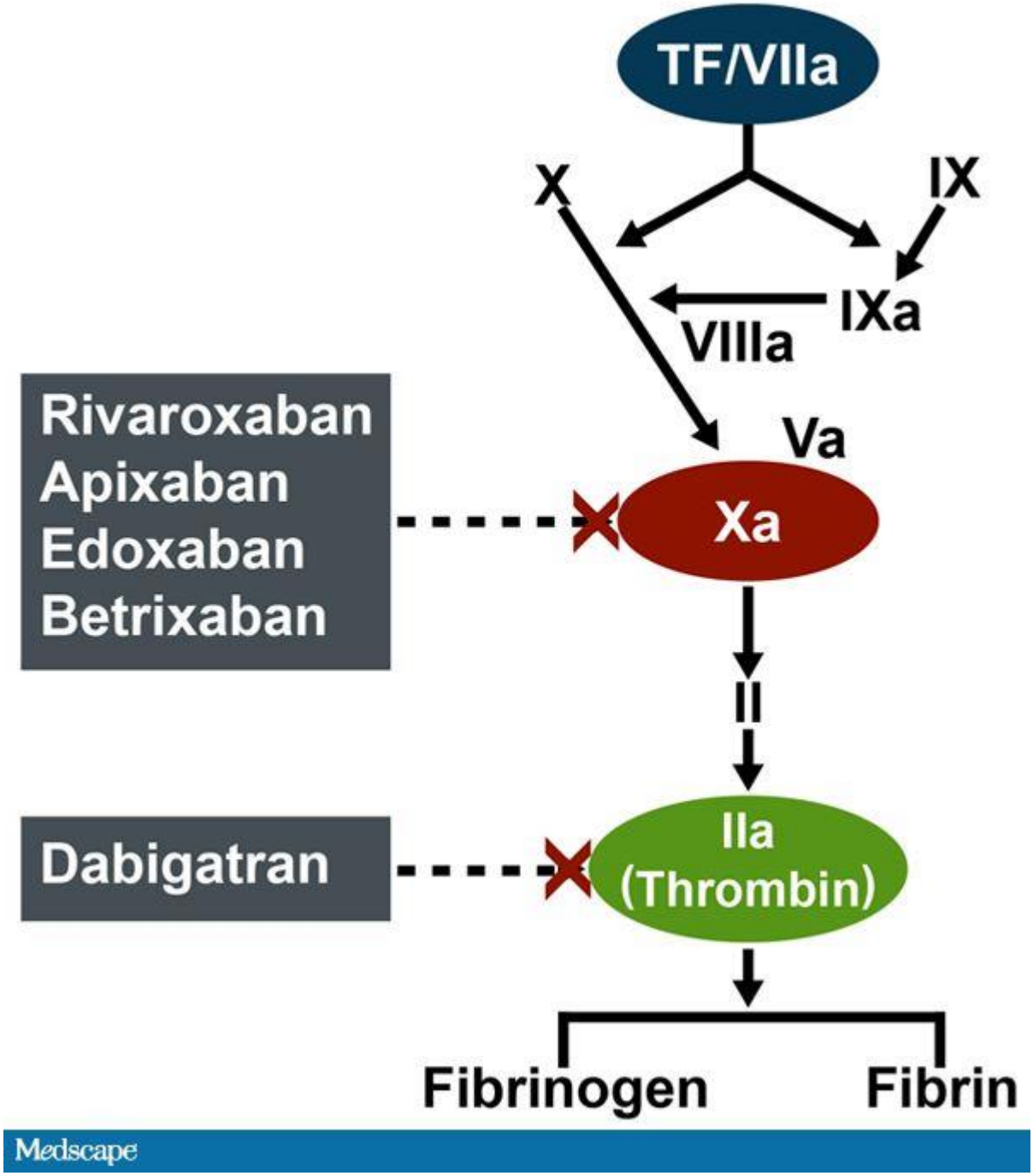
Novel Oral Anticoagulant Drugs

The pharmacodynamics of the different NOACs are relatively similar, in contrast to their pharmacokinetics, which are best understood in the context of each individual agent.
Current NOACs target either factor Xa or thrombin.

