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Measuring Direct Oral Anticoagulants (DOACs)

Whatever Happened to the PT and PTT?

George A Fritsma MS, MLS
The Fritsma Factor, Your interactive Hemostasis Resource
www.fritsmafactor.com

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Bottom Line at the Start (BLATS)

- Monitor Coumadin (1954)
- Monitor unfractionated heparin (1936)
- Measure intravenous Xa inhibitors: low molecular weight heparin (1996), fondaparinux (2003)
- Measure oral Xa inhibitors: rivaroxaban (2011), apixaban (2012), edoxaban (2015), betrixaban (Phase III)
- Measure oral direct thrombin inhibitor dabigatran (2010)
- Anticoagulant reversal agents

Baglin T, Hillarp A, Tripodi A, et al. Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the SSC of the ISTH. J Thromb Haemost 2013;11:756–60.

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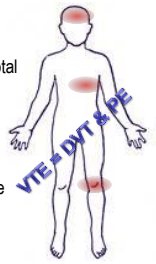
Indications for Anticoagulant Therapy

- Rx to prevent recurrence of venous thromboembolism (VTE)
- Prophylaxis to prevent VTE in medical patients and after orthopedic surgery: total hip and knee replacement (THR, TKR)
- Ischemic stroke prevention in prosthetic heart valves and in non-valvular atrial fib (NVAF, "AFIB")
- Acute coronary syndromes (ACS): acute myocardial infarction, peripheral artery obstruction, ischemic stroke, cardiac insufficiency



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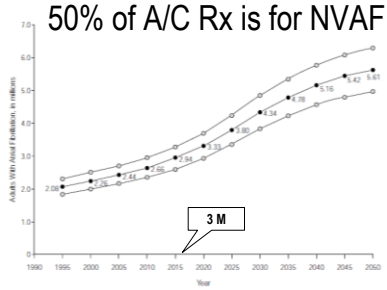
NVAF Prevalence Projections 50% of A/C Rx is for NVAF



Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370–75.

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Venous Thromboembolism

- 23,000,000 US residents/y have high risk surgery; ~20% acquire deep venous thrombosis (DVT)
- 1,000,000 USA residents/y acquire VTE as inpatients or 30d post hospitalization
- A 400-bed hospital will document 200 hospital-acquired VTEs/y, 50% preventable
- Pulmonary emboli (PE) are the most common cause of preventable death, fatality rate 15%
- Traditional and new oral A/Cs play large role in effective prevention and treatment of VTE
  - Anticoagulant drug prophylaxis reduces VTEs 30–65%
- 58% of eligible patients receive anticoagulant

US Dept of HHS Agency for Healthcare Research and Quality
http://www.ahrq.gov/qual/vtguide/vtguideapa.htm accessed 10/19/14

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DOACs: "The Girls"

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US FDA-Cleared DOACs

DOAC	Prevent stroke in NVAF	Prevent VTE post TKR & THR	Treat, prevent 2° VTE
Dabigatran Pradaxa®	2010	2014	2014
Rivaroxaban Xarelto®	2011	2011	2012
Apixaban Eliquis®	2012	2014	2014
Edoxaban Savaysa®	2015	2015	2015
Betrixaban	Phase III, non-significant results		

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Why Measure Fonda, LMWH or DOACs?

- Renal disease, CrCl (GFR, eGFR) <30 mL/m
- Noncompliance or underdosing
- Screening for co-medication interference
- Determining cause of acute hemorrhage
  - ER or surgery
  - To identify anticoagulant or monitor its reversal
- Bridging from one anticoagulant to another

Monitor or Measure?

Measure, but no dose adjustment except in renal disease

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Why Measure Fonda, LMWH & DOACs?

- Discontinuation before surgery
- Resumption of anticoagulation after surgery
- Unstable coagulation: pregnancy, liver disease, renal disease, malignancy, DIC
- Patients >75 YO (excluded from clinical trials)
- Patients with marginal fluid compartment (excluded from clinical trials)
  - >150 kg: proportionally reduced plasma volume
  - <40 kg or ped: proportionally increased plasma volume
- Confirm and monitor A/C reversal

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Coumadin

warfarin
Coumarin
warfarin Sodium
dicumarol
Warfilone
Miradon
Sintrom
acenocoumarol
Anisindione
DB00266

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Coumadin Indications

- Cardiac insufficiency in ACS, ejection fraction <30%
- NVAF to prevent ischemic stroke
- Prosthetic heart valves
- VTE: DVT and PE

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Coumadin Limitations

- >80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway
- Diet supplies vitamin K and reduce efficacy
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba and glucosamine, parenteral nutrition formulations
- Coumadin overdose is most common reason for hemorrhage-related ER visits
  - Reversal with VK requires 6–10 hours
  - Improved with Kcentra (Beriplex) 4-factor prothrombin complex concentrate
- Coumadin allergy with anaphylaxis

