Measuring Direct Oral Anticoagulants (DOACs)

Whatever Happened to the PT and PTT?
George A Fritsma MS, MLS
www.fritsmafactor.com

Indications for Anticoagulant Therapy

- Rx 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 prosthetic heart valves and in non-valvular atrial fibr (NVAF, “AFIB”)
- Acute coronary syndromes (ACS): acute myocardial infarction, peripheral artery obstruction, ischemic stroke, cardiac insufficiency

Venous Thromboembolism

- 23,000,000 US residents have high risk surgery; ~20% acquire deep venous thrombosis (DVT)
- 1,000,000 USA residents acquire VTE as inpatients or 30d post hospitalization
- A 400-bed hospital will document 200 hospital-acquired VTEs/y, 50% preventable
- Pulmonary emboli (PE) are the most common cause of preventable death, fatality rate 15%
- Traditional and new oral A/Cs play large role in effective prevention and treatment of VTE
  - Anticoagulant drug prophylaxis reduces VTEs 30-65%
- 58% of eligible patients receive anticoagulant

Bottom Line at the Start (BLATS)

- Monitor Coumadin (1954)
- Monitor unfractionated heparin (1936)
- Measure oral direct thrombin inhibitor dabigatran (2010)
- Anticoagulant reversal agents


DOACs: “The Girls”

NVAF Prevalence Projections

50% of A/C Rx is for NVAF


DOAC Measurement
### DOAC Measurement

**US FDA-Cleared DOACs**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Prevent stroke in NVAF</th>
<th>Prevent VTE post TKR &amp; THR</th>
<th>Treat, prevent 2° VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran Pradaxa®</td>
<td>2010</td>
<td>2014</td>
<td>2014</td>
</tr>
<tr>
<td>Rivaroxaban Xarelto®</td>
<td>2011</td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
<td>Apixaban Eliquis®</td>
<td>2012</td>
<td>2014</td>
<td>2014</td>
</tr>
<tr>
<td>Edoxaban Savaysa®</td>
<td>2015</td>
<td>2015</td>
<td>2015</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Phase III, non-significant results</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Why Measure Fonda, LMWH or DOACs?**

- Renal disease, CrCl (GFR, eGFR) <30 mL/m
- Noncompliance or underdosing
- Screening for co-medication interference
- Determining cause of acute hemorrhage
  - ER or surgery
  - To identify anticoagulant or monitor its reversal
- Bridging from one anticoagulant to another

**Why Measure Fonda, LMWH & DOACs?**

- Discontinuation before surgery
- Resumption of anticoagulation after surgery
- Unstable coagulation: pregnancy, liver disease, renal disease, malignancy, DIC
- Patients >75 YO (excluded from clinical trials)
- Patients with marginal fluid compartment (excluded from clinical trials)
  - >150 kg: proportionally reduced plasma volume
  - <40 kg or ped: proportionally increased plasma volume
- Confirm and monitor A/C reversal

**Coumadin**

- warfarin
- Miradon
- Coumarin
- Sintrom
- warfarin Sodium
- acenocoumarol
- dicumarol
- Anisindione
- Warfilone
- DB00266

**Coumadin Indications**

- Cardiac insufficiency in ACS, ejection fraction <30%
- NVAF to prevent ischemic stroke
- Prosthetic heart valves
- VTE: DVT and PE

**Coumadin Limitations**

- >80 drugs unpredictably interfere in CYP2C9 cytochrome oxidase pathway
- Diet supplies 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 hemorrhage-related ER visits
  - Reversal with VK requires 6-10 hours
  - Improved with Kcentra (Beriplex) 4-factor prothrombin complex concentrate
- Coumadin allergy with anaphylaxis
The Fritsma Factor

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><em>1</em>1 (WT)</th>
<th><em>1</em>2</th>
<th><em>1</em>3</th>
<th><em>2</em>2</th>
<th><em>2</em>3</th>
<th><em>3</em>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (wild-type)</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AG</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>


VKORC1 Genotypes

Cytochrome Oxidase Pathway (CYP) 2C9 Genotypes

*1*1 (WT) *1*2 *1*3 *2*2 *2*3 *3*3
GG (wild-type) 5-7 5-7 3-4 3-4 3-4 0.5-2
AG 5-7 5-7 3-4 3-4 0.5-2 0.5-2
AA 3-4 3-4 0.5-2 0.5-2 0.5-2 0.5-2

Coumadin Dose & Pharmacodynamics

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


Coumadin Therapeutic Window

- Ischaemic stroke
- Intracranial bleeding

Turpie AGG. New oral anticoagulants in atrial fibrillation. Eur Heart J 2006;29:156-65

Is the PT/INR All it Could Be?

