The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Managing Direct Oral Anticoagulants

Dabigatran, Apixaban, Rivaroxaban

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

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Bottom Line at the Start [BLAST]

- Manage and measure direct oral Xa inhibitors: rivaroxaban [2011], apixaban [2012], Edoxaban [2015]
  - Betrixaban [2017, discontinued 4-2020]
- Measure oral direct thrombin inhibitor dabigatran [2008]
- Anticoagulant reversal agents idarucizumab [2016], andexanet alpha [2018], ciraparantag [pending]
- The future of anticoagulation

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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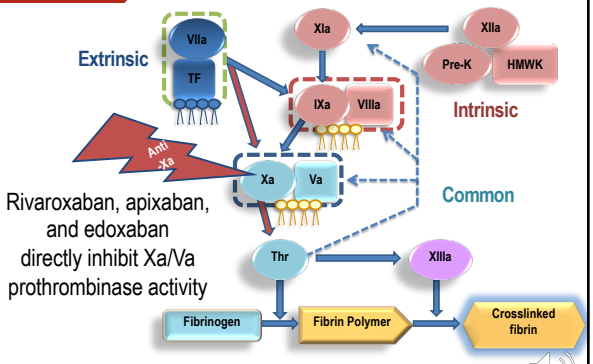
DOACs: Direct Xa Inhibitors



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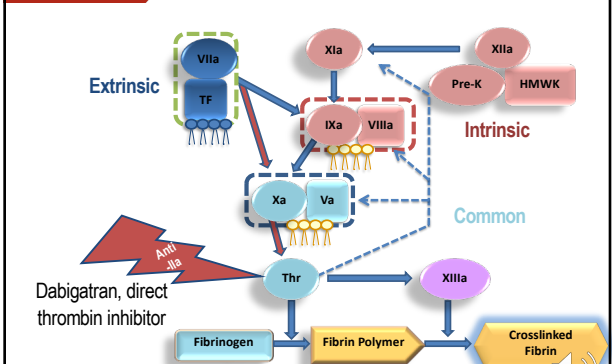
DOACs: Direct Thrombin Inhibitor



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DOAC Considerations

DOACS…

- Nearing 50% of all anticoagulant scrips, 3 m USA residents
- Improved efficacy and safer than warfarin
- Few drug interactions, some CYP450–metabolized drugs interfere
- Require kidney and liver assessment every 6–12 months
- Short half-life demands strict patient compliance
- Fixed dosage and broad range requires no lab monitoring, but…
- Lab measurement necessary in many circumstances

Samama MM, Martinoli JL, et al. Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. Thromb Haemost 2010; 103: 815-25.

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DOAC Lab Considerations

- Measurement timing-dependent due to short half-life
- Qualitative PT & PTT assays are reagent-dependent
- Quantitative DOAC assays in Canada and Europe
  - RUO in US
  - Dabigatran: plasma-diluted TT, ecarin chromogenic assay
  - Anti-Xa drugs: chromogenic anti-Xa, requires drug-specific calibrators and controls

Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. Pharmacotherapy 2017;37:236–48

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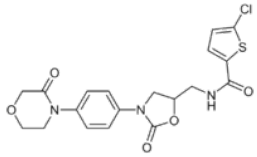
Rivaroxaban

- Excretion: 66% renal, 28% hepatic
- Stoichiometric inhibition, steady state at 2–4 h
- Half-life 5–13 h but Xa remains suppressed 24 h



Jansson M, Själander S, Sjögren V, et al. Direct comparisons of effectiveness and safety of treatment with apixaban, dabigatran and rivaroxaban in atrial fibrillation. Thromb Res. 2020; 185: 135–41

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Rivaroxaban Indications & Dosages

- 10 mg/d for VTE prophylaxis post TKR, THR, 7-1-11
  - TKR 12 d, THR: 35 d
- 20 mg/d for stroke prophylaxis in NVAF, 11-4-11
- 15 mg/BID Rx 20 d post DVT/ PE then 20 mg/d, 12-2-12
- 2.5 mg/BID with ASA to prevent 2° event in ACS 10-11-18
- Avoid use if CRCL is <30 mL/m, avoid use in liver disease
- Discontinue 24 h before invasive procedure