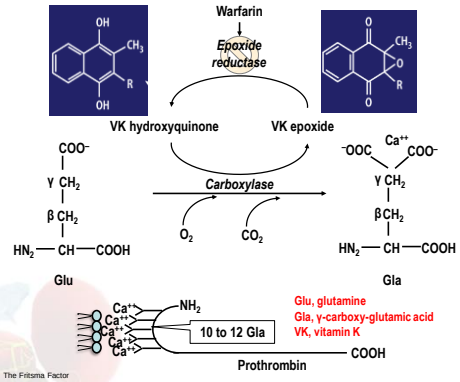
Coumadin Dosage Anomalies

- Coumadin receptor insufficiency
  - Require dosages of 25 mg/d or more
  - CYP4F2 variant raises dosage 1 mg/d (Feb 08)
- Polymorphisms raise sensitivity
  - CYP2C9*2 and CYP2C9*3, VKORC1:

VKORC1 Genotypes	Cytochrome Oxidase Pathway (CYP) 2C9 Genotypes					
	*1*1 (WT)	*1*2	*1*3	*2*2	*2*3	*3*3
GG (wild-type)	5–7*	5–7	3–4	3–4	3–4	0.5–2
AG	5–7	3–4	3–4	0.5–2	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

*mg/day Coumadin

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



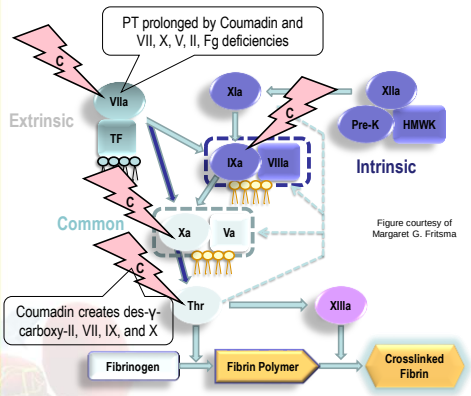


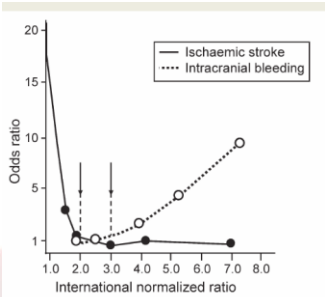
Figure courtesy of Margaret G. Fritsma

Coumadin Dose & Pharmacodynamics

- Start @ 5 mg/d, adjust to PT-based international normalized ratio (INR) 2–3
  - When over 70 yo, start @ 2 mg/d
  - Onset 8−12 hours
- Requires 4−5 days to stabilize
- Daily PTs until consecutive INRs match in Rx range
- Then two PT-INRs/w for two weeks
  - Confirm stability
- Then PT-INRs every 4–12 (?) weeks

Witt DM. Approaches to optimal dosing of vitamin K antagonists. Semin Thromb Hemost 2012;38:667–72.

Coumadin Therapeutic Window

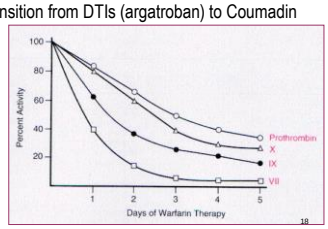


Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2008;29:155–65

Is the PT/INR All it Could Be?

- Inter-platform variation
- INR invalid in first five days of therapy
- Optical coagulometers affected by lipemia
- PT falsely prolonged by lupus anticoagulant
- POC INR internally adjusted to match plasma INR
- INR invalid in transition from DTIs (argatroban) to Coumadin

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



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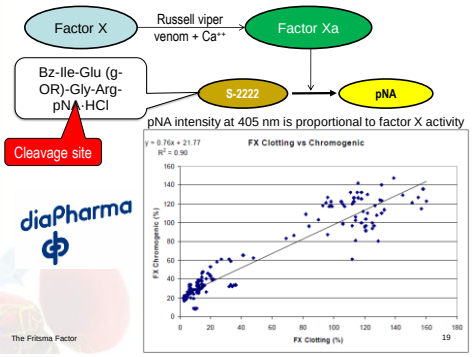
Chromogenic Factor X (CFX)



diaPharma

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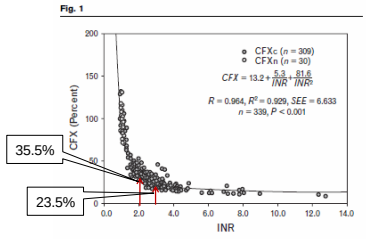
CFX In Place of PT/INR?



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;19:513–17.

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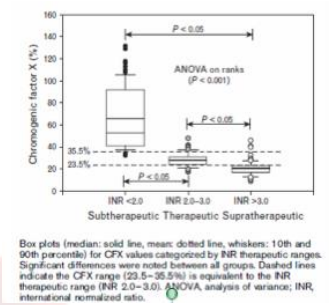
CFX in Place of PT/INR?



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.

"Data suggest the CFX can be a useful tool for monitoring VKA when INR confounders are present."

