Whatever Happened to the PT and PTT?

How to Measure the New Anticoagulants

George A Fritsma MS, MLS
The Fritsma Factor, Your interactive Hemostasis Resource
www.fritsmafactor.com
Objectives

- Monitor Coumadin (1954)
- Monitor unfractionated heparin (1936)
- Measure oral, direct Xa inhibitors: rivaroxaban (2011), apixaban (2012), edoxaban (next)
- Measure intravenous direct thrombin inhibitors argatroban (1997), bivalirudin (2000)
- Measure oral DTI dabigatran (2009)

Indications for Anticoagulant Therapy

- Treatment 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 non-valvular atrial fibrillation
- Prosthetic heart valves
- Acute coronary syndromes: acute myocardial infarction, peripheral artery obstruction, ischemic stroke, cardiac insufficiency
AFIB Prevalence Projections

Venous Thromboembolism

- 23,000,000 USA residents/y have high risk surgery; ~20% acquire 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
- PE is the most common cause of preventable death
- Traditional and new oral A/Cs play large roles 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 7/5/12
New Oral Anticoagulants (NOACs)

“The Girls”

Do they work?

Fonda

How to measure?

Riva

Why measure?

Edi

Dabi

Pixi
# US FDA-Cleared NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Stroke prophylaxis in AFIB</th>
<th>TKR &amp; THR prophylaxis</th>
<th>Post-VTE treatment</th>
<th>CAD treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>2009</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>2011</td>
<td>2011</td>
<td>2012</td>
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<td>Apixaban (Eliquis®)</td>
<td>2012</td>
<td>FDA 501K</td>
<td>FDA 501K</td>
<td>FDA 501K</td>
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<tr>
<td>Edoxaban (Lixiana®)</td>
<td>Phase 3</td>
<td>Phase 3</td>
<td>Phase 3</td>
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</tbody>
</table>
**Anticoagulant Measurement**

**Not The Same as Monitoring**

- Renal disease: inadequate excretion, CrCl <30 mL/m
- Patients not included in clinical trials, >75 YO, for example
- Compliance and underdosing
- Potential parallel drug interference
- Acute hemorrhage (usually in ER)
  - Overdose, effects of co-medication
  - Detection & identification; what A/C is it?
  - Is reversal working?
- Bridging from one A/C to another before surgery
- Marginal fluid compartment (not included in clinical trials)
  - >150 kg: proportionally reduced fluid compartment
  - <40 kg or ped: proportionally increased fluid compartment
- Unstable coagulation mechanism
  - Pregnancy, liver disease, malignancy, chronic DIC
The Fritsma Factor

History of Warfarin (Coumadin)

- 1940: Campbell K: coumarin extracted from clover
- 1945: Warfarin patented as rodenticide
- 1951: attempted suicide reversed
- 1954: FDA-cleared
Coumadin Indications

• Cardiac insufficiency secondary to acute coronary syndrome (ACS)
  – Ejection fraction <30%

• Venous thromboembolism (VTE)
  – Deep venous thrombosis (DVT)
  – Pulmonary embolism (PE)

• Atrial fibrillation (AFIB)
  – Prevent secondary stroke

• Prosthetic heart valves
Coumadin Dose & Pharmacodynamics

- Start at 5 mg/d, adjust to PT-based international normalized ratio (INR) 2–3
  - When over 70 yo, start at 2 mg/d
  - Onset 8–12 hours
- Requires 4–5 days to achieve stability
- Daily PTs until 2 consecutive INRs match in Rx range
- Then two PT-INRs/week for two weeks
  - Confirm stability
- Then PT-INRs every 4–12 (?) weeks

Coumadin Limitations

• >80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway

• These supply vitamin K and reduce efficacy
  – Green vegetables, avocados, liver, nutrition drinks like Ensure, dietary supplements like ginkgo biloba and glucosamine, parenteral nutrition formulations

• Coumadin overdose is most common reason for ER hemorrhage visits
  – Reversal with VK requires 6–10 hours

• Coumadin allergy with anaphylaxis
Coumadin Dosage Anomalies

- **Coumadin receptor insufficiency**
  - Require dosages of 25 mg/d or more
  - CYP4F2 variant raises dosage 1 mg/d (Feb 08)

- **Polymorphisms raise sensitivity**
  - CYP2C9*2 and CYP2C9*3, VKORC1:

