Warfarin

- Vitamin K antagonist
- Blocks γ-carboxylation of 10-12 glutamic acids near the N-terminus of the VK-dependent coagulation factors
  - Factors II, VII, IX, X
  - Control proteins C, S and Z
- Metabolized by cytochrome P450 (CYP450) pathway



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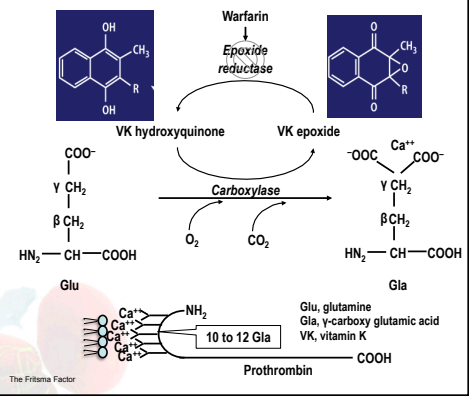

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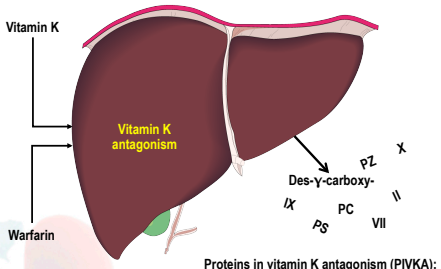
Vitamin K Antagonist Products "PIVKA"



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

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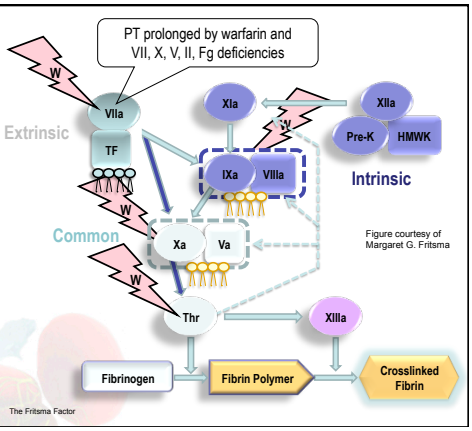

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Warfarin Dose & Pharmacodynamics

- 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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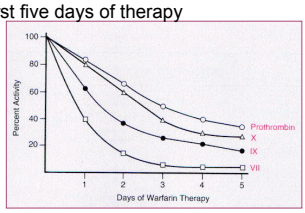
Is the PT/INR All it Could Be?

- 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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International Normalized Ratio

- Perform prothrombin time (protime, PT)
- PT is normalized world-wide by applying the INR formula:
  - $INR = (PT_{patient}/PT_{normal\ mean})^{ISI}$
    - INR = international normalized ratio
    - $PT_{patient}$ = PT of patient plasma
    - $PT_{normal\ mean}$ = PT of mean of normal range
    - ISI = international sensitivity index assigned by manufacturer based on comparison to international thromboplastin reagent
- The laboratory computes the formula and reports all PTs in seconds and as INRs

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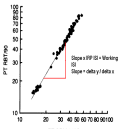
International Sensitivity Index (ISI)

- Manufacturers assay 20 normal and 60 stable warfarin plasmas using:
  - A WHO international reference preparation (IRP) of thromboplastin with ISI established at 1.0
  - Their commercial lot number of reagent
  - The manual tilt-tube technique in multiple expert labs
  - Various representative instruments
- They generate instrument-specific ISIs for each thromboplastin/ instrument combination by regression analysis



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Recommended INRs

Indication	Range
Prophylaxis and therapy for DVT, PE, atrial fibrillation, cardiac insufficiency	2–3
Therapy for mechanical valves, complicated or recurrent AMI	2.5–3.5
Risk of hemorrhage critical value	> 5.0

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PT Variation Among Four Thromboplastins

	Mean (n=9)		Example Patient	
Reagent	PT (sec)	INR	PT (sec)	INR
A	16.1	1.5	67.4	31.3
B	16.9	1.3	81.9	8.7
C	13.7	1.2	169.0	15.4
D	17.5	1.5	78.3	9.3

Despite normalization, the INR varies significantly as a function of thromboplastin sensitivity. Quarles LA and Harmon SL, personal communication,1997

Rosborough TK, Jacobsen JM, Shepherd MF. Factor X and factor II activity levels do not always agree in warfarin-treated lupus anticoagulant patients. Blood Coagul Fibrinolysis 2010;21:242-4.