- Inter-platform variation
- 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

The Fritsma Factor

DOAC Measurement

Chromogenic Factor X (CFX)

Russell viper venom + Ca

9-222

pNA

pNA intensity at 405 nm is proportional to factor X activity

Cleavage site

Bz-Ile-Glu(g-OR)-Gly-Ang-pNA·HCl

CFX In Place of PT/INR?

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”

CFX Resolves INR Affected by LAC

- INR & CFX assayed in 44 control Coumadin patients and 46 LA patients on Coumadin

CFX in Place of PT/INR?

CFX could be used instead of the PT-INR as this method is unaffected by LA. However, there is no evidence from clinical trials that the CFX is effective and safe in monitoring VKA patients. Further, although there is a linear relationship between factor X activity and the PT-INR in patients on VKA, the precise therapeutic interval based on factor X is still unknown.

Current ISTH Recommendations

1. The PT-INR measured with the vast majority of commercial thromboplastins can be safely used to monitor LA-positive patients on VKA, keeping in mind that there may be occasional patients for whom the INR is affected by LA.
2. New thromboplastins, especially those based on recombinant relipidated tissue factor, should be checked for their sensitivity to LA before they are used to monitor VKA in LA-positive patients.
3. Whenever possible the PT should be measured with the local thromboplastin before starting VKA. If the PT is beyond the upper limit of the reference range it is likely that the local thromboplastin and therefore the PT-INR following VKA will be affected by LA. Alternative LA-insensitive thromboplastins should be used.

Current ISTH Recommendations


george@fritsmafactor.com
Current ISTH Recommendations

4. If the baseline PT is within the reference range, the local thromboplastin can be safely used to monitor LA-positive patients, provided that an instrument-specific ISI has been determined according to WHO recommendations.

5. The so-called “combined” thromboplastins can be used instead of the “plain” thromboplastins if an instrument-specific ISI is available, keeping in mind there is no strong and independent evidence that they work in this context.

6. The INR measured with POC devices could be variably affected by the LA. Unless information on specific evaluation is provided, INR results from POC in patients with LA should be interpreted with caution.

50 YO Man with Bilateral PE

- Obese, sedentary, swollen ankle, short of breath
- Unfractionated heparin (UFH) Rx two days
  - Bolus: 5000–10,000 units or 80 U/kg to prevent 2nd thrombosis
  - Maintenance: 1600 U/hour or 18 U/kg/h, >30,000/24 h minimum
  - Switched to LMWH twice a day
- UFH history
  - Jay MacLean, med student at Johns Hopkins 1916
    - Isolated from dog liver and described anticoagulant property
  - William Howell lab, Howell named it heparin
  - Trials 1935, Karolinska Institut, Stockholm, Vitrum AB
    - FDA-cleared 1936 (first ever)
- Also used in coronary artery bypass graft

Heparin

MONITORING UFH THERAPY WITH THE PTT

- Perform “baseline” PTT to rule out factor deficiency, inhibitors, lupus anticoagulant (LAC)
  - 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
  - Formerly 1.5–2.5 x mean of normal range
- Schedule generalized to post-CABG therapy

UFH Rx Range Using the PTT Normalized to Anti-Xa
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

HEPARIN THERAPEUTIC RANGE

Why Monitor UFH Therapy?
- Several 1990s studies showed that VTE inpatients treated with an initial bolus of 5000 U and continuous IV of >30,000 U/d, risk of 2° thrombosis was 6.3% independent of PTT results.
- Anand et al, OASIS-II, showed bleeding incidence increased 7% for every 10 seconds PTT is prolonged
  - However, trauma, age, comorbidity, and simultaneous coagulopathies have greater effects.

Heparin doses now color-coded

Joint Commission Requires Monitoring
- National Patient Safety Goals, 2008
  - Must monitor Coumadin, UFH and LMWH
  - Reduce iatrogenic adverse events
  - Methods not specified
- Why monitor?
  - UFH used in inpatients with comorbidities
  - UFH pharmacokinetics complex and dose-response uncertain
  - High prevalence of UFH medication errors

PTT UFH Monitoring Limitations
- Antithrombin deficiency or consumption renders PTT non-responsive, "heparin resistance"
- Elevated FVIII renders PTT insensitive
- Lupus anticoagulant in 1–3% of unselected subjects prolongs baseline PTT, renders PTT more sensitive
- Coagulopathy & factor inhibitor prolong baseline PTT
- Simultaneous Coumadin renders PTT more sensitive
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot
- Many reagents with variant formulations and no normalization, the Brill-Edwards doesn't really help
- Pre-analytical variables; lipemia, icterus, and hemolysis
**Anti-Xa UFH Monitoring Limitations**