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CFX Resolves INR Affected by LAC

- INR & CFX assayed in 44 control Coumadin patients and 46 LA patients on Coumadin
  - All 90 subjects were in CFX Rx range: 22–40%
- 4 (9%) control Coumadin Pts 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.
Rosborough TK1, 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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Current ISTH Recommendations

CFX could be used instead of the PT-INR as this method is unaffected by LA. However, there is no evidence from clinical trials that the CFX is effective and safe in monitoring VKA patients. Further, although there is a linear relationship between factor X activity and the PT-INR in patients on VKA, the precise therapeutic interval based on factor X is still unknown.

Tripodi A, de Laat B, Wahl D, et al, for the Subcommittees on Control of Anticoagulation and on Lupus Anticoagulant/Antiphospholipid Antibodies. Monitoring patients with the lupus anticoagulant while treated with vitamin K antagonists: communication from the SSC of the ISTH. J Thromb Hemostas 2016, Pre-publication, doi: 10.1111/jth.13481

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Current ISTH Recommendations

1. The PT-INR measured with the vast majority of commercial thromboplastins can be safely used to monitor LA-positive patients on VKA, keeping in mind that there may be occasional patients for whom the INR is affected by LA.
2. New thromboplastins, especially those based on recombinant relipidated tissue factor, should be checked for their sensitivity to LA before they are used to monitor VKA in LA-positive patients.
3. Whenever possible the PT should be measured with the local thromboplastin before starting VKA. If the PT is beyond the upper limit of the reference range it is likely that the local thromboplastin and therefore the PT-INR following VKA will be affected by LA. Alternative LA-insensitive thromboplastins should be used.

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Current ISTH Recommendations

4. If the baseline PT is within the reference range, the local thromboplastin can be safely used to monitor LA-positive patients, provided that an instrument-specific ISI has been determined according to WHO recommendations.
5. The so-called "combined" thromboplastins can be used instead of the "plain" thromboplastins if an instrument-specific ISI is available, keeping in mind there is no strong and independent evidence that they work in this context.
6. The INR measured with POC devices could be variably affected by the LA. Unless information on specific evaluation is provided, INR results from POC in patients with LA should be interpreted with caution.

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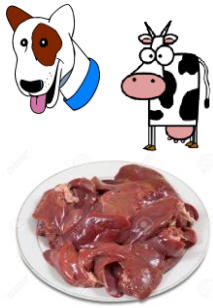
Heparin

- heparin sodium
- unfractionated heparin (UFH)
- standard heparin
- heparin systemic



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50 YO Man with Bilateral PE

- Obese, sedentary, swollen ankle, short of breath
- Unfractionated heparin (UFH) Rx two days
  - Bolus: 5000–10,000 units or 80 U/kg to prevent 2° thrombosis
  - Maintenance: 1600 U/hour or 18 U/kg/h, >30,000/24 h minimum
  - Switched to LMWH twice a day
- UFH history
  - **Jay MacLean**, med student at Johns Hopkins 1916
    - Isolated from dog liver and described anticoagulant property
    - **William Howell** lab, Howell named it heparin
  - Trials 1935, Karolinska Institut, Stockholm, Vitrum AB
    - FDA-cleared 1936 (first ever)
- Also used in coronary artery bypass graft

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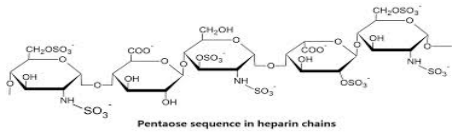
UFH: Crude Extract of Porcine Mucosal Mast Cell Secretion

Unbranched highly sulfated mucopolysaccharide glycosaminoglycan



Pentaose sequence in heparin chains

Heparin from porcine digestive mucosa

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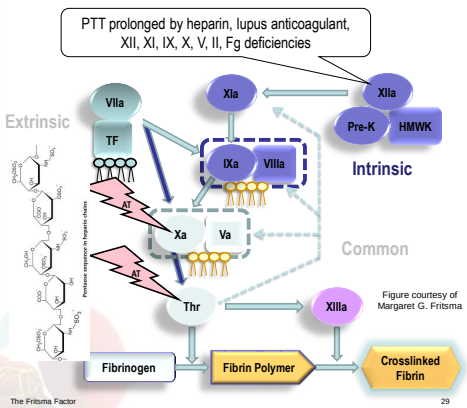

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Monitoring UFH Therapy with the PTT Standard VTE Schedule

- Perform "baseline" PTT to r/o factor deficiency, inhibitors, lupus anticoagulant (LAC)
  - 1–3% have baseline PTT >upper limit of RI: alternative?
- Initiate therapy: bolus + continuous infusion
- At least 4–6 h after bolus, but not >24 h, collect & perform second PTT
- Adjust dose to PTT therapeutic range
  - Lab-published range: *ex vivo* curve, not *in vitro* curve
  - *Formerly* 1.5–2.5 x mean of normal range
- Schedule generalized to post-CABG therapy

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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UFH Rx Range Using the PTT Normalized to Anti-Xa
The "Brill-Edwards" Curve

