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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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Objectives

- 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 (in trials)
- Measure intravenous direct thrombin inhibitors argatroban (1997), bivalirudin (2000)
- 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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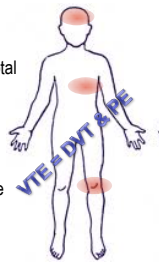
Indications for Anticoagulant Therapy

- 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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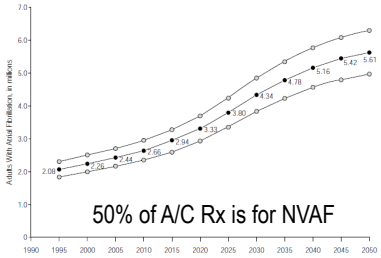
NVAF Prevalence Projections



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 USA 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
- Traditional and new oral A/Cs play large role in effective prevention and treatment of VTE
  - Anticoagulant drug prophylaxis reduces VTEs 50–65%
- We need more clinical guidelines

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	Stroke prophylaxis in NVAF	TKR & THR prophylaxis	Post-VTE treatment
Dabigatran Pradaxa®	2010	2014	2014
Rivaroxaban Xarelto®	2011	2011	2012
Apixaban Eliquis®	2012	2014	2014
Edoxaban Savaysa®	2015	2015	2015

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Why Measure Fonda, LMWH or DOACs?

- Renal disease with CrCl (GFR) <30 mL/min
- 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 LMWH & DOACs? (More)

- 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

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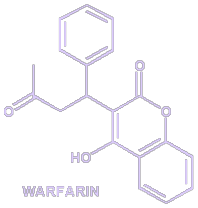
Coumadin Indications

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



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Coumadin 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.

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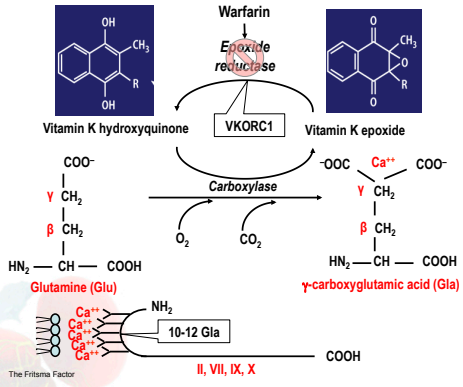

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Coumadin Limitations

- >80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway
- Diet supplies vitamin K and reduces efficacy
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba and glucosamine, parenteral nutrition formulations (TPN, but must be individually formulated)
- Coumadin (and now DOAC) overdose is most common reason for hemorrhage-related ER visits
- Reversal with VK requires 12–24 h
  - Immediate with Kcentra (Beriplex) 4-factor prothrombin complex concentrate (PCC)
- Coumadin allergy with anaphylaxis

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Coumadin Dosage Anomalies

- Coumadin receptor insufficiency
  - Require dosages of 25 mg/d or more
  - CYP4F2 variant raises dose 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.

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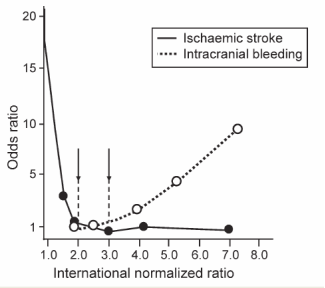
Coumadin Therapeutic Window



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

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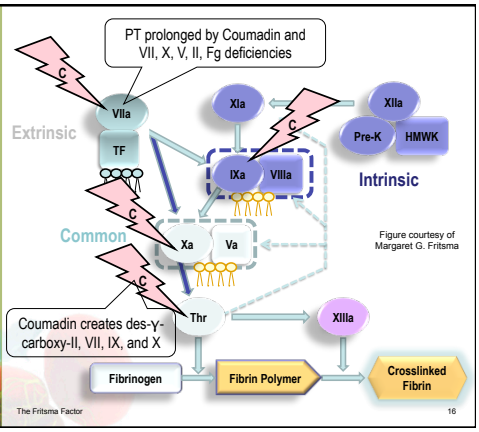

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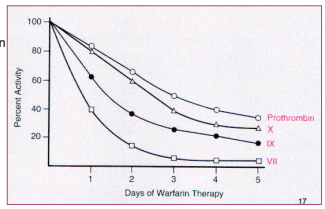
Is the PT/INR All it Could Be?