- More expensive (but fewer adverse events)
- Interpretation unfamiliar to docs & nurses
- Antithrombin deficiency or consumption renders anti-Xa non-responsive (considered desirable by most)
- Interference by icterus, lipemia, and hemolysis
- Less reproducible than PTT on CAP surveys
  - When PTT reagent is a single lot from a single manufacturer
- The anti-Xa and PTT do not measure the same thing

**Discordant PTT and Anti-Xa Values**

- 42% with anti-Xa in Rx range and PTT above Rx range
- Most were on simultaneous Coumadin
- Elevated risk of major bleed and death

<table>
<thead>
<tr>
<th></th>
<th>2321 paired values from 539 patients</th>
<th>2 consecutive long PTT versus in-range anti-Xa n = 163</th>
<th>Long PTT versus in-range anti-Xa n = 85</th>
<th>PTT and in-range anti-Xa concordant n=112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed in 21 d</td>
<td>15 (9%)</td>
<td>5 (6%)</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>p = .03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd thrombotic event in 21 d</td>
<td>9 (6%)</td>
<td>3 (4%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Death in 30 d</td>
<td>23 (14%)</td>
<td>18 (21%)</td>
<td>6 (5%)</td>
<td></td>
</tr>
<tr>
<td>p = .02</td>
<td></td>
<td>p = .0008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Outcome Recommendation**

- Perform first 3 UFH assays w/ both anti-Xa and PTT
- If PTT > anti-Xa, high risk
- Use lower target range:
  - e.g., anti-Xa 0.3–0.5 units
- Discontinue UFH, revert to vena caval filter

**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

**PTT/anti-Xa Discordance**


**Low Molecular Weight Heparin**

- enoxaparin
- Lovenox
- dalteparin
- Fragmin
- tinzaparin
- Innohep

**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

**Measuring Fonda**
- Fonda: 2.5 mg subcutaneous injection
  - Therapeutic range: 0.60–1.50 mg/L
  - Prophylactic range: 0.10–0.50 mg/L
  - Discontinue if creatinine >2.0 mg/dL or GFR <30 mL/min
- Anti-Xa chromogenic heparin assay
  - Collect 3 h after injection
  - Requires fonda calibrators and controls
  - PTT insensitive to fonda
- Regular CBCs, monitor platelet count, stool for blood

**Arixtra**

**Parenteral Synthetic Pentasaccharide**

- **Fondaparinux (Fonda)**
  - Glucosamine
  - Glucuronic acid
  - Iduronic acid

**Fonda Functions Through 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

**Fonda Advantages**
- Half-life 17 h; one SC 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 event costs
• Renal disease: contraindicated if GFR <30 mL/m
  • Weight <50 kg 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 S1109 Lovenox patent expired
• Curve for fonda requires calibrators and controls
  − Separate, mg/dL, not international units


Rivaroxaban (Riva)—Xarelto

Rivaroxaban (Riva) — Xarelto

ROCKET AF Clinical Trial
• 83 trials; ROCKET AF results primary but questionable
• Excretion: 66% renal, 28% hepatic
• Stoichiometric inhibition, steady state at 4 h
• Half-life 12 h but Xa remains suppressed 24 h

Oxazolinone-derived oral direct Xa inhibitor peptidomimetic, < 500 daltons


Cohen D. Rivaroxaban: can we trust the evidence? BMJ. 2016;352: i575

Riva, Plxi, Edi, Trixi Inhibit Xa Directly

Riva, Plxi, Edi, Trixi Inhibit Xa Directly

Riva Indications and Dosages
• 10 mg/d for VTE prophylaxis post TKR, THR
• 15 mg/bid to prevent 2° event post DVT or PE
• 20 mg/d stroke prophylaxis in NVAF
• 10 mg/d to prevent 2° event in ACS
  − Dosed with dual antiplatelet therapy
  − FDA-defended, 3–4–13 (10 mg): doubled bleeding risk
  − Approved 3-22-13 by EMA @ 2.5 mg/d
• APPLIASE trial: 2.5 & 5 mg/d
  − Effective, but bleeding events doubled


George Fritsma

george@fritsmafactor.com
The Fritsma Factor

Oral Apixaban ("Pixi")
- 28 trials: ADVANCE 1,2,3, ADOPT, APROPOS, ARISTOTLE
- Renal excretion 30%, hepatointestinal 70%
- Stoichiometric inhibition, steady state at 4 h
- Half-life 12 h, Xa suppressed for 24 h

ARISTOTLE: Pixi
- Compared to Coumadin at 2.5 mg BID...
  - Reduced NVAF stroke & embolism 21% (p<0.01)
  - 31% fewer intracranial bleeds (p<0.001)
  - 11% lower mortality (p=0.047)
  - Lower discontinuation rate
- VTE Rx: THR: 32–38 days; TKR: 10–14 days
- Off-label recommendation for antiphospholipid syndrome