- Collect 20–30 specimens from pts on UFH
  - No Coumadin, PT normal
  - No more than 10% repeat specimens from single patient
  - Representative of demographics race, sex, age
- Collect 10 normals
- Assay PTT and chromogenic anti-Xa
- Graph paired results
- Select PTT limits in seconds that equals 0.3–0.7 chromogenic Xa heparin units

Marlar RA, Gausman J. The optimum number and type of plasma samples necessary for an accurate activated partial thromboplastin time-based heparin therapeutic range. Arch Pathol Lab Med 2013;137:77–82

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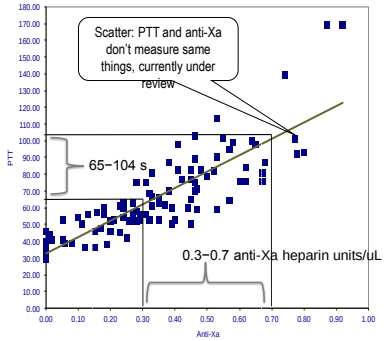
HEPARIN THERAPEUTIC RANGE



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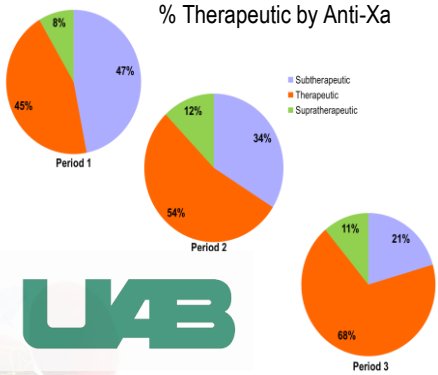
% Therapeutic by Anti-Xa



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Why Monitor UFH Therapy?

- Several 1990s studies showed that VTE inpatients treated with an initial bolus of 5000 U and continuous IV of >30,000 U/d, risk of 2° thrombosis was 6.3% independent of PTT results.
- Anand et al, OASIS-II, showed bleeding incidence increased 7% for every 10 seconds PTT is prolonged
  - However, trauma, age, comorbidity, and simultaneous coagulopathies have greater effects.

Anand SS, Ginsberg JS, Kearon C, et al. The relation between the activated partial thromboplastin time response and recurrence in patients with venous thrombosis treated with continuous intravenous heparin. Arch Inter Med 1996;156:1589–95.
Anand SS, Yusuf S, Pogue J, et al. Relationship of activated partial thromboplastin time to coronary events and bleeding in patients with acute coronary syndromes who receive heparin. Circulation 2003: 107:2884–8.

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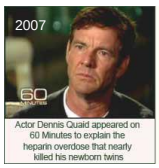
Joint Commission Requires Monitoring

- National Patient Safety Goals, 2008
  - Must monitor Coumadin, UFH and LMWH
  - Reduce iatrogenic adverse events
  - Methods not specified
- Why monitor?
  - UFH used in inpatients with comorbidities
  - UFH pharmacokinetics complex and dose-response uncertain
  - High prevalence of UFH medication errors



Actor Dennis Quaid appeared on 60 Minutes to explain the heparin overdose that nearly killed his newborn twins

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PTT UFH Monitoring Limitations

- Antithrombin deficiency or consumption renders PTT non-responsive, "heparin resistance"
- Elevated FVIII renders PTT insensitive
- Lupus anticoagulant in 1–3% of unselected subjects prolongs baseline PTT, renders PTT more sensitive
- Coagulopathy & factor inhibitor prolong baseline PTT
- Simultaneous Coumadin renders PTT more sensitive
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot
- Many reagents with variant formulations and no normalization, the Brill-Edwards doesn't really help
- Pre-analytical variables; lipemia, icterus, and hemolysis

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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Anti-Xa UFH Monitoring Limitations

- More expensive (but fewer adverse events)
- Interpretation unfamiliar to docs & nurses
- Antithrombin deficiency or consumption renders anti-Xa non-responsive (considered desirable by most)
- Interference by icterus, lipemia, and hemolysis
- Less reproducible than PTT on CAP surveys
  - When PTT reagent use is a single lot from a single manufacturer
- The anti-Xa and PTT do not measure the same thing

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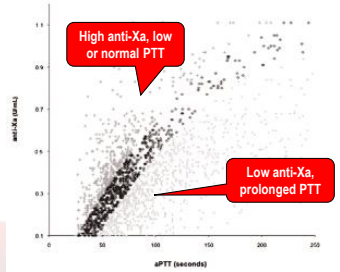
PTT/anti-Xa Discordance



Price EA, Jin J, Nguyen H, Krishnan G, Bowen R, Zehnder JL. Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. Annal Pharmacol 2013;47:151–8.