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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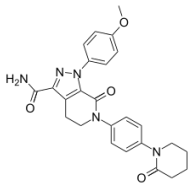
Apixaban

- Renal excretion 30%, hepatic/intestinal 70%
- Stoichiometric inhibition, steady state at 4 h
- Half-life 12 h, Xa suppressed for 24 h



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Apixaban Indications and Dosages

- Compared to warfarin…
  - In NVAF, 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
- 5 mg BID to reduce risk of stroke in NVAF [12/12]
- 2.5 mg BID for TKR or THR VTE prophylaxis [7/14]
  - THR 35 d; TKR 12 d
- VTE therapy: 10 mg BID 7 d, 5 mg BID until D/C
- Renal disease, no change in dosage
- Liver disease, contraindicated when severe

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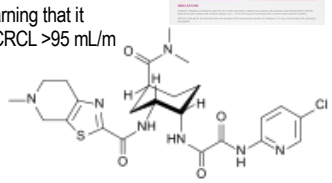
Edoxaban

- Reaches therapeutic levels in 1–2 h
- Half-life 10–14 h
- Excreted 50% kidney, 50% liver
- NVAF, VTE Rx: 60 mg/d, 30 if CRCL <50 mL/m
- FDA-approved 2015 with warning that it increases stroke risk when CRCL >95 mL/m



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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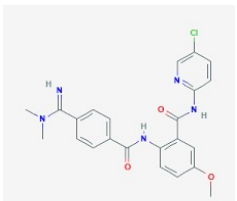
Betrixaban

- Time to max activity 3–4 h, half-life 19–27 h
  - Longest half-life of all DOACs
- Renal excretion 15%, hepatic/intestinal 85%
- Inpatients w/ acute medical illness and restricted mobility at risk for VTE [6/17]
- 160 mg once initially, then 80 mg/d, 35–42 d
- If CYP450 comedication or CRCL <30 mL/m, 80 mg, then 40 mg/d
- Avoid in moderate or severe liver disease



Lekura J, Kalus JS. Overview of betrixaban and its role in clinical practice. Am J Health Syst Pharm. 2018;75:1095–1102.

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DOACs Versus Warfarin

Feature	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	VK	Thrombin	Xa	
Dosing	Daily	BID		
Onset	5 d	0.5–1 h	2–4 h	3–4 h
Half-life	40 h	12–14 h	5–13 h	12 h
Peak Assay	5 d	1 h	4 h	4 h
Trough Assay	5 d	12 h		
Renal clearance	0%	80%	66%	25%
Reversal	VK, Kcentra	Idarucizumab	Andexanet alfa	

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Initial Rivaroxaban Detection

Primary detection is *qualitative*: PT thromboplastins in 1000 ng/mL rivaroxaban-spiked plasma with sensitivity in rank order:

1. TriniclotTM PT Excel S
2. RecombiPlastin 2G most sensitive in TKR & THR patients
3. Neoplastin R
4. Neoplastin CI Plus also sensitive in TKR & THR patients
5. TriniclotTM PT Excel
6. TriniclotTM PT HTF
7. Innovin & Thromborel insensitive in TKR & THR Pts

- PTT is insensitive to all anti-Xa DOACs
- All PT thromboplastins are insensitive to apixaban
- Reflex to chromogenic anti-Xa using specific calibrators and controls

Ten Cate H, Henskens YMC, Lancé MD. Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. Vascular Health and Risk Management 2017:13 457–67.

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Initial Dabigatran Detection

Primary detection is *qualitative*

- Thrombin time is sensitive, normal TT R/O dabigatran
- PTT response depends on individual reagent, flattens out at 200 ng/mL
- Reflex to plasma-diluted thrombin time or ecarin chromogenic assay

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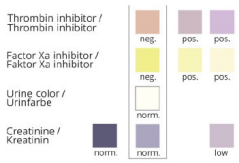
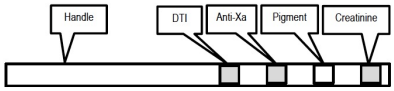
DOASENSE® DOAC Dipstick®

- Detects and distinguishes anti-Xa from DTI in urine
- Creatinine pad estimates CRCL, binary results detects <30 mL/m
- CE Mark 2018: Canada and Europe
- DOAC typical values above 200 ng/mL in urine, exceeds corresponding plasma levels





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Why Measure DOACs?

