THE FRITSMA FACTOR
Your Interactive Hemostasis Resource

Case Studies in Antithrombotic Therapy

Consumer access to laboratory information:

Lab tests online: AACC/ASCLS
Consumer web forum: ASCLS
www.fritsmafactor.com
www.uabcoag.net

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The Fritsma Factor, Your interactive Hemostasis Resource
www.fritsmafactor.com

Disclosure
Precision BioLogic, Inc

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Unsuspecting 54 YO Male With an Acute Anterior MI: 1997

- Moderate substernal pain upon exercise
- 325 mg ASA PO on arrival in ED
- Tissue plasminogen activator (TPA)
  - Alteplase® rTPA standard 1997 reperfusion
  - 15 mg IV bolus, 5 mg IV 30", 35 mg IV 60"

Molk B. Acute myocardial infarction in an unsuspecting male. Clin Hemostas Rev 1997; 11: 14.
Marder VJ Thrombolytic Therapy. In Kitchens CS, Alving BM, Kessler CM. Consultative Hemostasis and Thrombosis, 2nd Ed. 2007, Elsevier.

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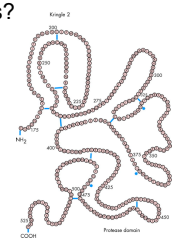
Thrombolytic Therapy

- Routinely used for reperfusion? When?
- Alternative for reperfusion?
- Risks of thrombolytics?
- How to monitor
- Other indications



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Other Indications for Thrombolytics

- Ischemic stroke
  - First r/o hemorrhagic stroke with MRI
  - Must treat within 3 h
  - Systemic administration
- Pulmonary embolism
  - Systemic administration
- Peripheral artery disease
  - Site-directed
- Deep venous thrombosis
  - Site-directed
- Viscous pleural effusion
  - Through chest tube

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Thrombolytic Risks

- Free plasmin may trigger systemic "lytic syndrome" (primary fibrinolysis)
  - Digests VWF, FG, factors V and VIII
  - Bleeding at fibrin-protected sites
  - Platelet hypo- or hyperaggregation
  - Decreased plasminogen, PAI-1
- Intracranial hemorrhage consistent at ~1% despite formulation, dosage
  - Prior stroke, trauma, surgery, tumor, hypertension, advanced age

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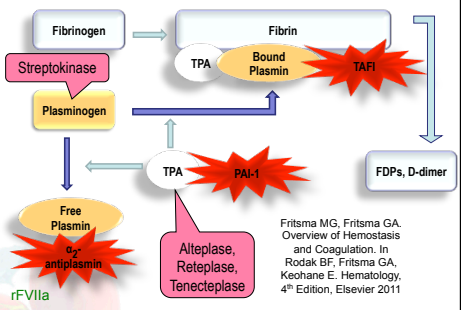
Fibrinolysis



Fritsma MG, Fritsma GA. Overview of Hemostasis and Coagulation. In Rodak BF, Fritsma GA, Keohane E. Hematology, 4th Edition, Elsevier 2011

"Lytic Syndrome"

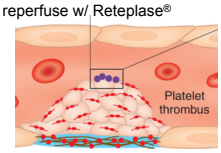
	Fibrinogen	TPA	PAI-1	D-dimer
RI: TPA	200–400 mg/dL	0.5–14 ηg/mL	2.5–27.5 U/mL	0–240 ηg/mL
Baseline	331	13.4	30.9	48
10m	118	18.8	29.6	662
1h	138	2999	0	1275
End: 2h	125	180	0	2350
4h	114	31.5	15.8	1916
24h	227	24	17.9	142

- Tissue plasminogen activator (TPA)
- Plasminogen activator inhibitor 1 (PAI-1)

The Fritsma Factor — Unsuspecting 54-YO Male — 7

Unsuspecting *65-YO* Male Acute Myocardial Infection

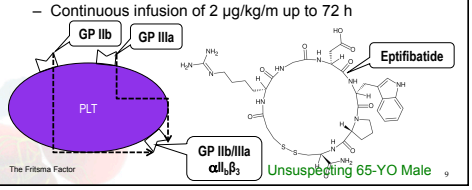
- Crushing substernal pain upon retiring
- 325 mg ASA PO at home
  - Reduce platelet activation and white clot formation
- Transported to cardiac catheterization lab
- <90 m for PCI, angioplasty and stent
  - If >3 hours in transport, reperfuse w/ Reteplase®