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Discordant PTT and Anti-Xa Values

- 42% with anti-Xa in Rx range and PTT above Rx range
- Most were on simultaneous Coumadin
- Elevated risk of major bleed and death

2321 paired values from 539 patients	2 consecutive long PTT versus in-range anti-Xa n = 163	Long PTT versus in-range anti-Xa n = 85	PTT and in-range anti-Xa concordant n=112
Major bleed in 21 d	15 (9%) p = .03	5 (6%)	3 (3%)
2° thrombotic event in 21 d	9 (6%)	3 (4%)	2 (2%)
Death in 30 d	23 (14%) p = .02	18 (21%) p = .0008	6 (5%)

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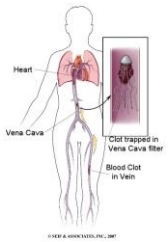
Outcome Recommendation

- Perform first 3 UFH assays w/ both anti-Xa and PTT
- If PTT > anti-Xa, high risk
- Use lower target range; e.g., anti-Xa 0.3–0.5 units
- Discontinue UFH, revert to vena caval filter



Zehnder J, Price E, Jin J. Controversies in heparin monitoring. Am J Hematol 2012;87:S137–40.

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Low Molecular Weight Heparin

- enoxaparin
- Lovenox
- dalteparin
- Fragmin
- tinzaparin
- Innohep

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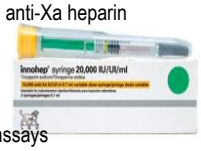
Low Molecular Weight Heparin

- Bridging to Coumadin therapy
- Hip or knee: 50% risk of DVT if no anticoagulant
  - Start 6 h after surgery
- Lovenox® 30 mg/300 uL SQ 12 hours 7−10 days
  - Therapeutic level 30" post-SQ; half-life 4 hours
- MW 2000−10,000 D, mean 5000 D
  - 13−22 saccharide units, mean 15
- Fixed dose-response relationship: no monitoring
- HIT rate 1% of UFH in de-novo Rx

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

Monitoring LMWH

- Monitor using chromogenic anti-Xa heparin
  - PTT insensitive
  - Collect 4 hours after injection
  - Therapeutic: 0.5−1 units/mL
  - Prophylaxis: 0.1−0.4 units/mL
- Periodic serum creatinine assays
  - D/C if creatinine >2.0 mg/dL or GFR <50 mL/min
- Regular CBCs, monitor platelet count
- Regular stool for occult bloods

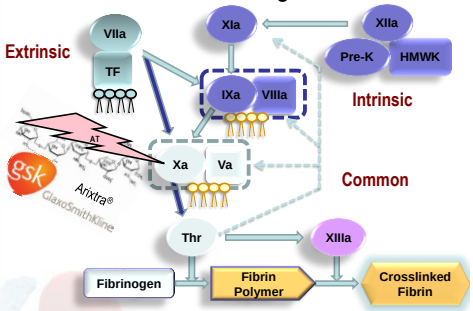


Arixtra

Parenteral Synthetic Pentasaccharide Fondaparinux (Fonda)

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

Fonda Functions Through Antithrombin



- Sulfate side-chains critical to high-affinity irreversible AT binding
- AT/fonda raises Xa affinity 300X
- No affinity for thrombin or other serine proteases

Figure courtesy of Margaret G. Fritsma

Measuring Fonda

- Fonda: 2.5 mg subcutaneous injection
  - Therapeutic range: 0.60–1.50 mg/L
  - Prophylactic range: 0.10–0.50 mg/L
  - Discontinue if creatinine >2.0 mg/dL or GFR <30 mL/min
- Anti-Xa chromogenic heparin assay
  - Collect 3 h after injection
  - Requires fonda calibrators and controls
  - PTT insensitive to fonda
- Regular CBCs, monitor platelet count, stool for blood

Fonda Advantages

ONCE-DAILY Arixtra (fondaparinux sodium) for injection

- Half-life 17 h; one SC 2.5 mg injection/24 h
- 50% reduction of venographic DVT
- Frequency of repeat DVT 11 days after surgery 6.8%, 13.7% for LMWH ($p=10^{-17}$)
- Fatal arterial or venous thromboembolic events 1% at day 49, same as LMWH

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 & Contraindications

- Risk of major bleed 2.7%, versus LMWH 1.7%
- Overdose: no direct reversal, 17 h half-life
- Cost exceeds LMWH by 50%
  - Offset by reduced adverse event costs
- Renal disease: contraindicated if GFR <30 mL/m
- Weight <50 kg excluded from clinical trials
- >75-YO excluded from clinical trials
- Bleeding Hx: contraindicated if…
  - Congenital or acquired coagulopathies
  - Ulcerative gastrointestinal disease, hemorrhagic stroke

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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Chromogenic Anti-Xa Heparin Curve

- Hybrid curve for UFH and LMWH
- Additional LMWH formulations: Tinzaparin
  - Aventis 5/1/09 Lovenox patent expired
- Curve for fonda requires calibrators and controls
  - Separate, mg/dL, not international units

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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Rivaroxaban (Riva)—Xarelto

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Riva, PIxi, Edi, Trixi Inhibit Xa Directly

