Whatever Happened to the PT and PTT?

How to Monitor the New Antithrombotics
George A Fritsma MS, MLS
The Fritsma Factor, Your interactive Hemostasis Resource
Sponsored by Precision Biologic, Dartmouth, Nova Scotia
www.fritsmafactor.com

The Fritsma Factor
Your interactive Hemostasis Resource

Whatever Happened?
What’s new in antithrombotics? Everything. We now monitor aniplatelet drugs aspirin, clopidogrel, and in 2009, prasugrel. What do we do about fondaparinux, and the 2011 oral anticoagulants rivaroxaban, apixaban and dabigatran? And we still don’t know how to monitor direct thrombin inhibitors. Are ecarin time, chromogenic X and chromogenic anti-Xa the answer?

Objectives:
1. Brief summary of current antithrombotics
2. Monitor aniplatelet drugs, fondaparinux, direct thrombin inhibitors, and 2010 oral anticoagulants
3. Employ chromogenic X and chromogenic anti-Xa to monitor several new anticoagulants

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71 YO Female, Atrial Fibrillation
30 Years of 7.5 mg/day Warfarin

• Monday: INR 11, no bleeding symptoms
  – Target range 2–3
  – Hx: when INR 5–6: bruising, bleeding gums, epistaxis
  – Just started on statin
    • Total cholesterol: 263 mg/dL
    • Triglycerides: 319 mg/dL
• Tuesday repeat: INR 11
  – Her PCP gave vitamin K 10 mg IV push, D/C warfarin
• Contacted ASCLS consumer web forum

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What Happened?
• Dietary change, increased vitamin K?
• Do statins, other drugs interfere with metabolism?
  – Lovastatin and fluvastatin metabolized by CYP450
• Age-related change in warfarin sensitivity?
• Optical coagulometer, lipemia?

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71 YO Female, Atrial Fibrillation
30 Years of 7.5 mg/day Warfarin

• Thursday: fasting INR 1.5
  – Lipemia or vitamin K?
  – Resumed warfarin 7.5 mg/day
• Following Monday: INR 2.5

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The Coumarins

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Warfarin Indications

- Cardiac insufficiency secondary to acute coronary syndrome
  - No longer indicated for uncomplicated acute myocardial infarction
  - Ejection fraction < 30%
- Venous thromboembolism
  - Deep venous thrombosis (DVT)
  - Pulmonary embolism (PE)
- Atrial fibrillation
  - Prevent secondary stroke
- Prosthetic heart valves
  - INR 2.5–3.5

Properties of Warfarin

- Vitamin K antagonist
- Blocks γ-carboxylation of 10-12 glutamic acids near the N-terminus of the VK-dependent coagulation factors
  - Factors II, VII, IX, X
  - Control proteins C, S and Z
- Metabolized by cytochrome P450 (CYP450) pathway

Vitamin K Antagonist Products “PIVKA”

Vitamins in vitamin K antagonism (PIVKA): non-functional coagulation factors

Vitamin K Antagonist Products

Vitamin K antagonist

Proteins in vitamin K antagonism (PIVKA):
- Vitamin K antagonism
- Vitamin K II, X, VII, IX, XIa, Xa, X, Pro-K, INLRK

Warfarin Dose & Pharmacodynamics

- Start 5 mg/d, adjust to PT-based international normalized ratio (INR) 2–3
  - When over 70 years of age, start at 2 mg/day
  - Screen for high risk polymorphisms CYP2C9*2 and *3 and VKORC1 to start at lower dosage
- Onset of action 8 to 12 hours
- Requires 4 to 5 days to achieve stability
- Daily INRs until two match in Rx range
- Observe two INRs/week for first two weeks
  - Confirm stability
- Then every four weeks for duration
Is the PT/INR All it Could Be?
- Optical coagulometers affected by lipemia
- PT prolonged by lupus anticoagulant
- PT invalid in coagulopathies
- INR invalid during transition from direct thrombin inhibitors (argatroban) to warfarin
- INR invalid in first five days of therapy