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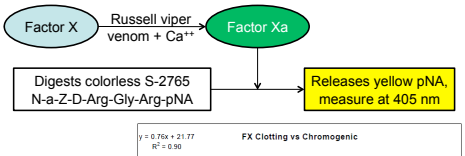
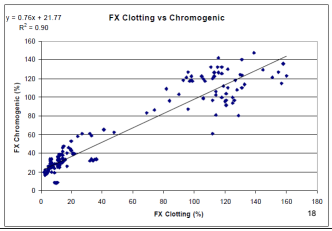
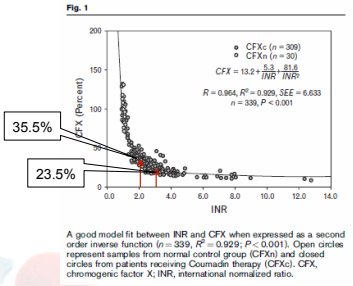
Chromogenic Factor X Assay



diaPharma



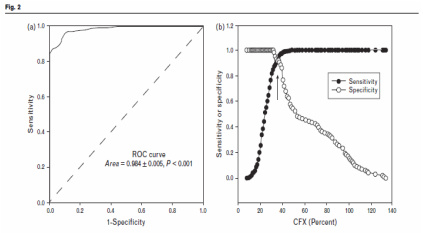
Chromogenic X In Place of PT?



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.

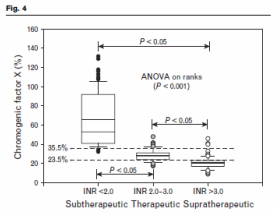
McGlasson DL, Romick BG, Rubal BJ. Comparison of a chromogenic factor X assay with INR for monitoring oral anticoagulation therapy. Blood Coag Fibrinolys 2008;19:513–517

Chromogenic X in Place of PT?



(a) An ROC curve using INR of at least 2.0 as the criterion for the threshold of therapeutic anticoagulation. (b) (arrow) A plot of sensitivity and specificity over the range of CFX values tested ($n = 339$). The arrow indicates the CFX value of 35.5% or less that has maximum combined sensitivity and specificity for the INR therapeutic threshold (INR ≥ 2.0). CFX, chromogenic factor X; INR, international normalized ratio; ROC, receiver-operator curve.

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."

Warfarin Limitations

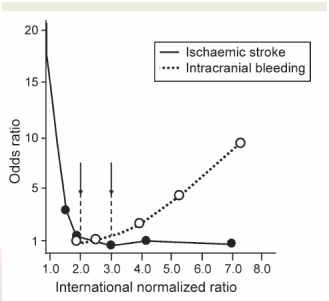
- These supply vitamin K and reduce warfarin efficacy:
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba, parenteral nutrition formulations
- Over 80 drugs unpredictably influence CYP2C9 cytochrome oxidase pathway
- Warfarin allergy with anaphylaxis

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.

Warfarin Therapeutic Window



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

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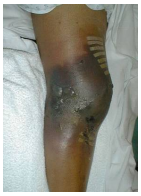
Risk of Thrombosis During First Five Days of Therapy

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	6 h	2-6 mcg/mL
Protein S		20-25 mcg/mL



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

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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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Cumulative Adverse Outcomes in VTE Patients on Anticoagulation

Outcome	30-d	1-y	3-y
Major bleed	9.4%	11.6%	15.8%
Recurrent VTE	3.5%	10.7%	15.0%
Mortality	13.0%	26.0%	35.3%

N= 549; VTE, venous thromboembolism, includes pulmonary emboli (PE) and deep vein thrombosis (DVT)

Adapted from Spencer FA, Gore JM, Lessard D, et al. Patient outcomes after DVT & PE: the Worcester Venous Thromboembolism Study. Arch Intern Med 2008;168:425–430.

