Reversing the New Anticoagulants

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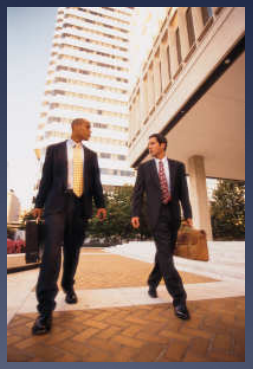
Disclosure



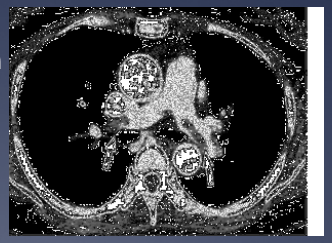
Roadmap for today

Roadmap for today

- Characteristics of novel anticoagulants
- Approach to the bleeding patient
- Specific reversal agents
- UCSF guidelines

Scope of Problem

- Prevalence atrial fibrillation
  - 3.03 million in 2005
  - 7.56 million by 2050
- VTE = 900K/yr in US
- 1-2% of adults take warfarin



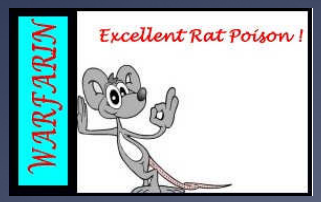
Warfarin

1920s – Outbreak hemorrhagic disease in cattle in northern US and Canada

1933 – Isolated by Karl Link

1948 – Rodenticde

1954 – Approved in humans



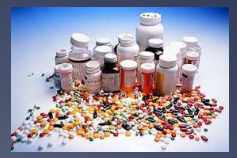
WARF-arin

Wisconsin Alumni Research Foundation
Coumarin, plant molecule in sweet clover

Warfarin Disadvantages

- Bridging
- Drug and food interactions
- Long half-life
- Close monitoring required



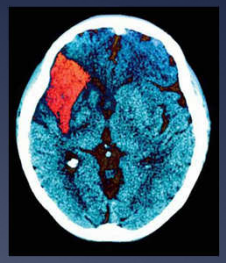


Why New Anticoagulants?

- Rapid onset/shorter half-life
- Fewer drug and no food interactions
- No lab monitoring
- Equivalent to warfarin
  - Prevention of stroke, VTE
  - Bleeding rates

New Anticoagulant Disadvantages

- Limited experience treating bleeding
- No proven reversal agent
- No monitoring



What's in a name?

- Direct Thrombin Inhibitors (DTIs)
- Novel Oral Anticoagulants (NOACS)
- Target Specific Oral Anticoagulants (TSOACS)

Roadmap for today

- **Characteristics of novel anticoagulants**
- Approach to the bleeding patient
- Specific reversal agents
- UCSF Guidelines

New Anticoagulants

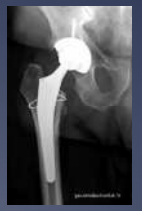
- Dabigatran (Pradaxa®)
- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)

New Anticoagulants

- **Dabigatran (Pradaxa®)**
- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)

Dabigatran Indications

- FDA approved
  - Stroke prevention in non-valvular afib
- Under FDA review
  - VTE prophylaxis in hip or knee replacement
  - Approved in Europe/Canada

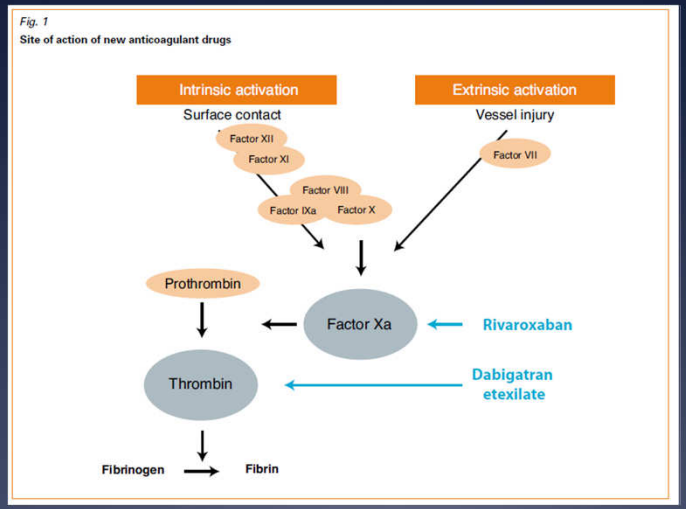


Dabigatran Dose

- Stroke prevention
  - 150 mg, po bid
  - Renal insufficiency 75 mg, po bid
- DVT prophylaxis
  - 220 mg, po qd

Dabigatran Mechanism

- Direct Thrombin (Factor IIa) inhibitor
- Blocks conversion of fibrinogen to fibrin



Dabigatran Pharmacology

- Dabigatran etexilate = inactive pro-drug
- Rapidly absorbed
- Active form binds active site of thrombin
- Inhibits free and clot-bound thrombin

Dabigatran Pharmacokinetics

- Predictable
- Rapid onset
- Peak plasma level at 2 hours
- Half-life 14-17 hours

Dabigatran Pharmacokinetics

- No food interactions, few drug interactions
- Fixed dosing can be used
- No need for routine monitoring or dose adjustment

Dabigatran Metabolism

- 85% excreted via the kidneys
- Use caution with renal dysfunction
- Low protein binding
  - Eliminated by hemodialysis

Dabigatran Metabolism

- NOT metabolized by p450 system
- Substrate of efflux transporter P-glycoprotein
  - Inducers (e.g., rifampin) reduce effect
  - Inhibitors (e.g., verapamil) increase effect