- INR invalid in first five days of therapy
- Optical coagulometers affected by lipemia
- PT 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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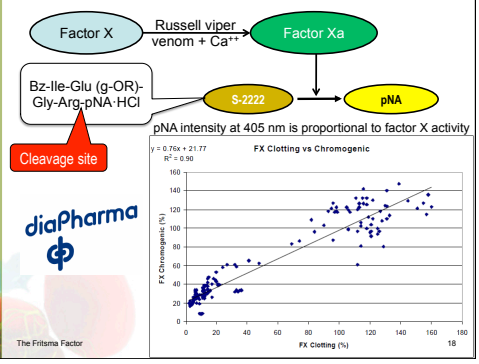
Chromogenic Factor X (CFX)



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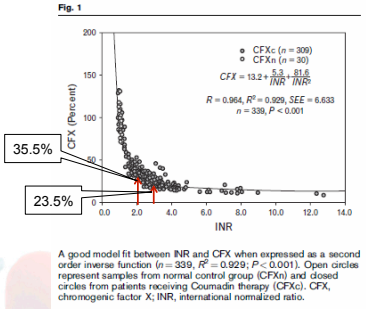
CFX In Place of PT/INR?



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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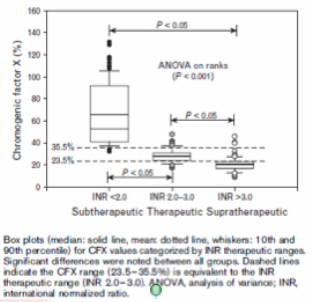
CFX in Place of PT/INR?



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 and INR Affected by Lupus Anticoagulant

- 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.

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50 YO Man with Bilateral PE

- Overweight, sedentary, swollen ankle, shortness 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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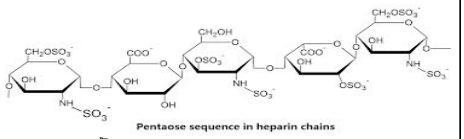
UFH: Crude Extract of Porcine Mucosal Mast Cell Secretion

Unbranched highly sulfated mucopolysaccharide glycosaminoglycan



Pentaose sequence in heparin chains

Heparin from porcine digestive mucosa

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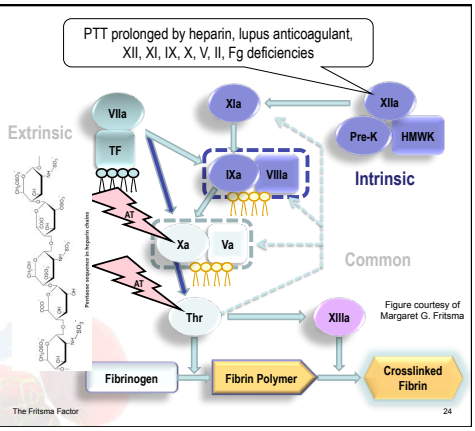

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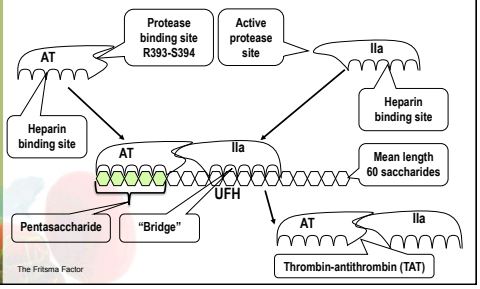
UFH Suppresses Thrombin

UFH binds antithrombin (AT) and thrombin (IIa), neutralizes IIa by allostery and co-localization