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Summary of Warfarin Disadvantages

- Five days' onset of therapy
  - Must bridge with heparin
  - Monitor daily until stable
- Narrow therapeutic window
  - Risk of secondary thrombotic event and hemorrhage
  - Need for lifelong monitoring
- Inter-individual dosing differences
  - Age: pediatric and geriatric variations
  - Three polymorphisms cause sensitivity
  - Warfarin resistance causes under investigation
- Neutralization by dietary vitamin K
- Interactions with drugs that metabolize via CYP450

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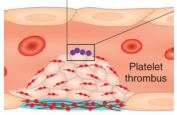
66 YO Male Acute Myocardial Infection

- 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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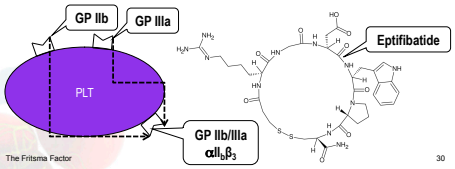
Platelet Membrane Glycoprotein IIb/IIIa Inhibitors (GPIs)

- 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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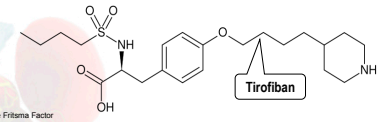
Two More Platelet Membrane Glycoprotein IIb/IIIa Inhibitors (GPIs)

- 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 Dosing and Thrombocytopenia

- 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: Accumetrix Ultegra IIb/IIIa assay using TRAP

- Risk of severe thrombocytopenia
  - 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.

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Multiplate Analyzer by DiaPharma

Introducing The Multiplate Analyzer

Assess Platelet Function Sensitive to:
+Clopidogrel
+Aspirin®
+GpIIb/IIIa Antagonists

Exclusive US & Canadian Distributor

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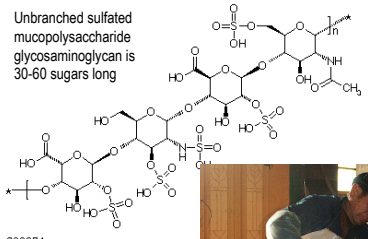
Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopolysaccharide glycosaminoglycan is 30-60 sugars long



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Coronary Bypass Graft Unfractionated Heparin (UFH)

- UFH bolus: 5000–10,000 IUs
  - Two hours after termination of thrombolytic therapy
  - Simultaneous with GPIs
- Maintenance dosage: 1600 IUs/hour
- Terminate at discharge, max 5 days

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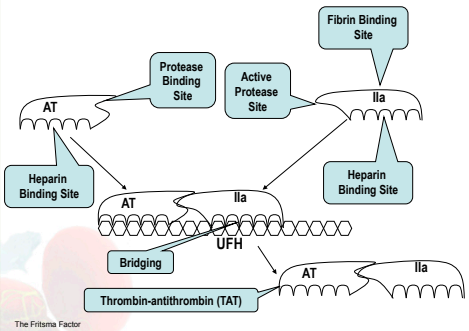
Unfractionated Heparin Binds Antithrombin With Thrombin



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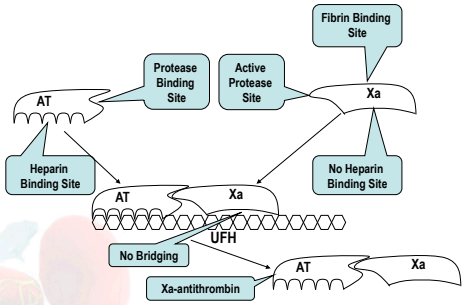
Unfractionated Heparin Binds Xa and Antithrombin



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PTT prolonged by heparin, LA and XII, XI, IX, X, V, II, Fg deficiencies

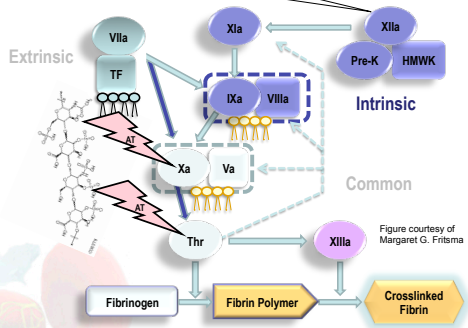

Figure courtesy of Margaret G. Fritsma

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UFH and LMWH Effect on PTT

Factor	UFH	LMWH	Fonda
XIIa, PK, HMWK	+/-	-	-
XIa	+	+/-	-
IXa	2+	-	-
Xa	3+	2+	2+
IIa (thrombin)	3+	+	-

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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 initiation, 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.