- Factor Xa serves as the link between the intrinsic and extrinsic coagulation systems. Activated factor Xa catalyzes the conversion of prothrombin to thrombin. Factor Xa inhibitors prevent formation of thrombin
- Direct thrombin inhibitors directly target coagulation cascade through inhibition of thrombin. Inactive thrombin is unable to convert fibrinogen to fibrin, thus decreasing formation of thrombus.



	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Daily dosing	Once	Twice	Once	Twice
Interactions	CYP3A4/P-gp	CYP3A4/P-gp	P-gp	P-gp

"All four of the agents appear safer than warfarin…the choice of agent may come down to the relationship between cost and how each suits individual patients more so than whether they are safe or not."

-- Patrick T. Ellinor, MD, Massachusetts General Hospital, Boston, Massachusetts

"The four agents are more similar than different, and when they're compared with warfarin they look better than warfarin. It's impossible to compare the drugs because they haven't been compared head to head. So one will look for certain patient characteristics that will favor one drug over the other -- such as once-a-day dosing, renal failure, and age."[8]

-- Mark S. Link, MD, Tufts Medical Center, Boston, Massachusetts

FACTOR Xa INHIBITORS ("-XABANS")

RIVAROXABAN (Xarelto®)

- current FDA indications:
  1) stroke prevention in patients with non-valvular atrial fibrillation
  2) prevention of DVT and PE following knee or hip replacement surgery

APIXABAN (Eliquis®)

- current FDA indications: stroke prevention in patients with non-valvular atrial fibrillation
- reversal
  - KCENTRA, ANDEXXA *see below >>*
  - from manufacturer website: specific antidote not available; no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose (i.e. about 2 half-lives).
- perioperative (from manufacturer website) - drug should be discontinued at least:
  a) 48 hours prior to elective procedures with a moderate or high risk of unacceptable or clinically significant bleeding.
  b) 24 hours prior to elective procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.
  - *bridging anticoagulation* during the 24-48 hours after stopping drug and prior to the intervention is ***not generally required***.
  - drug should be restarted after the procedures as soon as adequate hemostasis has been established.

EDOXABAN

BETRIXABAN (BEVYXXA®)

- current FDA indications: prophylaxis of venous thromboembolism (VTE) in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- dosage: single dose of 160 mg on day 1 → 80 mg daily for 35-42 days at the same time each day with food.

ANTIDOTES

See p. Rx0 >>

- **PCC** and **recombinant factor VIIa** are effective in reversal.

ANDEXXA (coagulation factor Xa [recombinant] inactivated-zhzo)
(Portola Pharmaceuticals)
- FDA approved to reverse the anticoagulation effects of factor Xa inhibitors: rivaroxaban, apixaban.
- imitation factor Xa without biological properties, which reverses anticoagulant action of factor Xa inhibitors.
- genetically engineered to exactly resemble factor Xa except that proteolytic site has been deactivated so it cannot cleave thrombin → not prothrombotic!

DIRECT THROMBIN (FACTOR IIa) INHIBITORS

XIMELAGATRAN (Exanta™)
- first oral anticoagulant in class of direct thrombin inhibitors!
- works faster than warfarin; does not require blood tests to adjust dosage (vs. warfarin).
- fixed dosage - 24mg × 2/d.
- **indications - short-term (up to 11 days) prevention of venous thromboembolism following orthopedic surgery.**
- **side effects – *serious liver injury* (even after stopping drug)**

14 February 2006 "**AstraZeneca" decided to withdraw drug from market and terminated its development!** - patients must switch to alternative anticoagulant!