International Normalized Ratio
- Perform prothrombin time (protime, PT)
- PT is normalized world-wide by applying the INR formula:
  \[ \text{INR} = \frac{\text{PT}_{\text{patient}}}{\text{PT}_{\text{normal mean}}} \times \text{ISI} \]
- INR = international normalized ratio
- PT patient = PT of patient plasma
- PT normal mean = PT of mean of normal range
- ISI = international sensitivity index assigned by manufacturer based on comparison to international thromboplastin reagent
- The laboratory computes the formula and reports all PTs in seconds and as INRs

International Sensitivity Index (ISI)
- Manufacturers assay 20 normal and 60 stable warfarin plasmas using:
  - A WHO international reference preparation (IRP) of thromboplastin with ISI established at 1.0
  - Their commercial lot number of reagent
  - The manual tilt-tube technique in multiple expert labs
  - Various representative instruments
- They generate instrument-specific ISIs for each thromboplastin/instrument combination by regression analysis

Recommended INRs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis and therapy for DVT, PE, atrial fibrillation, cardiac insufficiency</td>
<td>2–3</td>
</tr>
<tr>
<td>Therapy for mechanical valves, complicated or recurrent AMI</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Risk of hemorrhage critical value</td>
<td>&gt; 5.0</td>
</tr>
</tbody>
</table>

PT Variation Among Four Thromboplastins

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Mean (n=9)</th>
<th>Example Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT (sec)</td>
<td>INR PT (sec) INR</td>
</tr>
<tr>
<td>A</td>
<td>16.1</td>
<td>1.5 67.4 31.3</td>
</tr>
<tr>
<td>B</td>
<td>16.9</td>
<td>1.3 81.9 8.7</td>
</tr>
<tr>
<td>C</td>
<td>13.7</td>
<td>1.2 169.0 15.4</td>
</tr>
<tr>
<td>D</td>
<td>17.5</td>
<td>1.5 78.3 9.3</td>
</tr>
</tbody>
</table>

Despite normalization, the INR varies significantly as a function of thromboplastin sensitivity. Quarles LA and Hermann SL, personal communication,1997

Chromogenic Factor X Assay

- Digests colorless S-2765 N-a-Z-D-Arg-Gly-Arg-pNA
- Releases yellow pNA, measure at 405 nm

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Chromogenic X In Place of PT?


The data suggest the CFX can be a useful tool for monitoring oral anticoagulation in patients in which INR confounders are present.

Chromogenic X in Place of PT?

Warfarin Limitations

- These supply vitamin K and reduce warfarin efficacy:
  - Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba, parenteral nutrition formulations
- Over 80 drugs unpredictably influence CYP2C9 cytochrome oxidase pathway
- Warfarin allergy with anaphylaxis

Dosage Anomalies

- Polymorphisms
  - CYP2C9*2 and CYP2C9*3
  - VKOR1
  - Increased warfarin sensitivity
  - Screen and start with 2 mg/d
- Warfarin receptor insufficiency
  - Hereditary warfarin resistance
  - Require dosages of 25 mg/d or more
  - CYP4F2 variant raises dosage 1 mg/d (Feb 08)


Warfarin Therapeutic Window


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### Risk of Thrombosis During First Five Days of Therapy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-life</th>
<th>Mean Plasma Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin</td>
<td>60 h</td>
<td>10 mg/dL</td>
</tr>
<tr>
<td>VII</td>
<td>6 h</td>
<td>0.05 mg/dL</td>
</tr>
<tr>
<td>IX</td>
<td>24 h</td>
<td>0.3 mg/dL</td>
</tr>
<tr>
<td>X</td>
<td>50 h</td>
<td>1 mg/dL</td>
</tr>
<tr>
<td>Protein C</td>
<td>6 h</td>
<td>2-6 mcg/mL</td>
</tr>
<tr>
<td>Protein S</td>
<td>20-25 mcg/mL</td>
<td></td>
</tr>
</tbody>
</table>


### Warfarin Overdose

- Most common cause of ER hemorrhage
- Oral, IM, or IV vitamin K provides 6-hour reversal
- Frozen plasma, prothrombin complex concentrate, NovoSeven® (VIIa) provide immediate reversal