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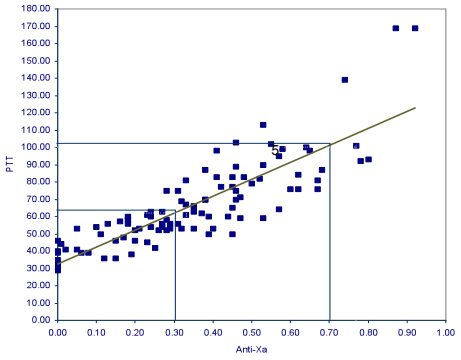
Establishing The PTT Heparin Therapeutic Range

- Collect at least 50 patient specimens
  - All heparin dosage ranges
  - No oral anticoagulant, PT normal
- Collect at least 20 normals
  - Representative demographics
- Chromogenic PTT and anti-Xa heparin
- 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.

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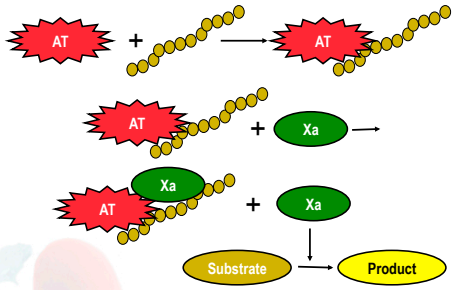
Chromogenic Anti-Xa Heparin Assay



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Chromogenic Anti-Xa Heparin Curve

- Separate curves for UFH and LMWH?
- Hybrid curve: one curve fits all
- Different LMWH formulations
  - Aventis 5/1/09 loses Lovenox patent
- 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.

The Fritsma Factor 45

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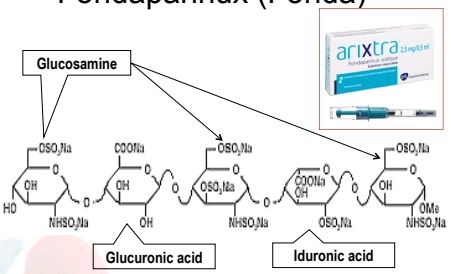
Synthetic Pentasaccharide, Fondaparinux (Fonda)



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

The Fritsma Factor 46

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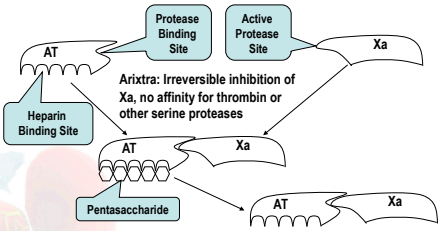
Fonda and Antithrombin

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



The Fritsma Factor 47

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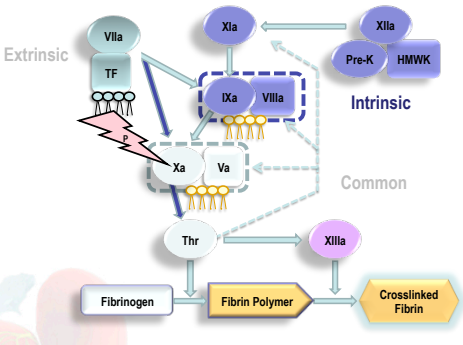

Figure courtesy of Margaret G. Fritsma

The Fritsma Factor

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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 Advantages

- Efficacy
  - 50% reduction in venographic DVT
  - Frequency of repeat DVT 11 days after surgery 6.8%
    - Compared to 13.7% for LMWH ($p=10^{-17}$)
  - Fatal thromboembolic 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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Fonda 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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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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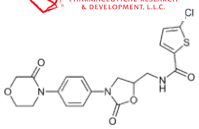
Rivaroxaban (Xarelto®)