- For efficacy and safety, we *monitor* warfarin and heparin, but *measure* DOACs
- Renal disease with CRCL <50 mL/min slows excretion
- Liver disease slows excretion, especially edoxaban
- Bridging from one anticoagulant to another [avoid PT/INR]
- Bleed risk If trough level [~12 h] exceeds 200 ng/mL
- Noncompliance, overdose, underdose
- Determine acute hemorrhage cause
- Identify co-medication interference
- Monitor reversal

Monitor or Measure?

Measure, but no dose adjustment except in renal disease

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Why Measure DOACs? [More]

- Discontinuation before surgery
  - 24 h if bleeding risk is low, 48 h if risk is high
  - Up to five days if CRCL <50 mL/m
- Resumption after surgery
- Check dosage if there is on-treatment thrombosis
- Unstable coagulation: pregnancy, liver disease, renal disease, malignancy, DIC
- Patients excluded from clinical trials
  - <18 YO; >75 YO
  - >150 kg: proportionally reduced plasma volume
  - < 40 kg or ped: proportionally increased plasma volume

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 International Society on Thrombosis and Haemostasis. J Thromb Haemost 2013; 11: 756–60.

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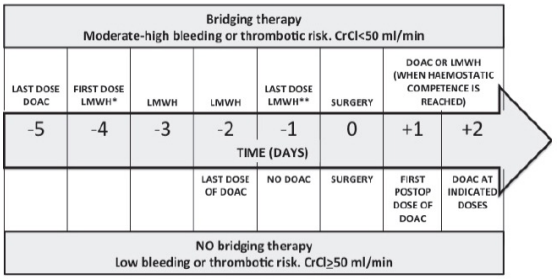
DOAC Bridging



Ferrandis R, Castillo J, de Andrés J, et al. The perioperative management of new direct oral anticoagulants: a question without answers. Thromb Haemost. 2013; 110: 515-22.

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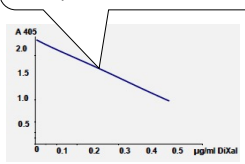
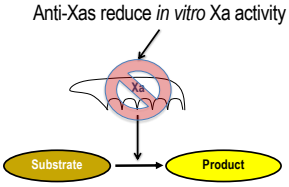
Anti-Xa Chromogenic Assay

Awaits FDA clearance for calibrators and controls, UFH/LMWH calibrators vary by formulation, but may be used for binary DOAC detection



Anti-Xas reduce *in vitro* Xa activity



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

Gosselin RC, Francart SJ, Hawes EM, Moll S, Dager WE, Adcock DM. Heparin-calibrated chromogenic anti-Xa activity measurements in patients receiving rivaroxaban: can this test be used to quantify drug level? Ann Pharmacother. 2015; 49: 777–83.

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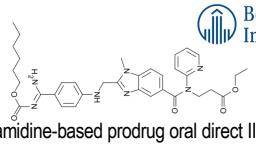
Dabigatran Etexilate

- FDA-approved 2008: 150 mg/bid stroke prevention in NVAF
- Approved for prophylaxis in TKR and THR subsequent to heparin Rx
- Also for treatment subsequent to VTE subsequent to 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

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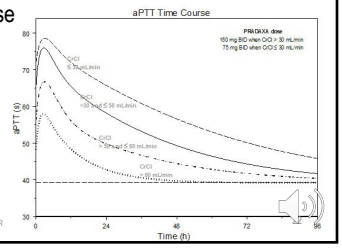
Dabigatran Pharmacokinetics