### Cumulative Adverse Outcomes in VTE Patients on Anticoagulation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30-d</th>
<th>1-y</th>
<th>3-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>9.4%</td>
<td>11.6%</td>
<td>15.8%</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>3.5%</td>
<td>10.7%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Mortality</td>
<td>13.0%</td>
<td>26.0%</td>
<td>35.3%</td>
</tr>
</tbody>
</table>


### Summary of Warfarin Disadvantages

- Five days’ onset of therapy
  - Must bridge with heparin
  - Monitor daily until stable
- Narrow therapeutic window
  - Risk of secondary thrombotic event and hemorrhage
  - Need for lifelong monitoring
- Inter-individual dosing differences
  - Age: pediatric and geriatric variations
  - Three polymorphisms cause sensitivity
  - Warfarin resistance causes under investigation
- Neutralization by dietary vitamin K
- Interactions with drugs that metabolize via CYP450

### Platelet Membrane Glycoprotein Iib/IIa Inhibitors (GPIs)

- GP Iib/IIa is a membrane arginine-glycine-aspartate (RGD) sequence receptor
  - Binds fibrinogen and vWF; supports aggregation
- Eptifibatide (Integrilin®) RGD mimic
  - Use with aspirin or clopidogrel (Plavix®) and heparin
  - IV loading dose of 180 mcg/kg over 1 to 2 minutes
  - Continuous infusion of 2 mcg/kg/m up to 72 h

66 YO Male

- Acute Myocardial Infection
  - Crushing substernal pain upon retiring
  - 325 mg ASA PO at home
  - Transported to cardiac catheterization lab within 90 minutes for percutaneous intervention (PCI, angioplasty and stent)
    - If >3 hours in transport, start thrombolytic therapy
      - Tissue plasminogen activator (TPA, Alteplase)

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Two More Platelet Membrane Glycoprotein IIb/IIIa Inhibitors (GPIs)

- **Abciximab (ReoPro®)** anti-IIb/IIIa antibody
  - 0.25 mcg/kg/1 min, then 0.125 mcg/kg/min to 10 mcg/min
  - Plasma half life 30 minutes
- **Tirofiban (Aggrastat®)** peptide inhibitor
  - Analogue of Echinus carinatus venom component
  - Use with aspirin or clopidogrel (Plavix®) and heparin
  - IV 0.4 mcg/kg/min for 30 minutes
  - Then 0.1 mcg/kg/min up to 48 hours

GPI Dosing and Thrombocytopenia

- Weight-adjusted GPI dose without lab monitoring is ineffective
  - Poor platelet suppression risks thrombosis
- Monitor with platelet aggregometry using thrombin receptor activation peptide (TRAP)
- POC: Accumetrix Ultegra IIb/IIIa assay using TRAP
- Risk of severe thrombocytopenia
  - Daily platelet counts

Multiplate Analyzer by DiaPharma

Introducing The Multiplate Analyzer
Assess Platelet Function Sensitive to:
- *Chlopropanol*  
- *Aspirin*  
- *GPIb/IIIa Antagonists*

Exclusive US & Canadian Distributor

Coronary Bypass Graft Unfractionated Heparin (UFH)

- UFH bolus: 5000–10,000 IUs
  - Two hours after termination of thrombolytic therapy
  - Simultaneous with GPIs
- Maintenance dosage: 1600 IU/hour
- Terminate at discharge, max 5 days

Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopoly saccharide glycosaminoglycan is 30-60 sugars long

Unfractionated Heparin Binds Antithrombin With Thrombin

AT

Fibrin Binding Site

Heparin Binding Site

Active Protase Site

Bridging

Thrombino-antithrombin (TAT)
Whatever Happened to the PT and PTT?