- An oxazolininone derivative direct anti-Xa
- Safety and efficacy exceed Lovenox in three out of four phase III trials

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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Prophylaxis: Four Phase III Studies

- Rivaroxaban at 10 mg po/daily is effective as VTE prophylaxis
- Mean risk of major and total VTE recurrence < 3%

Table 4: Key outcomes in phase III studies investigating rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip or knee replacement surgery [57–59, 80].

	Rivaroxaban (10 mg od) % (n/N)	Enoxaparin (40 mg od [RECORD1, 2, 3] or 30 mg bid [RECORD4]) % (n/N)	P-values
RECORD1 (THR)			
Total VTE	1.1 (18/1,595)	3.7 (58/1,558)	<0.001
Major VTE	0.2 (4/1,686)	2.0 (33/1,678)	<0.001
Major bleeding	0.3 (6/2,209)	0.1 (2/2,224)	0.18
RECORD2 (THR)			
Total VTE	2.0 (17/864)	9.3 (81/869)	<0.0001
Major VTE	0.6 (6/961)	5.1 (49/962)	<0.0001
Major bleeding	0.1 (1/1,228)	0.1 (1/1,229)	-
RECORD3 (TKR)			
Total VTE	9.6 (79/824)	18.9 (166/878)	<0.001
Major VTE	1.0 (9/908)	2.6 (24/925)	0.01
Major bleeding	0.6 (7/1,220)	0.5 (6/1,239)	0.77
RECORD4 (TKR)			
Total VTE	6.9 (67/965)	10.1 (97/959)	0.012
Major VTE	1.2 (13/1,122)	2.0 (22/1,112)	0.124
Major bleeding	0.7 (10/1,526)	0.3 (4/1,508)	0.11

bid, twice daily; od, once daily; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

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Treatment: EINSTEIN-DVT 2010

Rivaroxaban almost superior to usual care in treatment of DVT

AUGUST 31, 2010 | Lisa Nainggolan

ESC **Stockholm, Sweden** – Results from the EINSTEIN–DVT study, showing that **rivaroxaban** (Xarelto, Bayer/Johnson & Johnson) is noninferior to standard medical therapy for the treatment of acute symptomatic deep vein thrombosis (DVT), have been presented during a hot-line session at the **European Society of Cardiology (ESC) 2010 Congress** today by **Dr Harry R Buller** (Academic Medical Center, Amsterdam, the Netherlands).

Buller said that rivaroxaban, an oral factor Xa inhibitor, was close to demonstrating superiority, although the trial was designed specifically to demonstrate noninferiority, because "the standard medical treatment is so good." But although usual care is effective, it is inconvenient, requiring initial subcutaneous injections of **low-molecular-weight heparin** (LMWH) followed by **warfarin** treatment, with its own attendant problems. "It's a nightmare to manage, for patients and physicians," he commented to **heartwire**.

Dr Harry R Buller

American College of Cardiology president **Dr Ralph Brindis** (Kaiser-Permanente, San Francisco, CA), who was at the hot-line session press conference today, said: "This is a very important study. It increases our knowledge base regarding the safety and efficacy of factor Xa inhibitors, in this case in the management of DVT."

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Treatment: EINSTEIN-DVT 2010

- Study arms: n = 3449
  - Treatment: 15 mg rivaroxaban BID X 3 week, 20 mg daily
  - Usual care: LMWH 5 days; warfarin
- Efficacy: first VTE event
  - 2.1% V 3.0%, hazard ratio 0.68, p <0.0001
- Safety: composite of major & minor bleeds
  - 8.1% for both, p = 0.7
- Composite of efficacy and safety
  - 2.9% V 4.2%, hazard ratio 0.67
- No liver toxicity in all studies