The Fritsma Factor — Unsuspecting 65-YO Male — 8

Percutaneous Intervention Glycoprotein IIb/IIIa Inhibitors (GPI)

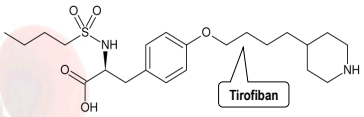
- GP IIb/IIIa is a platelet membrane arginine-glycine-aspartate (RGD) sequence receptor
  - Binds fibrinogen and VWF and supports aggregation
- Eptifibatide (Integrilin®); RGD mimetic
  - Use with aspirin and/or clopidogrel (Plavix®)
  - IV loading dose of 180 µg/kg 1–2 minutes
  - Continuous infusion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



The Fritsma Factor — Unsuspecting 65-YO Male — 9

Additional GPIs

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



The Fritsma Factor — Unsuspecting 65-YO Male — 10

GPI Dosing and Thrombocytopenia

- Weight-adjusted GPI dose without monitoring is ineffective
  - Poor platelet suppression risks thrombosis
  - Monitor with platelet aggregometry using thrombin receptor activation peptide (TRAP)
  - POC: VerifyNow® IIb/IIIa assay
  - POC: Multiplate® analyzer (RUO)
- Risk of severe thrombocytopenia
  - Daily PLT 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.

The Fritsma Factor — Unsuspecting 65-YO Male — 11

Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopolysaccharide glycosaminoglycan

The Fritsma Factor — Unsuspecting 65-YO Male

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Coronary Bypass Graft Unfractionated Heparin (UFH)

- UFH bolus: 5000–10,000 units; 60–80 units/kg
  - Two h after termination of thrombolytic therapy
  - Simultaneous with GPIs
- Maintenance: 1600 IUs/h; 12–18 units/kg/h
- Terminate at discharge, max 5 days
  - Risk of heparin-induced thrombocytopenia with thrombosis (HIT)
  - May substitute low molecular weight heparin

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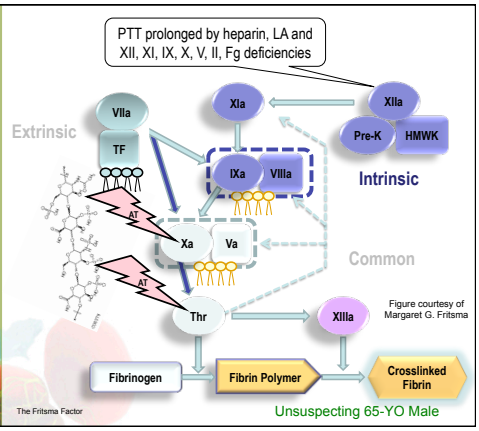

Figure courtesy of Margaret G. Fritsma

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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 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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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
- Antithrombin deficiency or consumption renders PTT non-responsive, "heparin resistance"
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot
  - Ex-vivo Brill-Edwards curve using heparin patient plasmas

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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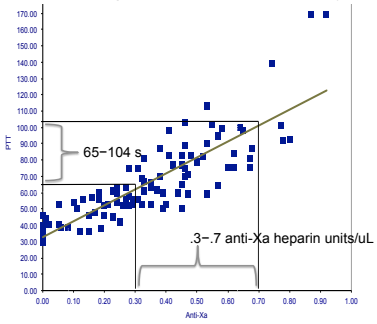
Develop UFH therapeutic range using Brill-Edwards curve; compare PTT to the chromogenic anti-Xa heparin assay



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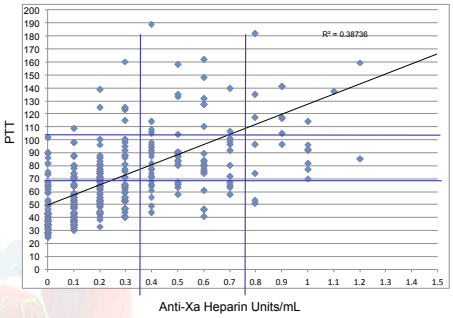
PTT/Anti-Xa Data, Three Routine Days



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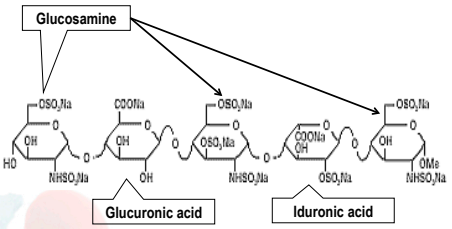
Synthetic Pentasaccharide, Fondaparinux



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

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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: mg/dL
  - 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.