<table>
<thead>
<tr>
<th>VKORC1 Genotypes</th>
<th>Cytochrome Oxidase Pathway (CYP) 2C9 Genotypes</th>
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<tbody>
<tr>
<td></td>
<td><em>1</em>1 (WT)</td>
</tr>
<tr>
<td>GG (wild-type)</td>
<td>5–7</td>
</tr>
<tr>
<td>AG</td>
<td>5–7</td>
</tr>
<tr>
<td>AA</td>
<td>3–4</td>
</tr>
</tbody>
</table>

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

- Monday: INR 11, no bleeding symptoms
  - Target range 2–3
  - Hx: when INR 5–6: bruising, bleeding gums, epistaxis

- Tuesday repeat collection: INR 11
  - Vitamin K 10 mg IV push, D/C Coumadin
  - Just started on statin
    - Total cholesterol: 263 mg/dL
    - Triglycerides: 319 mg/dL (lipemia?)

- Thursday collected fasting: INR 1.5
  - Resume Coumadin 7.5 mg/day
  - Was it the vitamin K or lipemia?

- Monday: INR 2.5: no additional follow-up
PT prolonged by Coumadin and VII, X, V, II, Fg deficiencies

Coumadin creates des-γ-carboxy-II, VII, IX, and X

Figure courtesy of Margaret G. Fritsma
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

Chromogenic Factor X (CFX)

Factor X → Russell viper venom + Ca++ → Factor Xa

Bz-Ile-Glu (g-OR)-Gly-Arg-pNA·HCl

Cleavage site

S-2222 → pNA

pNA intensity at 405 nm is proportional to factor X activity

\[ y = 0.76x + 21.77 \]

\[ R^2 = 0.90 \]
CFX In Place of PT?

“Data suggest the CFX can be a useful tool for monitoring VKA anticoagulation when INR confounders are present.”
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”

The Fritsma Factor

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50 YO Man with Bilateral PE

- Overweight, sedentary, swollen ankle, shortness of breath
- Heparin Rx two days
  - Bolus: 5000–10,000 units or 80 units/kg
  - Maintenance dosage: 1600 units/hour or 18 units/kg/hour
  - Switched to LMWH twice a day
- Heparin Hx
  - Johns Hopkins 1916
    - Pre-FDA: isolated from dog liver and described
  - Clinical trials 1935, Karolinska institut, Vitrum AB
    - FDA-cleared 1936
- Also used in coronary artery bypass graft
Unfractionated Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopolysaccharide glycosaminoglycan
Unfractionated Heparin

UFH binds antithrombin (AT) and thrombin (IIa), neutralizes IIa by allostery and bridging.
Unfractionated Heparin

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

\[ \text{IIa}:\text{Xa} = 4:1 \]
PTT prolonged by heparin, lupus anticoagulant, XII, XI, IX, X, V, II, Fg deficiencies

Figure courtesy of Margaret G. Fritsma
Monitoring UFH Therapy
Standard Schedule

- Perform “baseline” PTT to r/o factor deficiency, inhibitors, lupus anticoagulant
  - 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
  - *Never use* 1.5–2.5 x mean of normal range

UFH Rx Range Using the PTT
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
Chromogenic Anti-Xa Heparin Assay

Intensity at 405 nm is inversely proportional to patient heparin concentration
HEPARIN THERAPEUTIC RANGE

PTT 65−104 s
0.3−0.7 anti-Xa heparin units/μL
PTT/Anti-Xa Data, Three Routine Days

Low anti-Xa, prolonged PTT

High anti-Xa, normal PTT

$R^2 = 0.3874$

Anti-Xa Heparin Units/mL vs. PTT
Limitations of PTT in UFH Monitoring

- Antithrombin deficiency or consumption renders PTT non-responsive, “heparin resistance”
- Lupus anticoagulant, present in 1–3% of unselected individuals, prolongs baseline 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

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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

LMWH Binds Mostly Xa

\[ \text{IIa:Xa} = 1:2 \]
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
Parenteral Synthetic Pentasaccharide
Fondaparinux (Fonda)

Fonda and Antithrombin

- Sulfate residues critical to high-affinity AT binding
- AT allostery raises Xa affinity 300X

![Diagram showing the interaction between Antithrombin (AT) and Xa protease, highlighting the binding sites and irreversible inhibition of Xa.](image)
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
Measuring Fonda

- **Fonda: 2.5 mg SQ injection**
  - Rx range: 0.60–1.50 mg/L
  - Prophylactic range: 0.10–0.50 mg/L
  - Discontinue if creatinine >2.0 mg/dL or if GFR <30 mL/min

