

A New Kid in Town: Anticoagulation: Warfarin vs. Dabigatrin

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Warfarin

- Approved for use in the early 1950s
- Extensive experience in clinical use
- Medication interactions
- Food interaction
- Monitoring required, but well established and readily available
- Requires several days to reach therapeutic levels
- Cost of drug is low
- Clearance: non-renal
- Reversal: Vitamin K, FFP, PCC

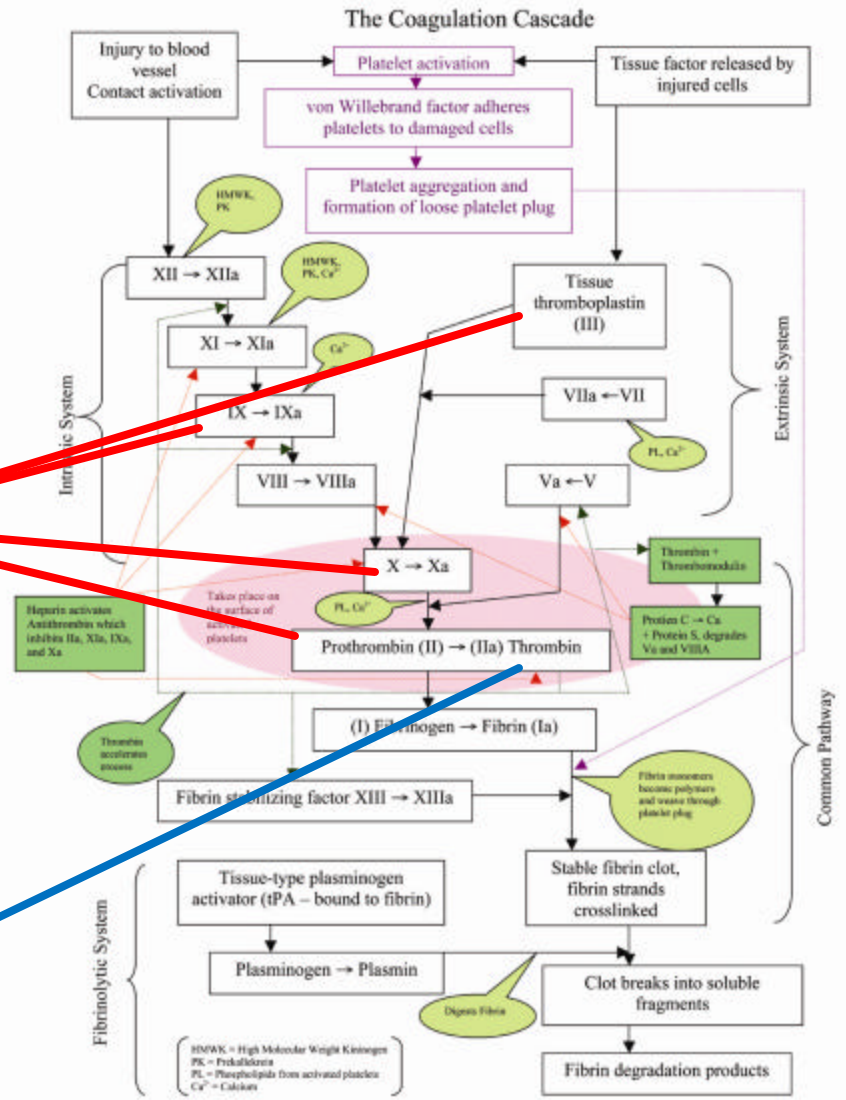
Dabigatrin

- Approved for use 2010
- Few Medication interactions
- No Food interactions
- No Routine Monitoring required
- Monitoring tests not routinely available (TT, ECT)
- Cost of drug is relatively high
- Clearance: Renal