Unfractionated Heparin Binds Xa and Antithrombin

UFH and LMWH Effect on PTT

<table>
<thead>
<tr>
<th>Factor</th>
<th>UFH</th>
<th>LMWH</th>
<th>Fonda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xlla, PK, HMWK</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xla</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>IXa</td>
<td>2+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Xa</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>IIa (thrombin)</td>
<td>3+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Monitoring UFH Therapy Standard Schedule

- Perform “baseline” PTT to rule out factor deficiency, inhibitors, lupus anticoagulant
- Initiate therapy: bolus + continuous infusion
- At least 4–6h after initiation, not >24h, perform second PTT
- Adjust dose to PTT therapeutic range
  - Never use 1.5–2.5 x mean of normal range
  - Use laboratory-published range
- Laboratory generates range using Brill-Edwards ex vivo curve

Establishing The PTT Heparin Therapeutic Range

- Collect at least 50 patient specimens
  - All heparin dosage ranges
  - No oral anticoagulant, PT normal
- Collect at least 20 normals
  - Representative demographics
- Chromogenic PTT and anti-Xa heparin
- Graph of paired results
- Correlate PTT range to the anti-Xa range
  - Therapeutic: 0.3-0.7 heparin anti-Xa units
  - Prophylactic: 0.2-0.4 heparin anti-Xa units

Limitations of PTT in UFH Monitoring

- Lupus anticoagulant, present in 1-2% of unselected individuals, prolongs PTT
- Coagulopathy prolongs PTT
- Coagulation factor inhibitor prolongs PTT
- Elevated FVIII renders PTT insensitive to heparin
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot

- Brit-Edwards curve
- Antithrombin deficiency or consumption renders PTT non-responsive, “heparin resistance”


Chromogenic Anti-Xa Heparin Assay

AT + Xa

AT + Xa

AT

Xa

Substrate

Product

Synthetic Pentasaccharide, Fondaparinux (Fonda)

Glucosamine

Glucuronic acid

Iduronic acid


Fonda and Antithrombin

- Sulfate residues critical to high-affinity AT binding
- Conformational change in AT raises Xa affinity 300X

Arixtra: Irreversible inhibition of Xa, no affinity for thrombin or other serine proteases


Synthetic Pentasaccharide, Fondaparinux (Fonda)

Glucosamine

Glucuronic acid

Iduronic acid


Monitoring Fondaparinux

- Chromogenic anti-Xa calibrated with pentasaccharide in mg/L
  - No international standard
  - Standards available from Beckman-Coulter and Ariara for their kits
- SC (never IM) injection; 2.5 mg
  - Peak plasma level at 3 h: 0.4–0.5 mg/L
  - Minimum steady state 0.14–0.19
- No current therapeutic range

Fonda Advantages

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

Fonda Disadvantages

- Risk of major bleed 2.7%, LMWH 1.7%
- Overdose: no direct reversal, long half-life
- Cost exceeds LMWH by 50%
  - Offset by reduced adverse events

Fonda Contraindications

- Renal disease: kidney only excretion route
- Weight less than 50 kg
- Over 75 years old; not included in studies
- Bleeding Hx
  - Congenital or acquired coagulopathies
  - Ulcerative gastrointestinal disease
  - Hemorrhagic stroke

Rivaroxaban (Xarelto®)

- An oxazolininone derivative direct anti-Xa
- Safety and efficacy exceed Lovenox in three out of four phase III trials

Prophylaxis: Four Phase III Studies

- Rivaroxaban at 10 mg po/daily is effective as VTE prophylaxis
- Mean risk of major and total VTE recurrence < 3%
Whatever Happened to the PT and PTT?

Treatment: EINSTEIN-DVT 2010

Study arms: n = 3449
- Treatment: 15 mg rivaroxaban BID X 3 week, 20 mg daily
- Usual care: LMWH 5 days; warfarin

Efficacy: first VTE event
- 2.1% vs 3.0%, hazard ratio 0.68, p < 0.0001

Safety: composite of major & minor bleeds
- 8.1% for both, p = 0.7

Composite of efficacy and safety
- 2.9% vs 4.2%, hazard ratio 0.67
- No liver toxicity in all studies

Rivaroxaban inhibits free, fibrin-bound Xa, and IXa-bound Xa, requires no AT

Rivaroxaban
- Oral dose: 10 mg/day; steady state at 4 hours
- Neutralizes free, clot-bound, and IXa-bound Xa
  - Interacts with no other serine proteases
- Excretion: 66% renal, 28% fecal
- Monitoring: none required?
  - Doubles PT interval at 230 nM
  - Doubles PTT interval at 690 nM
  - Neutralizes Xa
- No outcomes-based laboratory therapeutic range established
- Cleared for prophylaxis; Canada & Europe 5/2009