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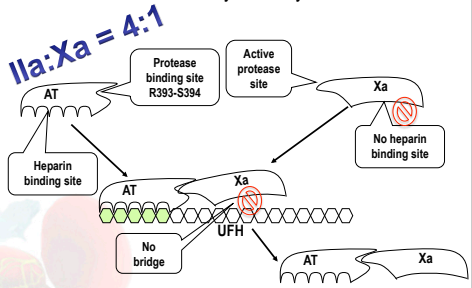
UFH Suppresses Xa

UFH binds antithrombin (AT) and Xa neutralizes Xa by allostery alone



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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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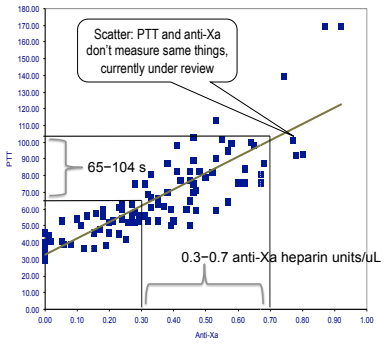
HEPARIN THERAPEUTIC RANGE



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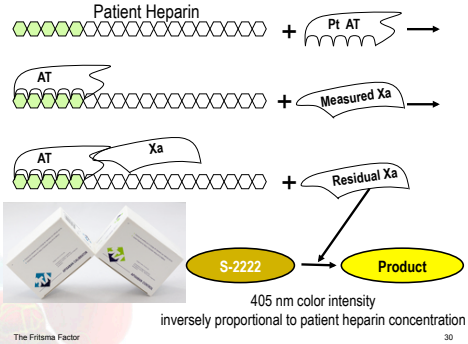
Chromogenic Anti-Xa Heparin Assay



405 nm color intensity
inversely proportional to patient heparin concentration

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Conversion to Anti-Xa Monitoring

- April–June, 2013: 165 patients
- % of patients in Rx range:
  - PTT 38% versus Anti-Xa: 54%
  - 85% of Pts on protocol for VTE: cardiac, neurology
- 45% disagreement between PTT and anti-Xa
- June–Aug, 2013; 171 patients
- % of patients in Rx range: 68%
  - 11 % > 0.7 U/mL
  - 90% on appropriate protocol for VTE: cardiac, neuro
  - 20 ± 2 hours from UFH start time

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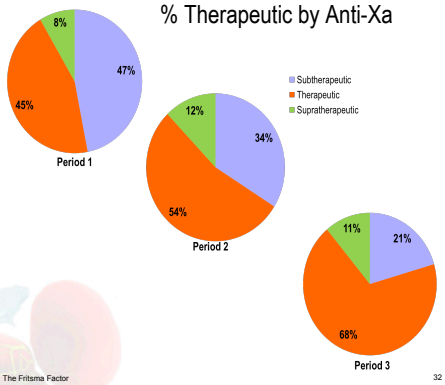
% Therapeutic by Anti-Xa



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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

Heparin doses now color-coded

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 Limitations in UFH Monitoring

- 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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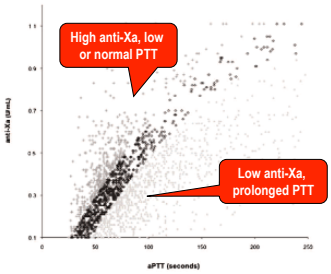
PTT/anti-Xa Discordance



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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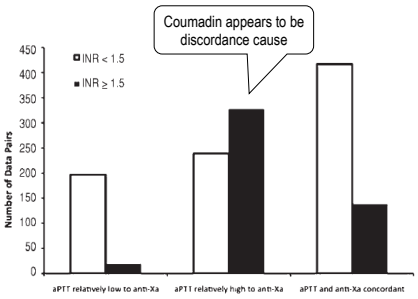
PTT/anti-Xa Discordance and INR



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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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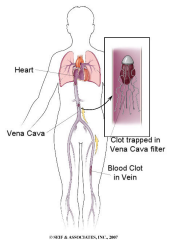
Outcome Recommendation

- 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

- 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

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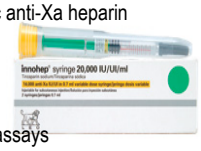
Monitoring LMWH

- 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

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Parenteral Synthetic Pentasaccharide Fondaparinux (Fonda)