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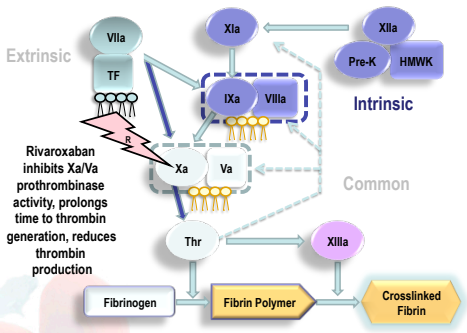

Figure courtesy of Margaret G. Fritsma

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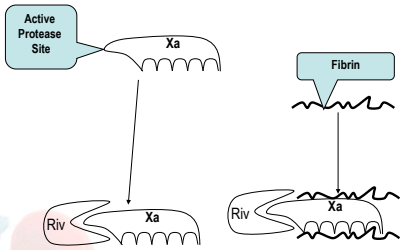
Rivaroxaban inhibits free, fibrin-bound Xa, and IXa-bound Xa, requires no AT



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Dose Response to Rivaroxaban by FXa, Prothrombinase (Xa/Va)

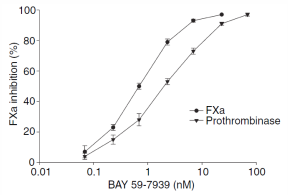

Fig. 2. Effect of BAY 59-7939 on purified human free Factor Xa (FXa) using a chromogenic substrate of FXa (●), and on prothrombinase activity on platelet surfaces using prothrombin as substrate (measuring generated thrombin; ▼). Each value represents the mean ± SEM of five measurements in triplicate.

Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939--an oral, direct Factor Xa inhibitor. J Thromb Haemost 2005;3:514–521.

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Rivaroxaban

- Oral dose: 10 mg/day: steady state at 4 hours
- Neutralizes free, clot-bound, and IXa-bound Xa
  - Interacts with no other serine proteases
- Excretion: 66% renal, 28% fecal
- Monitoring; none required?
  - Doubles PT interval at 230 nM
  - Doubles PTT interval at 690 nM
  - Neutralizes Xa
- No outcomes-based laboratory therapeutic range established
- Cleared for prophylaxis; Canada & Europe 5/2009

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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Apixiban in VTE Prophylaxis

- 12 days, 2.5 mg twice a day
- Comparator: enoxaparin
- Primary safety: major bleeding
- Primary efficacy: composite VTE

Study	N	Enox	Safety	Efficacy
ADVANCE 1	3195	30 mg	0.7 V 1.4%	9% V 8.9%
ADVANCE 2	1973	40 mg	0.6 V 0.93%	15% V 24%

Bristol-Myers Squibb Company

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Apixiban V Aspirin: AVERROES

AVERROES: Apixaban yields significant reductions in stroke, no increased bleeding

AUGUST 31, 2010 | Michael O'Riordan

Download slides

Stockholm, Sweden – Patients with atrial fibrillation unable to take **warfarin** who are treated with **apixaban** (Pfizer/Bristol-Myers Squibb), an investigational oral factor Xa inhibitor, had a significantly lower risk of stroke and systemic embolic events compared with patients treated with aspirin.

Importantly, the benefits of apixaban did not come at a cost of increased bleeding, with no observed increases in the risk of major bleeding, minor bleeding, or intracranial hemorrhage, among other end points, in those treated with apixaban.

The results of the study, known as the **Apixaban versus Acetylsalicylic Acid to Prevent Strokes** (AVERROES) trial, were presented today here at the **European Society of Cardiology 2010 Congress** by lead investigator **Dr Stuart Connolly** (McMaster University, Hamilton, ON). Asked his impression of the reduction in stroke risk, coupled with the safety of apixaban, in these difficult-to-treat patients, Connolly called the novel anticoagulant "superb."

"It's a very easy to use drug to give," Connolly told **heartwire**. "You take it twice a day, and it's well tolerated. It didn't have any liver toxicity, no particular adverse events that we saw. If anything, it's extremely safe. We consider aspirin to be a drug we can just about give any patient, but aspirin does cause bleeding. It's not completely benign."