Dose Response to Rivaroxaban by FXa, Prothrombinase (Xa/Va)

Rivaroxaban inhibits free, fibrin-bound Xa, and IXa-bound Xa, requires no AT
### Rivaroxaban Interactions

- **No food interactions**
- **P-glycoprotein inhibitors**
  - PGPs are enteric pathways that protect from toxins
  - Inhibitors include azole antimycotics (ketoconazole)
- **P450 3A4 inhibitors**
  - HIV protease inhibitors (ritonavir)
- **NSAIDS, aspirin, and clopidogrel**
- **OTC supplements such as St. John’s Wort, platelet inhibitors**


### Apixiban in VTE Prophylaxis

- **12 days, 2.5 mg twice a day**
- **Comparator: enoxaparin**
- **Primary safety: major bleeding**
- **Primary efficacy: composite VTE**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Enox</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE 1</td>
<td>3195</td>
<td>30 mg</td>
<td>0.7 V 1.4%</td>
<td>9% V 8.9%</td>
</tr>
<tr>
<td>ADVANCE 2</td>
<td>1973</td>
<td>40 mg</td>
<td>0.6 V 0.93%</td>
<td>15% V 24%</td>
</tr>
</tbody>
</table>

### Apixiban V Aspirin: AVERROES

- **Safety: major, minor, intracranial, and fatal bleeding: 13% increase (NS)**
- **Apixiban vs Aspirin: AVERROES**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixiban</th>
<th>Aspirin</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolic event</td>
<td>1.6</td>
<td>3.6</td>
<td>0.46</td>
</tr>
<tr>
<td>MI</td>
<td>0.7</td>
<td>0.8</td>
<td>0.85</td>
</tr>
<tr>
<td>Vascular death</td>
<td>2.5</td>
<td>2.9</td>
<td>0.86</td>
</tr>
<tr>
<td>Total death</td>
<td>3.4</td>
<td>4.4</td>
<td>0.79</td>
</tr>
</tbody>
</table>

### Direct Thrombin Inhibitors (DTIs)

- **Indication: heparin-induced thrombocytopenia (HIT)**
- **Do not generate or bind anti-heparin-PF4**
  - Platelet counts recover within three days
- **Rapidly reduce thrombin production in HIT**
  - Warfarin too slow
  - LMWH may cross-react
  - Fondaparinux OK


### Crosslinked Fibrin

[Diagram of Crosslinked Fibrin]

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Argatroban (Novastan®)
- Raises nitric oxide, causing vasodilatation
- Metabolized and excreted by liver CYP450

Argatroban Administration and Monitoring
- IV: 2 mcg/kg/m: immediate steady state
  - 5–7 d
  - Maintain PTT 1.5–3 x MRI
    - Linear to 40 mcg/kg/m
    - Ecarin clotting time
    - Prolongs PT
    - Doubles INR when bridging to Warfarin
- During PCI
  - Bolus 350 mcg/kg
  - Continuous infusion 15–40 mcg/kg/m
  - Maintain ACT 300–450 seconds

Argatroban Comments
- Safe to use in renal disease
- Liver disease
  - Reduce to 0.5 µg/kg/h and monitor with PT
- Major bleeds 5.3%, minor 14.4%
- No antidote, but half-life is 40 minutes
- Inhibits free and fibrin-bound thrombin

Hirudin: Lepirudin
- Inhibits free, not bound thrombin
- Metabolized and excreted by kidney
  - Monitor in kidney disease

Lepirudin Administration
- IV bolus: 0.4 mg/kg/h
- Infusion 0.1–0.15 mg/kg/h 11–14 d
- Steady state within 2.5 hours
- Maintain PTT at 1.5–3 x MRI
- Clearance half-life 20 minutes
- Coronary bypass: 0.25 mg/kg/h
  - ACT > 350 s
  - ECT > 250 s