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

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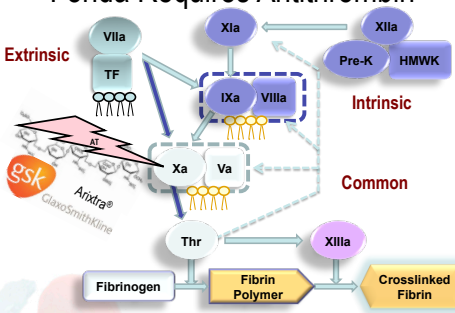
Fonda Requires Antithrombin



- 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

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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

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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 GFRI <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

ONCE-DAILY Arixtra (fondaparinux sodium) for injection

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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Riva, PIxi, Edi, Trixi Directly Inhibit Xa

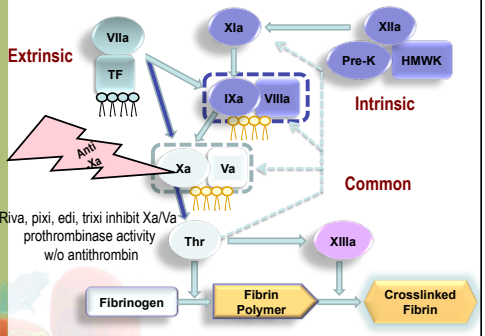

Figure courtesy of Margaret G. Fritsma

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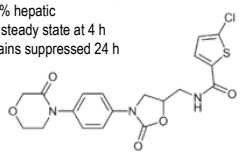
Oral Rivaroxaban ("Riva")

- 83 trials: ROCKET AF, EINSTEIN, RECORD, ATLAS ACS TIMI 46
- Excretion: 66% renal, 28% hepatic
- Stoichiometric inhibition, steady state at 4 h
- Half-life 12 h but Xa remains suppressed 24 h



janssen

Xarelto rivaroxaban

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

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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Riva Indications and Dosages

- 10 mg/d for VTE prophylaxis post TKR, THR
  - FDA-cleared 7-1-11
- 20 mg/d stroke prophylaxis in NVAF, 11-4-11
- 15 mg/bid treatment after DVT or PE, 12-2-12
- 10 mg/d to prevent 2° event in ACS
  - FDA-*deferred*, 3-4-13 (10 mg),cleared 3-22-13 by EMA @ 2.5 mg/d
- Measure: PT?, insensitive and variable
  - Anti-Xa chromogenic: need riva calibrator and controls
- PTT: only slightly prolonged by riva

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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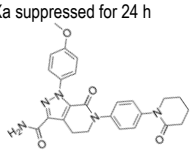
Oral Apixaban ("Pixi")

- 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…
  - In NVAF, pixi reduced stroke & systemic embolism by 21% (p<0.01)
  - 31% fewer intracranial bleeds (p<0.001)
  - 11% lower mortality (p=0.047)
  - Lower discontinuance rate than Coumadin
- FDA-cleared 12/12 to reduce risk of stroke & embolism in NVAF at 2.5 mg twice a day
- FDA-cleared 7/14 for VTE Rx
  - 2.5 mg twice a day (BID)
  - Hip (THR): 32–38 days; knee (TKR): 10–14 days
- Measure same as riva but need pixi calibrator and controls

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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)

Daiichi-Sankyo

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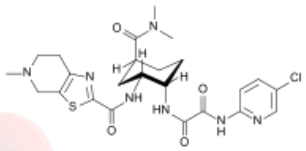
Edoxaban Dose and Pharmacokinetics

- 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



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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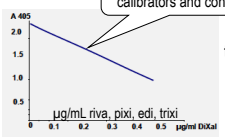
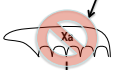
Anti-Xa Chromogenic Assay

Awaits FDA clearance for calibrators and controls



Direct anti-Xa's (riva, pixi, edi, trixi) reduce *in vitro* Xa activity



Or maybe just the PT?

Substrate → Product

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.