Dr Stuart Connolly

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Apixiban V Aspirin: AVERROES

Outcome	Apixiban	Aspirin	RR
n	2809	2791	
Stroke or systemic embolic event	1.6	3.6	0.46
MI	0.7	0.8	0.85
Vascular death	2.5	2.9	0.86
Total death	3.4	4.4	0.79

- Safety: major, minor, intracranial, and fatal bleeding: 13% increase (NS)

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Direct Thrombin Inhibitors (DTIs)

- Indication: heparin-induced thrombocytopenia (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
  - 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.

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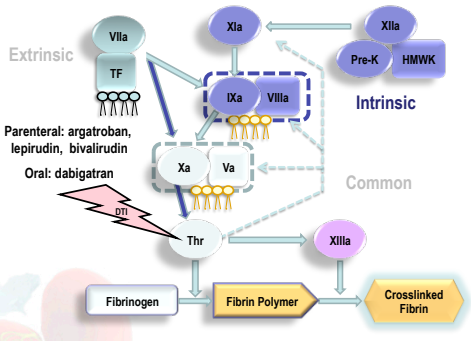

Figure courtesy of Margaret G. Fritsma

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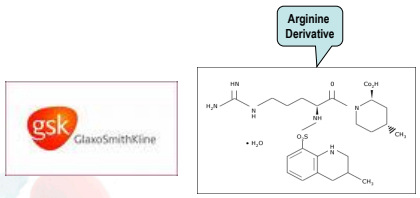
Argatroban (Novastan®)

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



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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 PCI
  - Bolus 350 mcg/kg
  - Continuous infusion 15–40 mcg/kg/m
  - Maintain ACT 300–450 seconds

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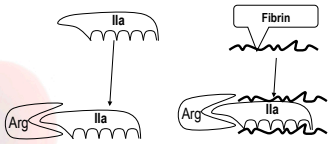
Argatroban Comments

- 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



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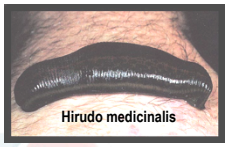
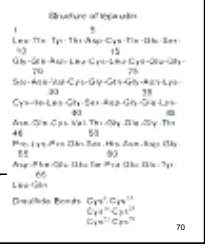
Hirudin: Lepirudin

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





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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

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

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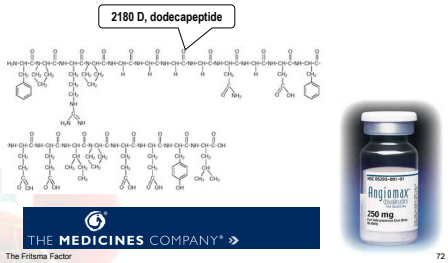
Bivalirudin

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



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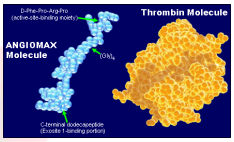
Bivalirudin

- Neutralizes free and bound thrombin
- FDA-cleared 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 creatinine clearance is <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 or ACT
  - Therapeutic range not defined

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Chromogenic X When Transitioning from a Direct Thrombin Inhibitor to Warfarin

Table 2. Daily Coagulation Variables Starting on Day 1 of Warfarin Therapy in the 62 Patients

Variable	Day 1	Day 2	Day 3	At Time of Chromogenic Factor X Measurement	At Time of Confirmatory Coagulation Studies[a]
Dosage					
Argatroban (μg/kg/min)	1.7 ± 1.2	1.6 ± 1.1	1.7 ± 1.2	1.8 ± 1.7	
Warfarin (mg/day)	4.3 ± 1.8	4.5 ± 1.7	4.7 ± 1.8	5.2 ± 2.3	
Laboratory tests					
aPTT (sec)	47 ± 13	50 ± 12	55 ± 15	58 ± 10	34 ± 5
PT (sec)	18 ± 3	20 ± 6	23 ± 8	28 ± 8	20 ± 5
INR	2.1 ± 0.7	2.7 ± 2.2	3.9 ± 3.0	5.3 ± 3.4	2.7 ± 1.4
CX (%)				43 ± 16	
CX (n=10) (%)[b]				41 ± 7	43 ± 10

Data are mean ± SD.
aPTT = activated partial thromboplastin time; PT = prothrombin time; INR = international normalized ratio; CX = chromogenic factor X.
[a]Confirmatory coagulation studies were obtained 9 ± 4 hrs after the chromogenic factor X level was measured.
[b]This value represents a second chromogenic factor X level from a sample of 10 patients at the time of the confirmatory coagulation studies 10 ± 3 hrs after the initial chromogenic factor X level.