DABIGATRAN (Pradaxa)
- direct competitive thrombin inhibitor (both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited)
- current FDA indication - stroke prevention in patients with non-valvular atrial fibrillation:
  a) in lower doses (110 mg q12h) prevents stroke as warfarin (1.44%/yr vs. 1.57 %/yr) but with lower risk of bleeding (2.71%/yr vs. 3.36%/yr)
  b) in higher doses (150 mg q12h) prevents strokes better than warfarin (1.01%/yr vs. 1.57%/yr) with the same risk of bleeding (3.11%/yr vs. 3.36%/yr)

RELY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial

Complication	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Strokes	1.44%/yr	1.01%/yr	1.57%/yr
Bleeds	2.71%/yr	3.11%/yr	3.36%/yr

Inmaculada Hernandez "Risk of Bleeding With Dabigatran in Atrial Fibrillation" JAMA Intern Med. November 03, 2014:
People with atrial fibrillation who take dabigatran or warfarin to prevent stroke (study included 9,400 people - 1,300 on dabigatran, 8,100 on warfarin) – within 1 year:
DABIGATRAN - 9% had major bleeding, 17% GI bleeding, 0.6% intracranial bleeding
WARFARIN - 6% had major bleeding, 10% GI bleeding, 1.8% intracranial bleeding

- onset of anticoagulant effect within 0.5–2 h after administration

- serum T½ is 12–17 h
- 80% is excreted by **kidneys**; dosage:

  CrCl > 30 mL/min - 150 mg twice daily, with or without food.
  CrCl 15-30 mL/min - 75 mg twice daily
  CrCL < 15 mL/min or on dialysis – no dosage provided.
- swallow capsules whole (breaking, chewing, or emptying the contents of the capsule can result in increased exposure)
- missing dose: dose should be taken ASAP (skip if cannot be taken ***at least 6 hours before*** the next scheduled dose).
- Pregnancy Category C
- disadvantages (compared with warfarin): GI side effects, myocardial infarction, twice-daily dose, high cost, lack of long-term safety data.
- contraindication - patients with mechanical heart valves (worse protection against strokes, heart attacks, and blood clot formation on mechanical heart valves than with warfarin)

MONITORING

- less susceptible to dietary and drug interactions - stable dosing regimen - no requirement of monitoring.
- **ecarin clotting time (ECT)** - better marker of the DABIGATRAN anticoagulant activity than aPTT, INR, or thrombin time (TT).
- if ECT is not available, aPTT provides rough approximation of DABIGATRAN anticoagulant activity; vs. normal aPTT or thrombin time exclude presence of dabigatran.

REVERSAL

See p. Rx0 >>

- short acting.
- in case of bleeding:
  a) **hemodialysis** - decreases serum drug levels up to 60% (but takes 2-3 hours)
  b) **charcoal**
  c) **factor VIIa** - has not been thoroughly studied
  d) **PCC** not effective

IDARUCIZUMAB (Praxbind, Boehringer Ingelheim) – FDA approved to rapidly reverse DABIGATRAN.

- given IV - works by binding to drug compound to neutralize its effect.
- anticoagulant effect of Pradaxa is fully reversed in 89% of patients within 4 hours of receiving Praxbind.

CONVERSIONS

- converting from **WARFARIN**: discontinue WARFARIN and start DABIGATRAN when INR is < 2.0.
- converting to **WARFARIN**:

  CrCl > 50 mL/min, start warfarin 3 days before discontinuing DABIGATRAN.
  CrCl 31-50 mL/min, start warfarin 2 days before discontinuing DABIGATRAN.
  CrCl 15-30 mL/min, start warfarin 1 day before discontinuing DABIGATRAN.
  CrCl < 15 mL/min, no recommendations can be made.
- converting from **PARENTERAL ANTICOAGULANTS**: start DABIGATRAN 0-2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., IVI heparin).
- converting to **PARENTERAL ANTICOAGULANTS**: wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of DABIGATRAN before initiating treatment with a parenteral anticoagulant

SURGERY

- discontinue DABIGATRAN 1-2 days (CrCl ≥ 50 mL/min) or 3-5 days (CrCl < 50 mL/min) before invasive procedures
    a. consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port

In NSGY, stop DABIGATRAN for 3-5 days

- if surgery cannot be delayed, bleeding risk can be assessed by the ecarin clotting time (ECT).