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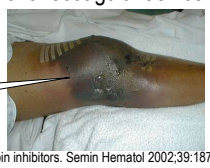
Direct Thrombin Inhibitors (DTIs)

- Intravenous argatroban and bivalirudin
  - Indication: substitute for UFH in heparin-induced thrombocytopenia
- Dabigatran, the first oral anticoagulant since Coumadin
  - FDA-approved in 2009

HIT



- Kaplan KL, Francis CW. Direct thrombin inhibitors. Semin Hematol 2002;39:187–96.
- 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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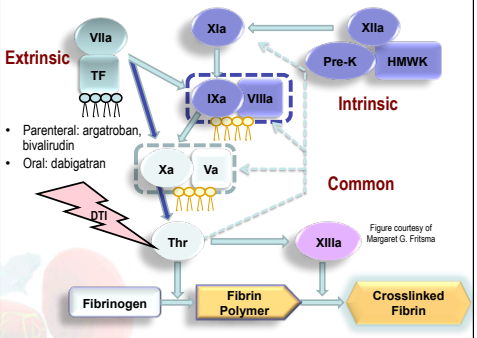
DTIs: Argatroban, Bivalirudin, Dabigatran



- Parenteral: argatroban, bivalirudin
- Oral: dabigatran

Figure courtesy of Margaret G. Fritsma

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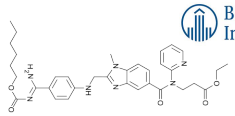
Oral Dabigatran Etexilate (dabi)

- 60 trials completed; RE-LY
- FDA-approved10/19/10: 150 mg/bid stroke prevention in NVAF
- Now approved for prevention in TKR and THR
- Also for treatment subsequent to VTE

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

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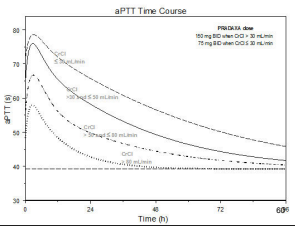
Dabi Pharmacokinetics

- 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%



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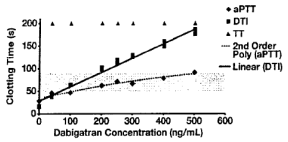
Measuring Dabigatran

- 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.

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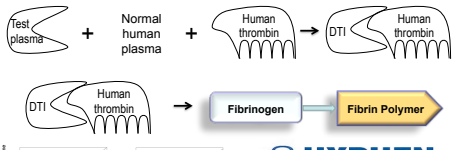
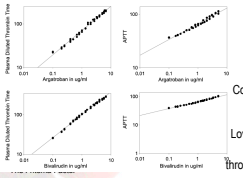
Plasma-Diluted Thrombin Time





HYPHEN BioMed

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.

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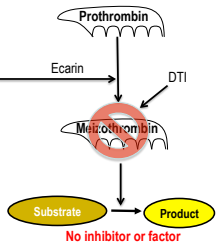
Ecarin Chromogenic Assay (ECA)

Saw-scale Viper: Echis carinatus



No inhibitor or factor deficiency effects
Color intensity at 405 nm inversely proportional to DTI concentration

Stago

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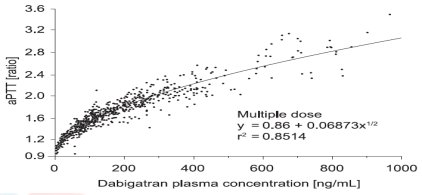
PTT and Dabi

- Normal PTT does not exclude anticoagulation
- "Curvilinear" response to dabi; steep rise at low concentrations



Van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thrombos Haemostas 2010;103:1116–27

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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
- Calibrators: parent drug for riva, pixi, edi & trixi
- Dabi: plasma-diluted TT or ECA
- Anti-Xa DOACS use anti-Xa chromogenic
  - Calibrators and controls available for all

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

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Dabi Risks

- During 1st quarter of 2011 FDA received 932 reports involving Pradaxa, including 120 deaths
  - At least 505 involved bleeding
  - Rx with 2nd most bleeds was Coumadin with 176 cases
  - Dabigatran reports had mean age of 80
- Concerns for renal patients dose adjustment
  - 75 mg vs 150 mg/d
  - Mild renal impairment may = 3X higher levels
- Bleeding incidence similar to enoxaparin