- **Anti-Xa chromogenic heparin assay**
  - Collect 3 h after SC injection
  - Requires fonda calibrators and controls
  - PTT insensitive to fonda

- **Regular CBCs, monitor platelet count, stool for blood**
Fonda Advantages

- Half-life 17 h; one SQ 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

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 events
- Renal disease: contraindicated if CrCl <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

Chromogenic Anti-Xa Heparin Curve

- Hybrid curve for UFH and LMWH
- Additional LMWH formulations: Tinzaparin
  - Aventis 5/1/09 Lovenox patent expired
- Separate curve for fonda requires calibrators and controls
  - mg/dL, not international units

Riva, Plxi, Edi Directly Inhibit Xa

Riva, pixi, edi inhibit Xa/Va prothrombinase activity w/o antithrombin
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, no reversal


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
Riva Indications and Dosages

- 10 mg/d for VTE prophylaxis
  - TKR, THR
  - FDA-cleared 7-1-11, Canada and EMA 5-2009
- 20 mg/d stroke prophylaxis in AFIB, 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, but cleared 3-22-13 by EMA @ 2.5 mg/d
- Measure: PT or PTT?, insensitive and variable
  - Anti-Xa chromogenic: calibrate to riva formulation
  - Therapeutic range?

Riva STEMI study: 7800 Patients (ST-segment elevation MI)

- Dosage 2.5 mg/d
- Patients on aspirin and clopidogrel
- Reduced risk of CV death, MI, or stroke by 19%
- Benefits emerged within 30 days and persisted
- Metabolized through CYP3A4
  - CYP3A4 inducers reduce rivaroxaban plasma concentration: rifampicin, phenytoin, carbamazepine, phenobarbital, St John’s Wort
  - CYP3A4 inhibitors lead to a 1.3–1.7-fold rise in rivaroxaban concentration: ketoconazole, ritonavir, erythromycin
Oral Apixaban ("Pixi")

- 28 trials: ADVANCE 1,2,&3, ADOPT, APROPOS, ARISTOTLE
- Excretion: 27% renal, ~70% hepatic and intestinal
- Stoichiometric inhibition, steady state at 4 h
- Half-life is 12–15 h, Xa suppressed 24 h

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
ARISTOTLE: Pixi

• Compared to Coumadin…
  – In AFIB, Pixi reduced stroke & systemic embolism by 21% (p<0.01)
  – 31% fewer bleeds (p<0.001)
  – 11% lower mortality (p=0.047)
  – Lower discontinuance rate than Coumadin

• Cleared 5-20-11 for VTE therapy by EMA
  – 2.5 mg twice a day
  – Hip: 32–38 days
  – Knee: 10–14 days

• FDA-cleared 12-12 to reduce risk of stroke & embolism in AFIB at 2.5 mg twice a day

• Measure same as riva
Oral Edoxaban ("Edi")

- Cleared in Japan July, 2011 for VTE prophylaxis in TKR and THR
- 15 current phase III trials: VTE prophylaxis and Rx, AFIB, peripheral artery disease

\[
N'-(5\text{-chloropyridin-2-yl})-N\text{-}[(1S,2R,4S)-4-(\text{dimethylcarbamoyl})-2-\{(5\text{-methyl-6,7-dihydro-4H-[1,3]}\text{thiazolo}[5,4-c]pyridine-2-carbonyl)}\text{amino}]\text{cyclohexyl}\text{oxamide}
\]
Anti-Xa Chromogenic Assay

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

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

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Direct Thrombin Inhibitors (DTIs)

- **Indication**: heparin-induced thrombocytopenia (HIT)
  - Cause: antibodies specific for heparin-PF4 activate platelets
  - DTIs do not generate or interact with anti-heparin-PF4
  - Platelet counts recover three days after switch to DTI

- **Rapidly reduce thrombin production**
  - Coumadin too slow
  - LMWH may cross-react
  - Fonda OK

- **Prevent ischemic stroke in atrial fibrillation (AFIB)**
  - Dabigatran (dabi)

DTIs: Argatroban, Bivalirudin, Dabigatran

Extrinsic
- Parenteral: argatroban, bivalirudin
- Oral: dabigatran

Intrinsic

Common

DTIs: Argatroban, Bivalirudin, Dabigatran

Figure courtesy of Margaret G. Fritsma
Argatroban (Novastan®)