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71-YO Female, Afib Since 41
30 Years of 7.5 mg/day Coumadin

- From the ASCLS Consumer Web Forum
- Monday: INR 11, no bleeding symptoms
  - Target range 2–3
  - Hx: when INR 5–6: bruising, bleeding gums, epistaxis
    - Compliant and knowledgeable
  - One week of Lipitor®
    - Total cholesterol: 263 mg/dL (<200 mg/dL or <5.2 mmol/L)
    - Triglycerides: 319 mg/dL (<150 mg/dL or <1.7 mmol/L)
- Tuesday repeat: INR 11
  - PCP ordered D/C Coumadin
  - Vitamin K: 10 mg IV push

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ASCLS Consumer Web Forum

- Contacted ASCLS on Wednesday
- What may have caused INR elevation?
- What do you recommend she do?
- Do you support the Rx decision?

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Follow-up to ASCLS Consult

- Patient contacted lab director
  - Coagulometer: desktop optical endpoint device
- Thursday collected fasting: INR 1.5
  - Resume Coumadin 7.5 mg/day
  - Was it the vitamin K or lipemia?
- Monday: INR 2.5; no further follow-up

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What Happened?

- Dietary change, decreased vitamin K?
- Do statins interfere with metabolism?
  - Lovastatin & fluvastatin metabolized by CYP450, same as Coumadin
- Do statins interfere with PT/INR?
- Age-related change in Coumadin sensitivity?
- Remember: no bleeding symptoms
- Optical coagulometer, lipemia?
- What is a valid alternative to PT/INR?

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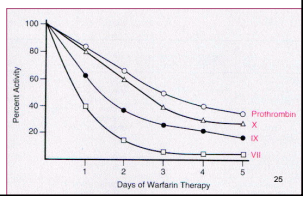
Is the PT/INR All it Could Be?

- INR invalid in first five days of therapy
- Optical coagulometers affected by lipemia
- PT may be falsely prolonged by LA
- INR invalid during transition from direct thrombin inhibitors (argatroban, bivalirudin) to coumadin
- POC INR adjusted to match plasma INR

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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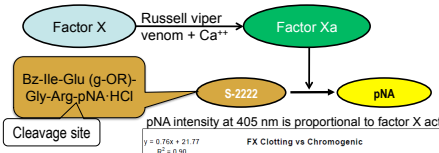
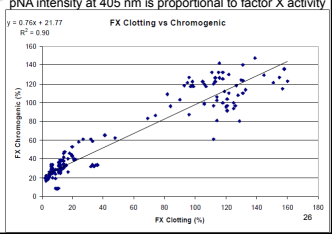
Chromogenic Factor X (CFX)



pNA intensity at 405 nm is proportional to factor X activity



The Fritsma Factor 26

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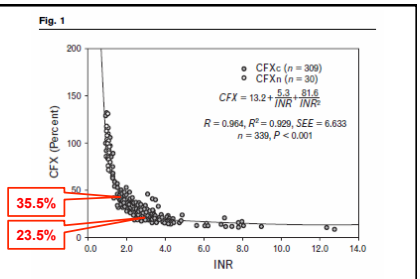
CFX In Place of PT?



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.

71-YO Female, Afib 30 Y

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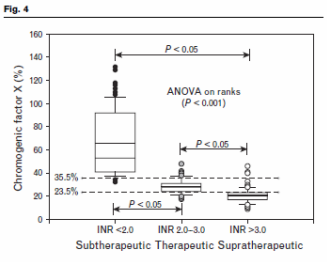
CFX in Place of PT?



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."

71-YO Female, Afib 30 Y

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INR & CFX in LA

- INR & CFX assayed in 44 control coumadin patients and 46 coumadin patients with LA
  - All were in therapeutic range for CFX 22–40% = INR 2–3
- 4 (9%) of controls had INR >3.0
- 18 (39%) LA patients had INR >3.0, 5 (11%) >4.0
- Monitoring Coumadin therapy by CFX in LA patients avoids INR artifact

Rosborough TK, Shepherd MF. Unreliability of international normalized ratio for monitoring warfarin therapy in patients with lupus anticoagulant. Pharmacotherapy. 2004;24:838–42.