Slide courtesy of David L. McGlasson, Wilford Hall USAF Medical Center

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Dabi: Reassuring Data: Major Bleeds

- "Though there are currently no effective reversal agents to neutralize the drug, outcomes after major bleeding are not worse than for warfarin and might actually be better." (ASH 2012, Dr. Sam Schulman, MD, McMaster University)
- Lower 30-day mortality rate than major bleeds on Coumadin
- If the drug is stopped, bleeding on dabigatran is manageable

Slide courtesy of David L. McGlasson, Wilford Hall Hospital

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Coumadin Versus DOACs

	RE-LY	ROCKET-AF	ARISTOTLE
Drug and dose	Dabigatran (Pradaxa) 150 mg BID	Rivaroxaban (Xarelto) 20 mg daily	Apixiban (Eliquis) 5 mg BID
Patients	18,113 (3 arms)	14,264	18,201
Design, randomized	Open label	Double blind	Double blind
Mean age	71.5	73	70
Male ratio	63.6%	60.1%	65.3%
Prior stroke	20%	54.7%	18.9%
Efficacy %	1.71 v 1.11 p <.001 More effective	2.42 v 2.12 p = 0.12 No difference	1.60 v 1.27 p <.001 More effective
Major bleed %	3.57 v 3.32 p = 0.31	3.45 v 3.6 p = 0.58	3.09 v 2.13 p <0.001
Intracranial hemorrhage %	0.74 v 0.3 p< .001	0.74 v 0.49 p = 0.019	0.47 v 0.24 p <0.001
Conclusion	Superior efficacy, similar bleeding, less ICH	Non-inferior	Superior efficacy, less major & ICH, lower mortality

www.theheart.org/documents/WarfarinComparisonTrials.ppt; accessed July 5, 2012

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Current Hemorrhage Reversal

- Coumadin overdose
  - VK 10–20 mg oral or IV; 12–24 h to stop bleediing
  - Simultaneously infuse PCC, APCC, or 4-factor PCC (Kcentra)
  - Limit PCC to 40 U/kg body weight to avoid thrombosis or DIC
- Heparin overdose
  - Rapid neutralization with protamine sulfate, which binds long chains
- LMWH overdose
  - Protamine sulfate binds longer molecules, 30–40% effective
- Fonda and DOAC overdose: reversal agents in trials

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

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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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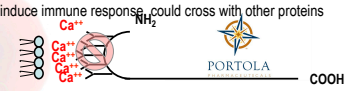
Developing Hemorrhage Reversal
IV Andexanet Alpha; Annexa-A®

- Non-carboxylated Xa—lacks Gla domain, competes
- Variably reverses all anti-Xa DOACs AND fonda
- Partially reverses LMWH— anti-Xa but not anti-IIa
- Phase 2: 2m reversal: pixi 93%, edi and riva 50%
- 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
  - May induce immune response, could cross with other proteins



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Developing Hemorrhage Reversal
Idarucizumab

- Current dabi reversal employs activated charcoal and dialysis
- Human monoclonal Fab fragment binds dabi
  - High affinity, effective sustained reversal in minutes
  - Phase 3 trials, applied to FDA
- Limitations
  - May induce immune response limiting further usage
  - Reversal determined using ECA and DTT, surrogates

RE-VERSE AD™ Study of reversal effects of idarucizumab in patients on active dabigatran

Boehringer Ingelheim

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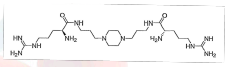
Developing Hemorrhage Reversal
Aripazine (PER 977)

- D-arginine derivative, non-immunogenic molecule
- Reverses all DOACs, UFH, LMWH, fonda by H_2 bonds
  - Produces no procoagulant signal; e.g. PF 1.2, D-d
- No interaction with albumin or coagulation factors
- Phase 1 human trial; no adverse events, edi reversal
- Limitations: action mode unclear, how is it so specific?
  - Only lab assay that monitors reversal is 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

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