- Raises nitric oxide, causing vasodilation
- Metabolized and excreted by liver CYP450
- IV: 2 µg/kg/minute 5–7 d: immediate steady state
- Cardiac catheterization: bolus 350 µg/kg; continuous infusion 15–40 µg/kg/minute
Argatroban Comments

- Major bleeds 5.3%, minor 14.4%
- Safe in renal disease
- Liver disease: 0.5 mcg/kg/h and measure
- No antidote, but half-life is 40 minutes
- Inhibits free and fibrin-bound thrombin

\[
\text{Arg} \quad \text{Ila}
\]

\[
\text{Fibrin}
\]
Bivalirudin

Thrombin active site-directed peptide, D-Phe-Pro-Arg-Pro, linked to an analogue of the carboxy-terminal of hirudin, derived from medicinal leech saliva

2180 D, dodecapeptide

Hirudo medicinalis
Bivalirudin

• Neutralizes free and bound thrombin
• FDA-cleared for use with aspirin 2000
  • Reduces major hemorrhage 41% to 61%
• Renal excretion, 25 m half-life
• Bolus 0.75 mg/kg + 1.75 mg/kg/h infusion
• If CrCl is <30 mL/m, reduce to 1 mg/kg/h
• In hemodialysis, reduce to 0.25 mg/kg/h
Oral Dabigatran Etexilate (dabi)

• 60 trials in progress or completed; e. g., RE-LY
• EMA-cleared 3-18-08: Health Canada 6-10-08: 220 mg/d
  – VTE prophylaxis post-TKR, THR, two 110 mg tablets/d
• FDA-cleared 10-19-10, EMA 7-1-11: 150 mg/bid for stroke prevention in AFIB

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
Dabi Pharmacokinetics

- Half-life 12–17 h, > 60 h in renal disease
  - Reduce dosage by 50%, measure repeatedly when CrCl < 30 mL/m
- No interaction with food, no liver toxicity
- Levels raised by quinididine and verapamil
- Metabolized by esterase
  - Not CYP450 pathway
- Renal excretion 80%
- Dyspepsia 10%
Measuring Dabi

- Thrombin time: hypersensitive, qualitative only
  - Normal implies absence, any DTI generates results >>20s
- Plasma-diluted thrombin time
- Ecarin chromogenic assay
  or ecarin clot
time
- PTT

Plasma-Diluted Thrombin Time and Chromogenic Assay for DTIs

Test plasma + Normal human plasma → Fibrin Polymer

Substrate → Product

OR

Fibrinogen → Fibrin Polymer


Ecarin Clotting Time/Chromogenic (ECA)

Chromogenic assay: Intensity at 405 nm is inversely proportional to DTI concentration

Clot-based assay: clotting time is inversely proportional to DTI concentration

No inhibitor or factor deficiency effects

Saw-scale Viper: Echis carinatus

Ecarin

Prothrombin

Meizothrombin

Thrombin

Fibrinogen

Fibrin Polymer

Substrate → Product

DTI

Stago
# Dabi Assay Comparisons: 70 Patients

<table>
<thead>
<tr>
<th>Assay</th>
<th>Reference</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-diluted thrombin time</td>
<td>Liquid chromatographic mass spectrometry (LCMS)</td>
<td>0.97</td>
</tr>
<tr>
<td>Ecarin clotting time</td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Endogenous thrombin potential</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
<td>No correlation</td>
</tr>
<tr>
<td>Plasma-diluted thrombin time</td>
<td>Ecarin clotting time</td>
<td>0.94</td>
</tr>
</tbody>
</table>

- Patient LCMS range 0–586 ng/mL dabi, median 45, 95% CI 48–111
- Plasma-diluted thrombin time and ecarin clotting time generate CVs >30% when dabi < 30 ng/mL, cannot use either to confirm dabi absence
- PTT remains within RI (<40s) even when dabi >60 mg/mL
- Prothrombin time and endogenous thrombin potential do not measure dabi

Dabi Assay Comparison, 6 Subjects

Plots of mean PTT, INR, TT and ECT prolongation ratios and concentration of dabigatran following a single dose oral dose of 200 mg dabigatran etexilate.