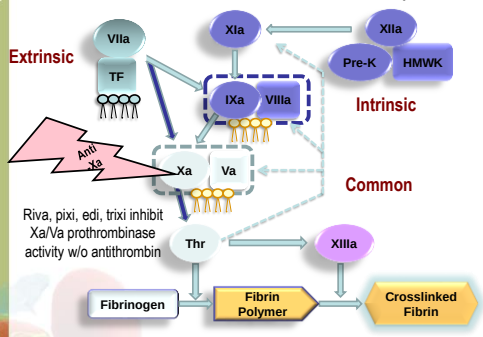

Figure courtesy of Margaret G. Fritsma

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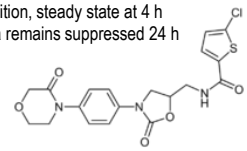
ROCKET AF Clinical Trial

- 83 trials; ROCKET AF results primary but questionable
- Excretion: 66% renal, 28% hepatic
- Stoichiometric inhibition, steady state at 4 h
- Half-life 12 h but Xa remains suppressed 24 h



Oxazolininone-derived oral direct Xa inhibitor peptidomimetic, < 500 daltons

(S)-5-chloro-N-[[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]oxazolidin-5-yl]methyl} thiophene-2-carboxamide

Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365:883–91.
Cohen D. Rivaroxaban: can we trust the evidence? BMJ. 2016 ;352: i575

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Riva Indications and Dosages

- 10 mg/d for VTE prophylaxis post TKR, THR
- 15 mg/bid to prevent 2°event post DVT or PE
- 20 mg/d stroke prophylaxis in NVAF
- 10 mg/d to prevent 2° event in ACS
  - Dosed with dual antiplatelet therapy
  - FDA-*deferred*, 3-4-13 (10 mg): doubled bleeding risk
  - Approved 3-22-13 by EMA @ 2.5 mg/d
- APPRAISE trial: 2.5 & 5 mg/d
  - Effective, but bleeding events doubled

janssen

Xarelto rivaroxaban

Laux V, Perzborn E, Kubitza D, Misselwitz F. Preclinical and clinical characteristics of rivaroxaban: A novel, oral, direct factor Xa inhibitor. Semin Thromb Hemost 2007;33:5115–23.
Tripodi A, Chantarangkul V, Guinet C, Samama MM. The international normalized ratio calibrated for rivaroxaban has the potential to normalize prothrombin time results for rivaroxaban-treated patients: results of an in vitro study. J Thromb Haemost. 2011;9:226-8.

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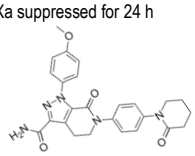
Oral Apixaban ("Pixi")

- 28 trials: ADVANCE 1,2,&3, ADOPT, APROPOS, ARISTOTLE
- Renal excretion 30%, hepatic/intestinal 70%
- Stoichiometric inhibition, steady state at 4 h
- Half-life 12 h, Xa suppressed for 24 h

Bristol-Myers Squibb



Eliquis (apixaban) tablets

Pfizer

Oxazolidinone-derived oral direct Xa inhibitor peptidomimetic, < 500 daltons

1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5-dihydropyrazolo[5,4-c] pyridine-3-carboxamide

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ARISTOTLE: Pixi

- Compared to Coumadin at 2.5 mg BID…
  - Reduced NVAF stroke & embolism 21% (p<0.01)
  - 31% fewer intracranial bleeds (p<0.001)
  - 11% lower mortality (p=0.047)
  - Lower discontinuance rate
- VTE Rx: THR: 32–38 days; TKR: 10–14 days
- Off-label recommendation for antiphospholipid syndrome

Woller SC, Stevens SM, Kaplan DA, et al. Apixaban for the secondary prevention of thrombosis among patients with antiphospholipid syndrome: study rationale and design (ASTRO-APS). Clin Appl Thromb Hemost. 2016;22:239–47.

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Oral Edoxaban ("Edi")

FDA-approved 2015 for NVAF with warning that it is less effective when CrCl >95 mL/minute (healthy kidneys)

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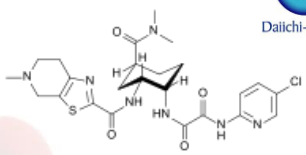
Edoxaban Dose and Pharmacokinetics

- NVAF, VTE Rx: 60 mg/d, 30 if GFR is <50, D/C if GFR is >95
- Reaches therapeutic levels in 1–2 hours
- Half-life 10–14 hours
- Excreted 50% kidney, 50% liver

Daiichi-Sankyo



N'-(5-chloropyridin-2-yl)-N-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-[(5-methyl-6,7-dihydro-4H-[1,3]thiazolo[5,4-c]pyridine-2-carbonyl)amino]cyclohexyl]oxamide

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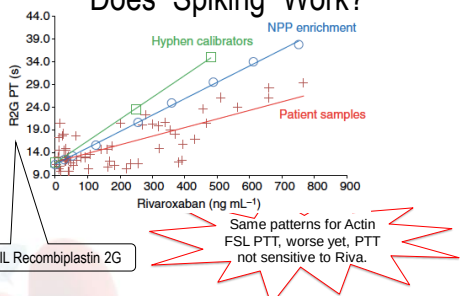
PT for Riva, Pixi, Edi, Trixi Does "Spiking" Work?