ARGATROBAN

- reversible direct thrombin inhibitor (binds to thrombin active site).
- does not interact with heparin-induced antibodies.
- indication - prophylaxis / treatment of thrombosis in patients with heparin-induced thrombocytopenia.
- dosage (N.B. drug must be diluted to concentration of 1 mg/mL) - 2 mcg/kg/min IVI:

Body Weight (kg)	Dose (mcg/min)	Infusion Rate (mL/hr)
50	100	6
60	120	7
70	140	8
80	160	10
90	180	11
100	200	12
110	220	13
120	240	14
130	260	16
140	280	17

- monitor aPTT (aPTT attains steady-state within 1-3 hours).
    a. dose can be adjusted (not to exceed 10 mcg/kg/min), until steady-state aPTT is 1.5-3 times baseline value (not to exceed 100 seconds)
- $T_{1/2}$ = 39-51 min.
- metabolized in liver, excreted in feces.

BIVALIRUDIN (Angiomax™) - synthetic reversible direct thrombin inhibitor (binds both to catalytic site and to anion-binding exosite of circulating and clot-bound thrombin).

- indication - patients with unstable angina undergoing PTCA (intended for use with aspirin 300-325 mg daily).
- dosage: 0.75-1.0 mg/kg IV bolus just prior to PTCA/stenting → 1.75-2.5 mg/kg/h IVI for 4 hours → 0.2 mg/kg/h IVI for another 20 hours
- $T_{1/2}$ = 25 min.
- eliminated by renal mechanisms and proteolytic cleavage.
- no known antidote.
- monitoring – aPTT.

REVERSAL

See p. Rx0 >>

HEPARINOIDS

FONDAPARINUX sodium (Arixtra®) – synthetic* specific inhibitor of Factor Xa.

***vs. LMWH (made from natural heparin)**

- **mechanism of action -** antithrombin III-mediated selective inhibition of Factor Xa.
- indications:
  1) prophylaxis of deep vein thrombosis in orthopedic / abdominal surgery patients.
  2) treatment of acute deep vein thrombosis / pulmonary embolism when administered in conjunction with warfarin.
- **administered SC × 1/d.**
- eliminated unchanged in urine; $T_{1/2}$ = 17-21 hrs.
- routine coagulation tests (PT, aPTT) are relatively insensitive - unsuitable for monitoring; *anti-Xa activity* can be measured by anti-Xa assay using appropriate calibrator.
- *no known antidote* (vs. LMWH – protamine).

DANAPAROID (Orgaran®) - mixture of low molecular weight sulfated glycosaminoglycuronans derived from porcine intestinal mucosa:

1) **heparan** sulfate with low affinity for AT-III (≈ 80%)
2) **heparan** sulfate with high affinity for AT-III (≈ 4%)
3) **dermatan** sulfate (8-16%)
4) **chondroitin** sulfate (< 8.5%)

N.B. danaparoid is devoid of heparin or heparin fragments!

- **administered SC × 2/d. (first dose may be IV bolus).**
- improved antithrombotic activity when compared to heparin.
- much higher* anti-factor Xa/anti-IIa ratio (> 20:1). *compared to heparin
- minimal or no effect on platelet function; but danaparoid-induced thrombocytopenia is possibility.
- cross-reactivity with heparin-associated antibody < 10% (vs. LMWH > 90%).
- *anti-Xa levels in plasma* is only method for monitoring danaparoid activity.
- main route of elimination is via kidney.
- most common adverse events – hemorrhages, rashes.
- *no known antidote* (vs. LMWH – protamine).

HIT

TREATMENT

FONDAPARINUX (prophylactic dose 2.5 mg; therapeutic dose - 7.5-10 mg)
If kidney failure - **ARGATROBAN**
If liver failure - **BIVALIRUDIN**