Arpino PA, Demirjian Z, Van Cott EM. Use of the chromogenic factor X assay to predict the INR in patients transitioning from argatroban to warfarin. Pharmacotherapy 2005;25:157–64.

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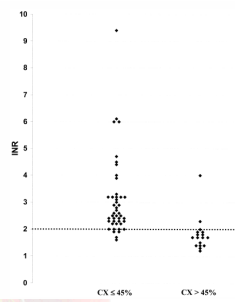
Chromogenic X When Transitioning from a Direct Thrombin Inhibitor to Warfarin



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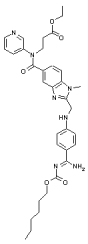
Dabigatran (Pradaxa®)

- Oral DTI cleared for prophylaxis 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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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

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Dabigatran Efficacy and Safety In Three Phase III Trials

	Dabigatran etexilate (150 mg od) % (n/N)	Dabigatran etexilate (220 mg od) % (n/N)	Enoxaparin (40 mg od [RE-NOVATE; RE-MODEL]; 30 mg bid [RE-MOBILIZE]) % (n/N)	P-values
RE-NOVATE (THR)				
Total VTE	8.6 (75/874)*	6.0 (53/880)*	6.7 (60/897)	*p<0.0001 for non-inferiority vs. enoxaparin
Major VTE	4.3 (38/888)	3.1 (28/909)	3.9 (36/917)	
Major bleeding	1.3 (15/1,163)	2.0 (23/1,146)	1.6 (18/1,154)	
RE-MODEL (TKR)				
Total VTE	40.5 (213/526)*	36.4 (183/503)**	37.7 (193/512)	*p=0.017; **p=0.0003 for non-inferiority vs. enoxaparin
Major VTE	3.8 (20/527)	2.6 (13/506)	3.5 (18/511)	
Major bleeding	1.3 (9/703)	1.5 (10/679)	1.3 (9/694)	
RE-MOBILIZE (TKR)				
Total VTE	33.7 (219/649)*	31.1 (188/604)**	25.3 (163/643)	*p=0.0009; **p=0.02 vs. enoxaparin
Major VTE	3.0 (20/656)	3.4 (21/618)	2.2 (15/668)	
Major bleeding	0.6 (5/871)	0.6 (5/857)	1.4 (12/868)	

bid, twice daily; od, once daily; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

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Dabigatran Vs Warfarin in Atrial Fibrillation

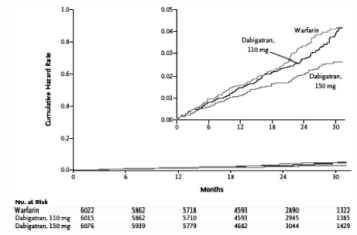

Figure 1. Dabigatran versus warfarin in patients with nonvalvular AF: cumulative hazard rates for the primary outcome of stroke or systemic embolism, according to treatment group. Reprinted from Connolly et al[11] with permission.

THE FRITSMA FACTOR
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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."

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Laboratory Assessment

Anti-coagulant	Dose	ECT	Anti-Xa	TCT	PT	PTT	Chromo II
Dabigatran	200 mg TID	5.2x	NE	27x	NR	2.3x	NR
Rivaroxaban	30 mg BID	NE	68%	NE	2.6x	1.8x	NR
Apixaban	25 mg BID	NE	NR	NR	NR	1.2x	NR

ECT, ecarin clotting time; Anti-Xa, chromogenic anti-Xa heparin; PT, prothrombin time; PTT, partial thromboplastin time; TID, three times a day; BID, twice a day; x, fold increase from baseline at peak concentration; NE, no effect; NR, not reported

Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood 2010;115:15–20.

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