Bivalirudin
- Thrombin active site-directed peptide, D-Phe-Pro-Arg-Pro, linked to an analogue of the carboxy-terminal of hirudin
**Bivalirudin**
- Neutralizes free and bound thrombin
- FDA-cleared spring, 2008
  - Reduced major hemorrhage by 41% to 61%
  - Use with aspirin only
  - Bolus 0.75 mg/kg plus 1.75 mg/kg/h
  - Renal excretion, 25 m half-life

**Bivalirudin in Renal Disease**
- If creatinine clearance is <30 mL/minute, reduce infusion to 1 mg/kg/h
  - No reduction in bolus
- If a patient is on hemodialysis, reduce infusion to 0.25 mg/kg/h
- Monitor with PTT or ACT
  - Therapeutic range not defined

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**Chromogenic X When Transitioning from a Direct Thrombin Inhibitor to Warfarin**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inr</td>
<td>14.3</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Tt</td>
<td>6.6</td>
<td>3.4</td>
<td>2.4</td>
</tr>
<tr>
<td>PT</td>
<td>1.0</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>ACT</td>
<td>20.5</td>
<td>13.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>


**Dabigatran (Pradaxa®)**
- Oral DTI cleared for prophylaxis in Canada and Europe
  - Application to US FDA 2008
- Indication: post-surgical VTE prevention
- Dose 110 mg/d with wide safety range
  - Immediate steady state
  - No laboratory monitoring
- Binds clot-bound and free thrombin
- Renal excretion 80%
  - Reduce dosage and monitor in renal disease
- Half-life 12–17 hours
- No interaction with food
- Not metabolized by CYP450 pathway
- Levels raised by quinidine and verapamil
- Predictable efficacy
- No liver toxicity
- Dyspepsia
Whatever Happened to the PT and PTT?

Dabigatran Efficacy and Safety In Three Phase III Trials

<table>
<thead>
<tr>
<th>Dabigatran placebo (150 mg bid)</th>
<th>Dabigatran 150 mg bid</th>
<th>Dabigatran 220 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPAIRED: 32.4%</td>
<td>6.5% (95% CI 1.0-4.0)</td>
<td>6.5% (95% CI 1.0-4.0)</td>
<td>6.5% (95% CI 1.0-4.0)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.3 (95% CI 1.0-6.0)</td>
<td>3.3 (95% CI 1.0-6.0)</td>
<td>3.3 (95% CI 1.0-6.0)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>22.0 (95% CI 15.0-30.0)</td>
<td>22.0 (95% CI 15.0-30.0)</td>
<td>22.0 (95% CI 15.0-30.0)</td>
</tr>
</tbody>
</table>

Dabigatran Vs Warfarin in Atrial Fibrillation

FDA Advisory Panel 9/20/2010
We’re getting ever closer


Laboratory Assessment

<table>
<thead>
<tr>
<th>Anti-coagulant</th>
<th>Dose</th>
<th>ECT</th>
<th>Anti-Xa</th>
<th>TCT</th>
<th>PT</th>
<th>PTT</th>
<th>Chromo II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>200 mg TID</td>
<td>5.2x</td>
<td>NE</td>
<td>27x</td>
<td>NR</td>
<td>2.3x</td>
<td>NR</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>30 mg BID</td>
<td>NE</td>
<td>68%</td>
<td>NE</td>
<td>2.6x</td>
<td>1.8x</td>
<td>NR</td>
</tr>
<tr>
<td>Apixaban</td>
<td>25 mg BID</td>
<td>NE</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.2x</td>
<td>NR</td>
</tr>
</tbody>
</table>

ECT, ecarin clotting time; Anti-Xa, chromogenic anti-Xa heparin; PT, prothrombin time; PTT, partial thromboplastin time; TID, three times a day; BID, twice a day; x, fold increase from baseline at peak concentration; NE, no effect; NR, not reported.

Safe, even during pregnancy
Does not bind plasma or cellular proteins
No laboratory monitoring
Wide therapeutic window
Best Anticoagulant Award
Prevents thrombosis
Cheap
Long half-life but reversible
No hemorrhage

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