71-YO Female, Afib 30 Y

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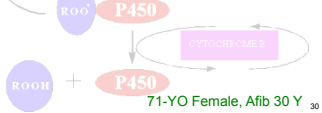
Coumadin Limitations

- These supply vitamin K and reduce efficacy
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba, parenteral nutrition formulations
- Over 80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway
- Coumadin overdose is most common reason for ER hemorrhage visits
  - Reversal with VK requires 6–10 hours



71-YO Female, Afib 30 Y

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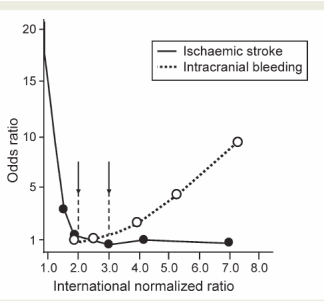
Coumadin Therapeutic Window



Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008;29:155–65

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Three Polymorphisms Raise Activity

CYP2C9*2, CYP2C9*3, VKORC1-1639 G>A

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes[1]

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

[1]Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 -1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

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

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60-YO Male, Post-TKR

- Coumadin, 5 mg/d for 3 weeks
- Malaise, loss of energy, depression, sleeplessness, chills
- D/C Coumadin, symptoms disappeared

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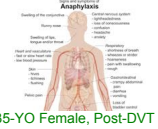
35-YO Female Post-DVT

- Patient taking Coumadin 15 mg/d, INR 1.1
  - Overweight, may not observe Coumadin diet restrictions
  - What do you advise?
- Raised dose repeatedly, up to 65 mg/d
- Developed rash, swelling, obstructed airway, and vomiting, went to ED
- Given epinephrine, D/C Coumadin, recovered



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Coumadin Resistance

- Coumadin resistance
  - VKORC1-3730 G>A variant raises dose 1 mg/d
  - CYP4F2 variant raises dose 1 mg/d
- Coumadin receptor insufficiency
  - Require dosages of 25 mg/d or more

Cini M, Legnani C, Cosmi B, Guazzaloca G, et al. A new warfarin dosing algorithm including VKORC1 3730 G > A polymorphism: comparison with results obtained by other published algorithms. Eur J Clin Pharmacol. 2012;68:1167–74.
Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. Blood 2008;111:4106–12.

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70-YO PCP, FVL Het Mutation

- Three major DVTs & PE from age 42
- FVL heterozygous, Coumadin 28 years
- Two recent potential DVTs R/O with negative D-dimer quantitative tests
- Current 10–20 mL superficial lower leg thrombophlebitis
  - Negative D-dimer days 2, 6, 11
- Clot resolving day 11
  - Increased Coumadin, INR 1.8 day 1, 3.1 day 11
  - Soaks and reasonable activities

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D-dimer in Coumadin Therapy

- Does heterozygous factor V Leiden mutation reduce D-dimer production?
- Does D-dimer response decrease with age?
- Is D-dimer insensitive to superficial thrombophlebitis?
- Does Coumadin decrease D-dimer?

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FVL Increases Fibrin Dissolution

FVL may mitigate DIC incidence and severity

"*Patients with FVL displayed higher levels of D-dimer and fibrinogen-fibrin degradation products in plasma after 24 hours. Patients with FVL generate higher levels of soluble fibrin, which may serve as cofactor in tissue plasminogen activator-induced plasminogen activation, leading to a more sustained activation of fibrinolysis with production of more fibrinogen- and fibrin-degradation products.*"

Imas E, Suvajac N, Jilma B, Weiler H, Borggrefe M, Dempfle CE. Factor V Leiden mutation enhances fibrin formation and dissolution in vivo in a human endotoxemia model. Blood 2010;116:801–5.