Gosselin RC, Adcock DM. The laboratory's 2015 perspective on direct oral anticoagulant testing. J Thromb Haemost 2016; DOI: 10.1111/jth.13266

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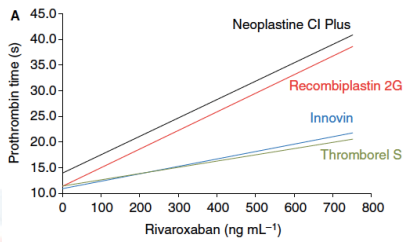
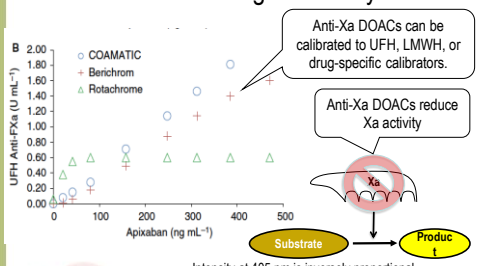
PT for Riva, Pixi, Edi, Trixi Can you use any reagent?



Anti-Xa Chromogenic Assay

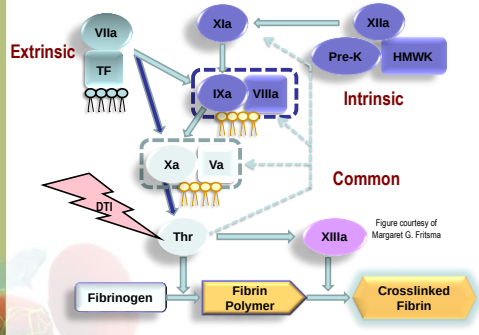


Intensity at 405 nm is inversely proportional to anti-Xa concentration

- Tripodi A. Which test to use to measure the anticoagulant effect of rivaroxaban: the prothrombin time test. J Thromb Haemostas 2013;11:576–8.
- Samama MM. Which test to use to measure the anticoagulant effect of rivaroxaban: the anti-factor Xa assay. J Thromb Haemostas 2013;11:579–80.

Dabigatran (Dabi)

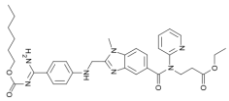
Dabigatran: Direct Thrombin Inhibitor



Oral Dabigatran Etexilate

- 60 trials; RE-LY is the only one FDA used to approve
- First oral anticoagulant since Coumadin, approved in 1952
- 150 mg/bid to prevent NVAF stroke
- Prophylaxis in TKR and THR
- Rx after VTE, but trials based on initial heparin Rx

Boehringer Ingelheim

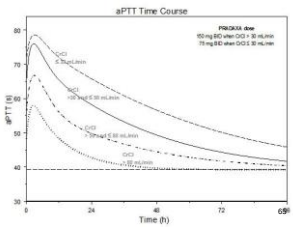


Benzamidine-based prodrug oral direct IIa inhibitor peptidomimetic, < 500 daltons

Ethyl 3-[[2-[[4-[N'-hexyloxycarbonyl carbamimidoyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl] (pyridin-2-yl-amino)propanoate

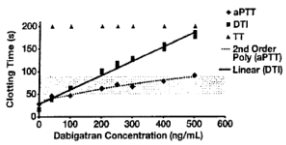
Dabi Pharmacokinetics

- Half-life 12–17 h, >60 h in renal disease
  - Reduce dosage by 50% when GFR < 30 mL/m
- No interaction with food, no liver toxicity
- Levels raised by quinidine and verapamil
- Metabolized by esterase
  - Not CYP450 pathway
- Renal excretion 80%
- Dyspepsia 10%



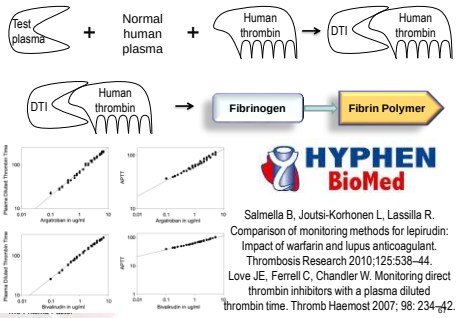
Measuring Dabigatran

- Thrombin time: hypersensitive, qualitative only
  - Normal implies absence, any DTI generates results >>20s
- Plasma-diluted thrombin time
- Ecarin chromogenic assay
- PTT



Avecilla ST, Ferrell C, Chandler WL, Reyes M. Plasma-diluted thrombin time to measure dabigatran concentrations during dabigatran etexilate therapy. Am J Clin Pathol 2012;137:572–4.

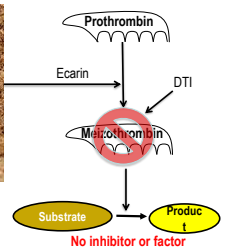
Plasma-Diluted Thrombin Time



Salmella B, Joutsi-Korhonen L, Lassilla R. Comparison of monitoring methods for lepirudin: Impact of warfarin and lupus anticoagulant. Thrombosis Research 2010;125:538–44.
Love JE, Ferrell C, Chandler W. Monitoring direct thrombin inhibitors with a plasma diluted thrombin time. Thromb Haemost 2007; 98: 234–42.