Coagulation Cascade

WARFARIN

DABIGATRAN

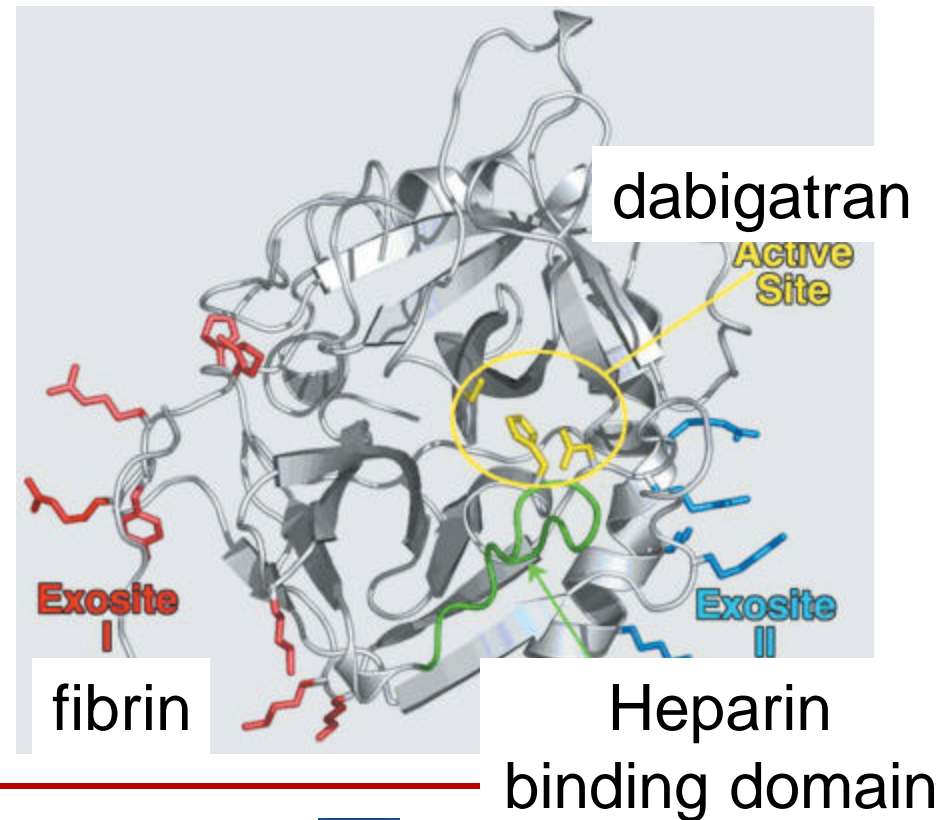


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Coagulation Cascade 2/19/2004

Dabigatran etexilate: Mechanism of Action

- After oral administration dabigatran etexilate is converted to its active form, dabigatran
- Inactivates both fibrin bound and unbound thrombin
- Heparinoids cannot inhibit fibrin bound thrombin
- Dabigatran prevents conversion of fibrinogen into fibrin, positive feedback amplification of coagulation activation, cross-linking of fibrin monomers, platelet activation and inhibition of fibrinolysis



Pharmacology

- Rapidly absorbed, quickly and completely hydrolyzed to active form with peak levels at 2 hours
- Absolute bioavailability is low, 6.5%
- Conversion of dabigatran occurs in the liver; 20% conjugated with glucuronic acid and excreted in bile
- NOT metabolized by P450 or other oxidoreductases but is a substrate for p-glycoprotein
- Half life: 8 hours after a single dose and 12-14 hours after multiple doses. Half life is 13 hours after single dose in older patients and >24 hours with Cr clearance <30mL/min
- Excretion: 80% renal. May be prudent to monitor renal function q 6-12 months

Interactions

- Dabigatran etexilate (not dabigatran) is a substrate of the efflux permeability glycoprotein transporter
- Coadministration of potent permeability glycoprotein inhibitors including quinidine, ketoconazole, amiodarone, verapamil can increase plasma concentrations of dabigatran by decreasing its reabsorption via permeability glycoprotein into the gut
- Potent inducers including rifampicin can reduce dabigatran levels by increasing its reabsorption via permeability glycoprotein into the gut
- Quinidine, ketoconazole and rifampicin are contraindicated with Dabigatran etexilate
- Protein pump inhibitors slightly reduced concentrations but does not affect efficacy and safety

Clinical Trials

- **RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy)**

- Phase III, multicenter, prospective, open-label, randomized trial with blinded outcome evaluation
- 18, 113 patient with nonvalvular atrial fibrillation assigned to dabigatran (110 or 150mg BID) or warfarin

	Stroke/systemic embolism	Major Hemorrhage	Intracranial Hemorrhage	Gastrointestinal Hemorrhage
Warfarin	1.71%	3.57%	0.76%	1.07%
Dabigatran 150mg	1.11%	3.32%	0.32%	1.56%
Dabigatran 110mg	1.54%	2.87%	0.23%	1.15%

RE-LY

- Rates of MI were higher with both doses of Dabigatran etexilate. Mechanism unclear.
- No evidence of hepatotoxicity
- Dyspepsia (including abdominal pain) are increased. Thought to be secondary to tartaric acid in dabigatran etexilate capsule
- Benefits of dabigatran in reducing stroke, bleeding and ICH were consistent regardless of the quality of INR control by study center
- Benefits in secondary outcomes (vascular events, non-hemorrhagic events and mortality) advantages of dabigatran were greater at sites with poor INR control
- Economic Analysis: dabigatran is likely to be cost-effective compared with warfarin if daily cost of does not exceed \$13.70.