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100 Patients with Superficial Thrombophlebitis, All Ages

- Mean D-dimer: 829 ŋg/mL
- DD <500 ŋg/mL in 32%; ≥500 ŋg/mL in 68%
- DD ≥500 in 100% >70 YO (n=22)
- Unselected healthy ≥70-YO (n=78)
  - DD ≥500 ŋg/mL in 59%
- DD positively correlated with thrombus volume in patients <70 YO (p<0.0001)
- DD does not contribute to ST diagnosis

Gillet JL, Ffrench P, Hanss M, Allaert FA, Chleir F. Predictive value of D-dimer assay in superficial thrombophlebitis of the lower limbs. [Article in French, English abstract] J Mal Vasc. 2007;32:90–5.

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High D-dimer Prevalence Rises with Age

"In a geriatric population, ELISA D-dimer is a good marker to exclude PE but, due to the co-morbid conditions, only a few patients presented with D-dimer values <500 ŋg/mL."

Tardy B, Tardy-Poncet B, Viallon A, et al. Evaluation of D-dimer ELISA test in elderly patients with suspected pulmonary embolism. Thromb Haemost 1998;79: 38–41.

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69-YO with Atrial Fibrillation Bleeding in ED: What's he Got?

	Result	RI
PT	13.1 s	8.3–10.8 s
INR	1.3	0.9–1.2
PTT	47 s	25–35 s
PTT 1:1 Imm Mix	44 s	Control 29 s
TT	> 200 s	17–20 s
Reptilase time	20 s	16–22 s
PTT-LA	77 s	36–47 s
PTT-LA 1:1 Mix	69 s	Control 45 s
StaClot LA δ	7 s	>8 s
DRVVT confirm ratio	1.3	<1.2

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Two Cases of Rectal Bleeding

- 79-YO woman, acute renal failure
  - Dabigatran 110 mg BID, 2 m for atrial fibrillation
  - 69 kg, GFR: 20.7 mL/min (>30), INR 14.5
  - Dabi stopped on admission, normalized after 11 days
- 84-YO man, acute renal failure, dehydration
  - Dabi 110 mg BID for atrial fibrillation
  - 74 kg, GFR 33.5 mL/min, INR 7.5
  - Dabi stopped on admission
  - Discharge GFR: 66.5 mL/min, INR 1.53
- "These cases indicate the importance of PT and INR monitoring when using dabigatran"

Béné J, Saïd W, Rannou M, Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. Ann Pharmacother 2012;46:e14.

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New Oral Anticoagulants

- Dabigatran (Pradaxa) indications?
  - Direct thrombin inhibitor
- Rivaroxaban (Xarelto) indications?
  - Xa inhibitor
- How to monitor Dabi and Riva?
- Reversal of Dabi and Riva?

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Dabigatran Etexilate (Pradaxa®)

- Binds clot-bound and free thrombin
- Renal excretion 80%
- Half-life 12–17 hours
  - Up to 28 hours when GFR <30 mL/min
- No dietary interaction
- Not metabolized in CYP450 pathway
- Levels raised by quinidine and verapamil
- Predictable efficacy, no liver toxicity
- Dyspepsia in 11% of subjects

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Dabigatran is a Direct Thrombin Inhibitor

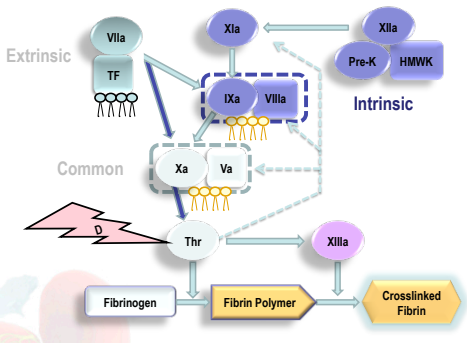

Figure courtesy of Margaret G. Fritsma

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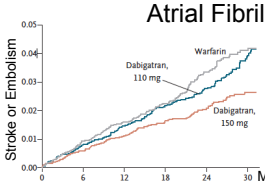
Dabigatran RE-LY Trial 2009
Atrial Fibrillation



Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009;361: 1139–51.