Ecarin Chromogenic Assay (ECA)

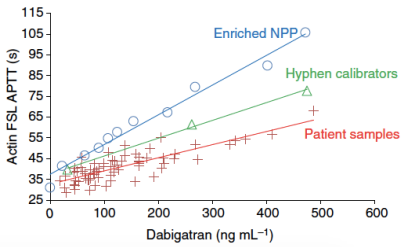
Saw-scale Viper: Echis carinatus



Stago

Chandler W. Assays for antithrombotic drugs. J Thromb Haemostas 2013;11 Suppl 2: ISTH Abstract AS 02

PTT for Dabi
Do spiked plasmas work?



Summary: DOAC Measurement

- Assay choice: stat, routine, point of care
- All are RUO, require therapeutic range data
- PT for anti-Xa's; PTT for DTI's
  - Stopgap: variation among reagents, insensitive
- Standardize collection time: peak and trough
- Dabi: plasma-diluted TT or ECA
- Anti-Xa DOACS use anti-Xa chromogenic
  - Calibrators and controls available for all

Hemorrhage Reversal

- Coumadin overdose: if bleeding…
  - VK 10–20 mg oral or IV; 12–24 h to stop bleeding
  - Simultaneously infuse PCC, APCC, or 4-factor PCC (Kcentra®)
  - Limit APCC to 40 U/kg body weight to avoid thrombosis or DIC
- Heparin overdose
  - Reverse in minutes with protamine sulfate, binds long molecules
- LMWH overdose
  - Protamine binds long but not short molecules, 30–40% effective

Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013 15:625–51
Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. Thromb Haemost 2015;113:931–42

DOAC Hemorrhage Reversal

- Mild bleeding
  - Delay or discontinue next dose, discontinue concurrent medication
- Moderate bleeding
  - Supportive measures: compression, surgical intervention, plasma, RBCs, platelet concentrate if count is <60,000
  - For dabi: Alimentary activated charcoal absorption, maintain diuresis, consider hemodialysis
- Severe, life-threatening hemorrhage
  - Four-factor prothrombin complex concentrate, 25 U/kg, repeat 1–2X
  - Activated prothrombin complex concentrate (FEIBA), 50 U/kg, ≤200/d
  - rFIIa 90 ug/kg, repeat as necessary

Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013 15:625–51

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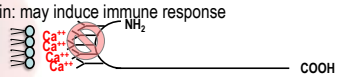
Developing Hemorrhage Reversal
IV Andexanet Alpha; Annexa-A®

- Non-carboxylated Xa—lacks Gla domain, "decoy"
- Variably reverses all anti-Xa DOACs and fonda
- 2m reversal: pixi 93%, edi & riva 50%
- Partially reverses LMWH
- Andexanet limitations
  - Reversal measured using anti-Xa, a surrogate
  - Dosage varies by AC, a limitation if AC not identified
  - Continuous drip required through half-life of AC
  - Protein: may induce immune response

PORTOLA



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Developing Hemorrhage Reversal
idarucizumab—Praxbind

- Human monoclonal Fab fragment binds dabi
  - High affinity, effective sustained reversal in 30 minutes
  - FDA-approved via fast-track 10/15
- Limitations
  - Modest risk of immune response limiting second usage
  - Reversal determined using ECA and DTT, surrogates
  - Hemostatic reversal requires 12 h

Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511–20.

Boehringer Ingelheim

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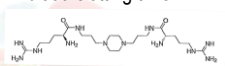
Developing Hemorrhage Reversal
ciraparantag—Aripazine (PER 977)

- D-arginine derivative, non-immunogenic molecule
- Reverses all DOACs, UFH, LMWH, fonda by H_2 bonds
- No interaction with albumin or coagulation factors
- Phase 2 human trial; no adverse events, edi reversal
- Limitations: action mode unclear, how is it so specific?
- Only functional reversal assay is Lee-White whole blood clotting time



Perosphere
The Rescue Drug Company™

Ansell JE, Bakhru SH, Laulicht BE, et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014; 371:214–42

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DOACs: What is Left to Do?

- Reduce risk of ICH by 50% compared to Coumadin
- GI bleed rate equals Coumadin
- Require no monitoring, occasional measurement
- Developing specific reversal agents
- No effective means for lab identification
- No FDA-approved specific assays

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Bottom Line at the End (BLATE)

- Monitor Coumadin (1954)
- Monitor unfractionated heparin (1936)
- Measure intravenous Xa inhibitors: low molecular weight heparin (1996), fondaparinux (2003)
- Measure oral Xa inhibitors: rivaroxaban (2011), apixaban (2012), edoxaban (2015), betrixaban (Phase III)
- Measure oral direct thrombin inhibitor dabigatran (2010)
- Anticoagulant reversal agents

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