How to start Dabigatran etexilate in patients not already on anticoagulation

- Dosing recommendations for patients with a CrCl >30 mL/min is Dabigatran etexilate 150mg twice daily
- Dosing recommendations for patients with CrCl 15-30 mL/min is Dabigatran etexilate 75mg twice daily
- Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided

How to start Dabigatran etexilate in patients currently on Warfarin

- Discontinue warfarin and start Dabigatran when the international normalized ratio (INR) is below 2.0

What to do if a Dabigatran dose is missed

- If a dose of Dabigatran is not taken at the scheduled time, the dose should be taken as soon as possible on the same day
- The missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose
- The dose of Dabigatran should not be doubled to make up for a missed dose

Monitoring of Dabigatran Etexilate

- When interpreting a coagulation assay it is essential to know when dabigatran etexilate was administered relative to the time of blood sampling
- aPTT: concentration curve is curvilinear and flattens at higher concentrations
- INR: is not substantially affected by dabigatran etexilate
- Thrombin clotting time (TT): direct measure of dabigatran activity but reagents are not standardized and the test may be too sensitive. Most useful for determining if any dabigatrin is present
- Activated clotting time (ACT): curve flattens at higher concentrations
- Haemoclot thrombin inhibitor assay: sensitive diluted TT
- Ecarin clotting time (ECT): some experience in orthopaedic and cardiac patients during CABG but not standardization or validation with dabigatran, not recommended for emergency monitoring

Management of Bleeding

Patient with bleeding on dabigatran

Mild


Delay next dose or discontinue treatment

Moderate-severe

Symptomatic treatment
Mechanical compression
Surgical intervention
Fluid replacement
Blood product transfusion
Oral charcoal (if < 2 hr)
hemodialysis

Life threatening

Plus:
Consideration of rFVIIa or PCC
Charcoal filtration



Clinical trials: Prevention of Venous Thromboembolism

Trial	Patients	N	Efficacy	Major Bleeding
RE-MODEL	Knee arthroplasty	2101	Non-inferior	No difference
RE-NOVATE	Hip arthroplasty	3494	Non-inferior	No difference
RE-MOBILIZE	Knee arthroplasty	2615	Inferior	No difference
RE-NOVATE II	Hip arthroplasty	2055	Non-inferior	No difference

Meta-analysis: Dabigatrin etexilate 220 has similar efficacy compared with enoxapain daily or 30mg BID in prevention of venous thromboembolism and all-cause mortality and a similar risk of causing major bleeding

- Licensed in >75 countries for the prevention of venous thromboembolism after elective hip or knee arthroplasty

Clinical Trial: Treatment of Venous Thromboembolism

RECOVER-1

-2564 patients with acute venous thromboembolism

	Recurrent VTE	Major Bleeding
Warfarin	2.4%	1.6%
Dabigatran etexilate 150mg	2.1%	1.9%

Newer Kids in Town:

- Apixaban: Xa inhibitor
 - **AVERROES**: double blind randomized study
 - enrolled 5,599 patients who were unsuitable for warfarin to either Apixaban 5mg BID (reduced dose for patients over 80 or CrCl >1.5) or ASA

	Stroke or systemic embolization	Death	Major hemorrhage
ASA 81-324mg	3.7%/yr	4.4%	1.2%
Apixaban 5mg BID	1.6%/yr	3.5%	1.4%

Another New Kid in Town

- Rivaroxaban: Xa inhibitor
 - **ROCKET AF:**
 - Double blind, randomized trial with 14,264 patients assigned to warfarin or rivaroxaban
 - Non-inferiority trial

	Stroke or systemic embolization	Bleeding	ICH	Fatal bleeding
Warfarin	2.2%	14.5%	0.7%	0.5%
Rivaroxaban	2.1%	14.9%	0.5%	0.2%