"RE-LY" 18,113 AF patients	Dabigatran 110 mg BID	Significance v. Coumadin	Dabigatran 150 mg BID	Significance v. Coumadin	Coumadin
Stroke or systemic embolism	1.11%/y	P<0.001 (non-inferiority)	1.53%/y	P<0.001 (superiority)	1.69%/y
Major bleed	2.71%/y	P=0.003	3.11%/y	P=0.310	3.36%/y
Hemorrhagic stroke	0.12%/y	P<0.001	0.10%/y	P<0.001	0.38%/y
Mortality	3.75%/y	P=0.130	3.65%/y	P=0.051	4.13%/y

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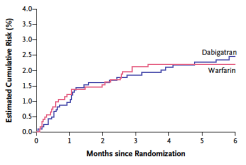
Dabigatran RE-Cover Trial 2009
Venous Thromboembolism



Shulman S, Kearon C, Kakkar AK. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. NEJM 2009;361:2342–52.

"Re-Cover" 1274 VTE patients	Dabigatran 150 mg BID	Coumadin	Significance v. Coumadin
VTE recurrence	2.4%/6 m	2.1%/6 m	P<0.001 (non-inferiority)
Major bleeds	1.6%/6 m	1.9%/6 m	NS
All bleeds	16.1%/6 m	21.9%/6 m	NS
Adverse events	9.0%/6 m	6.8%/6 m	P=0.05

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Dabigatran Risks: Meta-analysis

- 256 Pradaxa-related deaths since 2009
- Two studies of stroke prophylaxis in AF
- Four studies in VTE
- One in acute coronary syndrome (ACS)

Seven-trial meta-analysis, including RE-LY, 30,514 subjects	Dabigatran: 110 or 150 mg BID	Control: Coumadin, enoxaparin, or placebo	Significance
Overall ACS	237/20,000 (1.2%)	83/10,514 (0.79%)	OR 1.33, P=0.03*
RE-LY alone			OR 1.27, p=0.05*
*Not significant at P<0.01			

Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012;172:397–402.

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Summary of Dabigatran Risks

- Bleeds are equivalent to Coumadin
  - Hard to ID dabigatran in ED bleed
  - Reverse?: charcoal, rFVIIa?, FEIBA?, FFP?, dialysis
- Pradaxa should be used at lower doses for >75 y/o or those with GFR <30 mL/m. Not recommended for GFR <15 mL/m.
- John Smith, MD, Boehringer Ingelheim VP questions Uchino study. Smith notes that a recent manufacturer-funded study found that the increase in heart attacks with Pradaxa is not large enough to be scientifically meaningful. But more important, he says, is that even the authors of the current study find Pradaxa's benefits to outweigh its risks.

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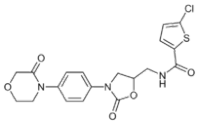
Rivaroxaban (Xarelto®)

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



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, clot-bound, and IXa-bound Xa
  - Interacts with no other serine proteases
- Excretion: 66% renal, 28% fecal (liver)
- Monitoring: renal, hepatic disease, obesity, cancer
  - No PT or PTT: insensitive and vary by reagent formulation
  - Hep-test, PiCT may monitor with incubation time modifications
  - Chromogenic anti-Xa: variability among formulations
  - Xa neutralization: see next slide
- FDA-cleared for VTE prophylaxis 7.1.11
  - Canada and EU 5.2009
- FDA-cleared for stroke prevention in AF 11.4.11

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 inhibits Xa independent of AT

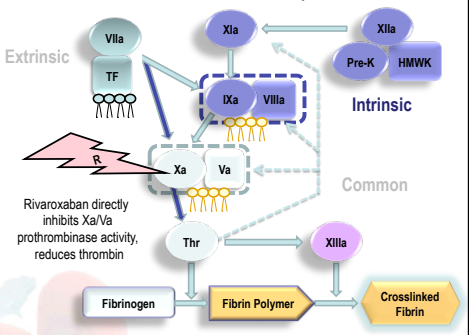

Figure courtesy of Margaret G. Fritsma

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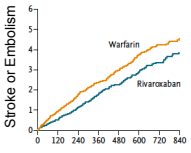
"Riva" ROCKET-AF Trial 2011
Atrial Fibrillation



Patel MR, Mahaffey KW, Garg J. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. NEJM 2011;365:883–91

"ROCKET-AF" 14,264 AF patients	Riva 20 mg/d	Coumadin 2.5 INR	Significance v. Coumadin
Stroke or systemic embolism	1.7%/y	2.2%/y	P<0.001 (non-inferiority)
Major and minor bleed	14.9%/y	14.5%/y	P=0.44
Intracranial hemorrhage	0.5%/y	0.7%/y	P=0.02
Fatal bleed	0.2%/y	0.5%/y	P=0.003