- Half-life 12–14 h, >60 h in renal disease
  - Reduce dosage by 50% when CRCL < 30 mL/m
- No interaction with food, no liver toxicity
- Levels raised by quinidine and verapamil
- Metabolized by esterase
  - Not CYP450
- Renal excretion 80%
- Dyspepsia 10%



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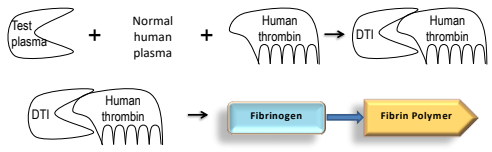
Plasma-Diluted Thrombin Time



- Standard thrombin time: hypersensitive, qualitative
  - Normal implies absence
  - Any DTI generates results >>20s

HYPHEN BioMed

- 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.
- 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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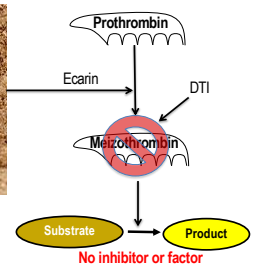
Ecarin Chromogenic Assay

Saw-scale Viper: Echis carinatus

Stago



No inhibitor or factor deficiency effects

Color intensity at 405 nm inversely proportional to DTI concentration

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

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Reversal in Hemorrhage

- Use reversal agent if DOAC level is >50 ng/mL [ISTH opinion]
  - >30 ng/mL if preparing for a procedure
- Non-specific reversal: prothrombin complex concentrate, 50 IU/kg followed by 25 IU/kg
  - *Activated* prothrombin complex concentrate, use 1 dose of 50 IU/kg
- PTT and PT for general coagulation restoration

Levy JH, Ageno W, Chan NC, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14:623–7.

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Idarucizumab

- Human monoclonal Fab fragment binds dabigatran
  - High affinity, effective sustained lab-measured reversal in minutes
  - Approved via FDA fast-track 2015
  - Dose: 5 g provided as two vials each containing 2.5 g/ 50 mL push
  - If bleeding continues, use additional 5 g
- Limitations
  - May induce immune response limiting further usage
  - Reversal determined using ECA and DTT, surrogates

Praxbind idarucizumab INJECTION 5g

Boehringer Ingelheim

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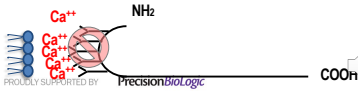
Andexanet Alpha; AndexXa®

- Surrogate non-carboxylated Xa—lacks Gla domain, competes for factor Xa binding
- Variably reverses rivaroxaban, apixaban [FDA 2017]
- AnddexXa® limitations
  - Reversal measured using anti-Xa, a surrogate
  - Dosage varies by DOAC, must Identify rivaroxaban or dabigatran
  - Bolus 30 mg/m & continuous drip 120 m or as required through half-life of DOAC
  - May induce immune response

amag PHARMACEUTICALS



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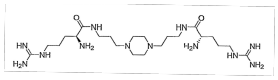
Aripazine [PER977, ciraparantag]

- Reverses all DOACs, UFH, LMWH and fondaparinux by H_2 bonds
- D-arginine derivative, small, non-immunogenic molecule
- Produces no procoagulant signal; e.g. PF 1.2, D-d
- No interaction with albumin or coagulation factors
- Phase 3 human trial; FDA fast-track designation 2019
- Limitations: action mode unclear, how is it so specific?
- Only assay that monitors reversal is WB clotting time

amag PHARMACEUTICALS



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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Current Efforts

- Establish "universal" DOAC assays
  - Thrombin generation, viscoelastometry, modified TT, PT or PTT?
- Establish target therapeutic ranges for all DOACs
- DOACs that target contact factors XI, XII, or prekallikrein
  - Underway: though activation is thrombotic, contact factor deficiencies have no bleeding consequence

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Bottom Line at the End [BLEAT]

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  - Betrixaban [2017, discontinued 4-2020]
- Measure oral direct thrombin inhibitor dabigatran [2008]
- Anticoagulant reversal agents idarucizumab [2016], andexanet alpha [2018], ciraparantag [pending]
- The future of anticoagulation

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