Oral Edoxaban ("Edi")
- FDA-approved 2015 for NVAF with warning that it is less effective when CrCl >95 mL/minute (healthy kidneys)

Edoxaban Dose and Pharmacokinetics
- NVAF, VTE Rx: 60 mg/d, 30 if GFR is <50, D/C if GFR is >95
- Reaches therapeutic levels in 1–2 hours
- Half-life 10–14 hours
- Excreted 50% kidney, 50% liver

PT for Riva, Pixi, Edi, Trixi Does "Spiking" Work?
- Same patterns for Actin FSL PTT, worse yet, PTT not sensitive to Riva

PT for Riva, Pixi, Edi, Trixi Can you use any reagent?
**DOAC Measurement**

---

**Anti-Xa Chromogenic Assay**

- Anti-Xa DOACs can be calibrated to UFH, LMWH, or drug-specific calibrators.
- Anti-Xa DOACs reduce Xa activity.

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

---

**Dabigatran (Dabi)**

**Dabigatran: Direct Thrombin Inhibitor**

- Extrinsic
- Intrinsic
- Common

**Dabi Pharmacokinetics**

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

**Measuring Dabigatran**

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

**Oral Dabigatran Eteixlate**

- 60 trials; RE-LY is the only one FDA used to approve
- First oral anticoagulant since Coumadin, approved in 1952
- 150 mg bid to prevent NVAF stroke
- Prophylaxis in TKR and THR
- Rx after VTE, but trials based on initial heparin Rx

**Dabi Pharmacokinetics**

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

**Measuring Dabigatran**

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


Human fibrinogen + Human thrombin → Fibrin Polymer

Ecarin Chromogenic Assay (ECA)

Saw-scaled Viper: Echis carinatus

No inhibitor or factor deficiency effects

Color intensity at 405 nm inversely proportional to DTI concentration


Summary: DOAC Measurement

- Assay choice: stat, routine, point of care
- All are RUO, require therapeutic range data
- PT for anti-Xa’s; PTT for DTI’s
- Stopgap: variation among reagents, insensitive
- Standardize collection time: peak and trough
- Dabi: plasma-diluted TT or ECA
- Anti-Xa DOACS use anti-Xa chromogenic
  - Calibrators and controls available for all

PTT for Dabi

Do spiked plasmas work?


Hemorrhage Reversal

- Coumadin overdose: if bleeding…
  - VK 10–20 mg oral or IV; 12–24 h to stop bleeding
  - Simultaneously infuse PCC, APC, or 4-factor PCC (Kcentra®)
  - Limit APC to 40 U/kg body weight to avoid thrombosis or DIC
- Heparin overdose
  - Reverse in minutes with protamine sulfate, binds long molecules
- LMWH overdose
  - Protamine binds long but not short molecules, 30–40% effective


DOAC Hemorrhage Reversal

- Mild bleeding
  - Delay or discontinue next dose, discontinue concurrent medication
- Moderate bleeding
  - Supportive measures: compression, surgical intervention, plasma, RBCs, platelet concentrate if count is <60,000
  - For dabigatran: Alimentary activated charcoal absorption, maintain diuresis, consider hemodialysis
- Severe, life-threatening hemorrhage
  - 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

Developing Hemorrhage Reversal

**IV Andexanet Alpha; Annexa-A®**

- Non-carboxylated Xa—lacks Gla domain, “decoy”
- Variably reverses all anti-Xa DOACs and fonda
- 2m reversal: pixi 93%, edr & riva 50%
- Partially reverses LMWH
- Andexanet limitations
  - Reversal measured using anti-Xa, a surrogate
  - Dosage varies by AC, a limitation if AC not identified
  - Continuous drip required through half-life of AC
  - Protein: may induce immune response

**DOACs: What is Left to Do?**

- Reduce risk of ICH by 50% compared to Coumadin
- GI bleed rate equals Coumadin
- Require no monitoring, occasional measurement
- Developing specific reversal agents
- No effective means for lab identification
- No FDA-approved specific assays

**Bottom Line at the End (BLATE)**

- Monitor Coumadin (1954)
- Monitor unfractionated heparin (1936)
- Measure oral direct thrombin inhibitor dabigatran (2010)
- Anticoagulant reversal agents

**Developing Hemorrhage Reversal**

**idarucizumab—Praxbind**

- Human monoclonal Fab fragment binds dabigatran
  - High affinity, effective sustained reversal in 30 minutes
  - FDA-approved via fast-track 10/15
- Limitations
  - Modest risk of immune response limiting second usage
  - Reversal determined using ECA and DTT, surrogates
  - Hemostatic reversal requires 12 h