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Apixaban in Hip/Knee VTE Prophylaxis

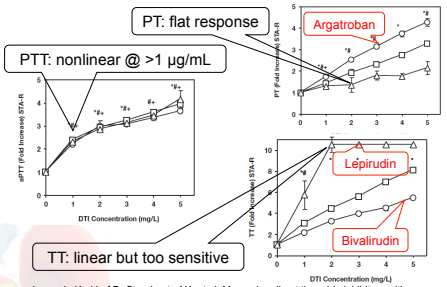
- 2.5 mg twice a day
  - Hip: 32–38 days, knee: 10–14 days
- Cleared 5.20.2011 for VTE Rx in EU
  - FDA clearance for VTE is imminent in US

ADVANCE-2 3057 TKR patients	Apixiban: 2.5 mg BID 14 d	Enoxaparin: 40 mg SC/d 14 d	Significance v. enoxaparin
Composite of VTE including death	15%	24%	OR 9.3 P<0.001
All bleeding	4%	5%	NS

- Apixiban or rivaroxaban in early acute coronary syndrome trials with ASA and clopidogrel improve outcomes (AHA, 11.11.11, not shown)

Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement: a randomised double-blind trial. Lancet 2010: 375: 807–15.

Monitoring DTIs Using Routine Assays
(new slide not in handout)



Curvers J, van de Kerkhof D, Stroobants AK, et al. Measuring direct thrombin inhibitors with routine and dedicated coagulation assays. Am J Clin Pathol 2012; 138: 551–8.

The Fritsma Factor 55

How to Monitor (All are RUO)

- Centerchem® Pefakit® Prothrombinase-induced clot time: direct anti-Xa *and* DTI
- BIOPHEN DiXal® chromogenic anti-Xa
- Stago chromogenic anti-Xa
  - Calibrators and controls
- Stago ecarin clotting and chromogenic assays: DTIs
- BIOPHEN thrombin inhibition assay: DTI
- Helena Cascade Abrazo DTM

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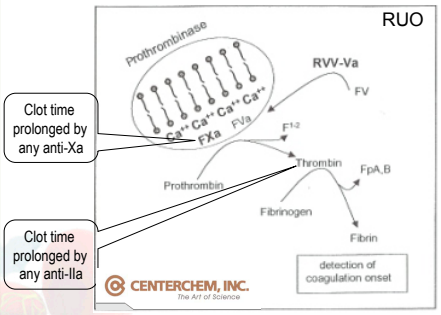
Pentapharm® Pefakit®
Prothrombinase-induced Clot Time (PiCT)

RUO



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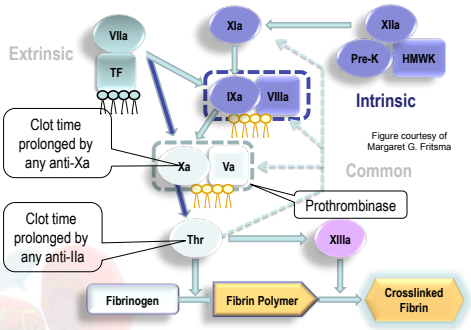
PiCT

RUO

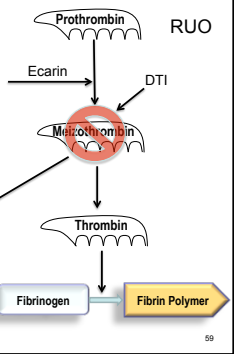


The Fritsma Factor

Ecarin Clotting Time/Chromogenic

Saw-scale Viper: Echis carinatus

RUO



Stago Ecarin Chromogenic Assay®
Intensity at 405 nm is inversely proportional to DTI concentration

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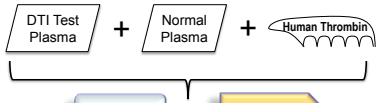
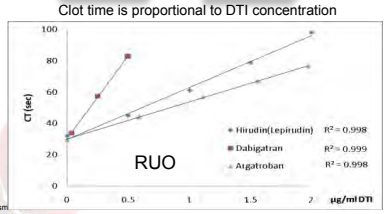
BIOPHEN Hemoclot® Thrombin Inhibitors
("dilute thrombin time")



Clot time is proportional to DTI concentration



The Fritsm 60