PTT and Dabi

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

Summary: NOAC Measurement

• Assay choice: stat, routine, point of care
• All are RUO
• PT for anti-Xa’s? PTT for DTIs?
  – Stopgap: variation among reagents
• Rx range: clinical trial levels do not predict therapeutic outcomes
• Standardize collection time: peak and trough
• Calibrators: parent drug for riva, pixi, & edi
  – Dabi: plasma-diluted TT calibrators and controls
  – Riva: calibrators and controls with anti-Xa assay

DRVVT Confirm?  (Added 9-19-13)

- Insensitive to VII, VIII, IX, XI, XII, PK, LMWH
- Use only DRVVT Confirm reagent
  - High PL, insensitive to LA
- Prolongs in ↓ Fll & FX
  - Direct antithrombin dabi (D)
  - Direct anti-Xa riva, pixi, edi (R, A, E)
- Near-linear: Stago, IL, Precision, Siemens
- PTT: “curvilinear,” variable

ISTH Measurement Guidelines

- DTIs; dabi
  - PTT is acceptable in emergency to determine relative treatment intensity, but response varies by reagent and lot
  - Normal thrombin time indicates low or undetectable dabigatran
  - Plasma-diluted thrombin time with calibrators and controls may be use for drug levels
  - Ecarin clotting time is recommended on package insert

- Anti-Xas; riva, pixi, edi
  - PT is acceptable in emergency to determine relative treatment intensity, but response is poor and varies by reagent and lot
  - Anti-Xa with calibrators and controls may be used for drug levels

## Comparing Dabi and Riva/Pixi Effects

<table>
<thead>
<tr>
<th>Assay</th>
<th>Dabi</th>
<th>Riva/Pixi</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vitro</em> experiment: added 0–2.5 ug/mL NOACs to normal plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated clotting time</td>
<td>306 s</td>
<td>149 s</td>
</tr>
<tr>
<td>Thromboelastograph</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>PT, PTT, Heptest (clot-based anti-Xa)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Suppressed thrombin-induced aggregation</td>
<td>None</td>
</tr>
<tr>
<td>Thrombin generation</td>
<td>0.19–0.23 ug/mL</td>
<td>0.43–0.90 ug/mL</td>
</tr>
</tbody>
</table>

Dabi Risks

• During 1\textsuperscript{st} quarter of 2011 FDA received 932 reports involving Pradaxa, including 120 deaths
  – At least 505 involved bleeding
  – Rx with 2\textsuperscript{nd} 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
Paradaxa (sic) Lawsuit

“Pradaxa (dabigotran) (sic) is a blood thinner used to prevent stroke in patients suffering from irregular heart beat. Medical journal studies have identified an increased risk of bleeding and hemorrhaging due to the use of Pradaxa. Also, a recent study showed that patients taking Pradaxa have a 33% greater chance of developing heart disease or experiencing cardiac arrest when compared to a popular alternative, warfarin.”

John Smith, MD, senior VP for Pradaxa maker Boehringer Ingelheim, claims the study was flawed. Smith notes that a recent manufacturer-funded study found that the increase in heart attacks with Pradaxa is not enough to be scientifically meaningful. But more important, he says, is that even the authors of the quoted study find Pradaxa's benefits to outweigh its risks.
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
### NOACs Versus Coumadin

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

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

- **Mild**
  - Delay or discontinue next dose, discontinue parallel medication

- **Moderate**
  - Supportive measures: compression, surgical intervention, colloids, frozen plasma, RBCs, platelet concentrate if count is <60,000
  - For dabigatran: Alimentary activated charcoal absorption, maintain diuresis, consider hemodialysis

- **Severe, life-threatening**
  - 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

Dabi Reversal by Hemodialysis in End-stage Renal Disease

- 7 pts on dabi were effectively reversed with dialysis
- ESRD without AFIB, up to 9 parallel drugs

NOAC Reversal

- Perosphere & Daiichi-Sakyo PER 977 small molecule neutralizes fonda, dabi, riva, pixi, and edi. In vitro and is effective without side effects in mice; human trials in progress.

**PER 977 neutralizes rivaroxaban**

Slide courtesy of Dave McGlasson, Wilford Hall USAF Medical Center

NOAC Reversal Agents
2013 ISTH Selected Abstracts

- PRT064445 recombinant human anti-Xa reduced pixi 65% in 9 normal subjects by chromogenic Xa; no D-dimer, OC 20.1
- Long-life plasma Xa reversed riva’s thrombin generation suppression and restored ROTEM clotting time, OC 36.4
- PCC: 3- or 4-factor (VII): 34 normals given riva overdoses, 3-factor shortened PT by 1s, 4-factor by 3s. OC 36.5
- rVIIa, OC 36.6, AS 46.3; antibody, OC 36.2; mutant thrombin; OC 36.3


The End