Dabigatran Metabolism

- Decreased effect with P-gP inducers
  - Rifampin
- Increased effect with P-gP inhibitors
  - Dronedarone
  - Ketoconazole, Itraconazole
  - Verapamil
  - Amiodarone
  - Quinidine
  - Clarithromycin

New Anticoagulants

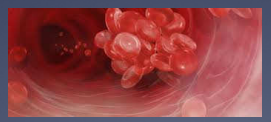
- Dabigatran (Pradaxa®)
- **Rivaroxaban (Xarelto®)**
- **Apixaban (Eliquis®)**

FACTOR Xa INHIBITORS

Rivaroxaban
(Xarelto®)Apixaban (Eliquis®)

Indications

- Rivaroxaban/Apixaban
  - Stroke prevention in non-valvular atrial fib
- Rivaroxaban only
  - VTE prophylaxis post-joint replacement
  - DVT/PE prophylaxis and treatment



Rivaroxaban and Apixaban Dose

Non-valvular afib

- Rivaroxaban, 20 mg po qd
- Apixaban, 5 mg po qd

DVT/PE

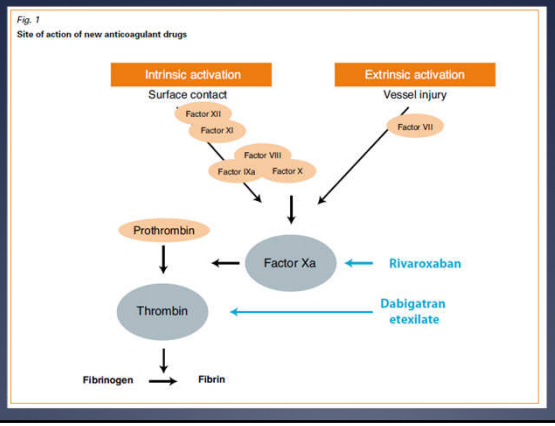
- Rivaroxaban, 15 mg po qd

DVT prophylaxis

- Rivaroxaban,10 mg po qd

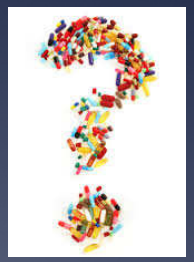
Rivaroxaban and Apixaban Mechanism

Selective, direct, factor Xa inhibitors



Rivaroxaban and Apixaban Pharmacology

- Highly protein bound
- Not easily dialyzed
- Few drug interactions



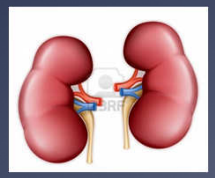
Rivaroxaban and Apixaban Pharmacokinetics

- Similar to dabigatran
- Predictable
  - Not affected by age, sex, body weight
  - Fixed dose
- Peak at 2 – 3h
- Half life 7-14h

Metabolism

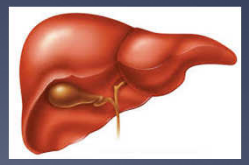
Rivaroxaban

- Excretion
  - 2/3rd renal
  - 1/3rd liver
- Dose adjusted for reduced CrCl



Apixaban

- Excretion
  - 2/3rd liver, biliary
  - 1/3rd renal



Coagulation Assays

- Not routinely necessary
- Indications
  - Major bleeding
  - Overdose
  - Emergent surgery

Coagulation Assays

Dabigatran

- Peak/trough 20-300 ng/ml
- aPTT
  - Prolonged at >50 ng/ml
  - Normal at 25 ng/ml
- Thrombin time
  - Prolonged at 3 ng/ml
  - Normal at 1 ng/ml

Coagulation Assays

Dabigatran

- aPTT not useful
- Thrombin time
  - If normal, dabigatran not present

Coagulation Assays

Rivaroxaban/Apixaban

- Peak/trough 25-400 ng/ml
- aPTT
  - Prolonged at 120 ng/ml
  - Normal at 60 ng/ml

Coagulation Assays

Rivaroxaban/Apixaban

- Anti-factor Xa assay
  - No assay for rivaroxaban available
  - Ask for assay calibrated for enoxaparin
  - Estimate of rivaroxaban/apixaban activity

Roadmap for today

- Characteristics of novel anticoagulants
- **Approach to the bleeding patient**
- Specific reversal agents
- UCSF guidelines

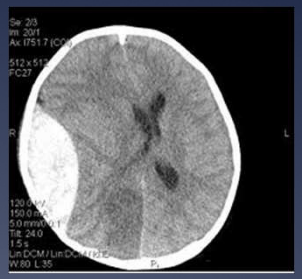
Approach to Bleeding

- Discontinue anticoagulant
- Compress
- Fluid replacement, transfusion

Approach to Bleeding

Consider emergent reversal

- Intracranial
- Pericardial
- Intraspinal
- Hemorrhagic shock
- Drug overdose
- Emergency surgery



Roadmap for today

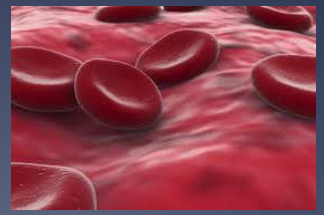
- Characteristics of novel anticoagulants
- Approach to the bleeding patient
- **Specific reversal agents**
- UCSF guidelines

Reversal Agents

NO ROLE FOR VITAMIN K IN REVERSAL OF NEW ORAL ANTICOAGULANTS

Reversal: Options

- Hemodialysis (dabigatran only)
- Prothombin complex concentrate (PCC)
- Recombinant Factor VIIa (rFVIIa)
- aPCC (FEIBA®)



Reversal: Hemodialysis

For reversing dabigatran

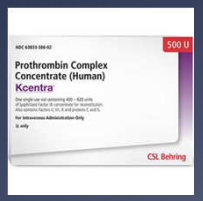
Evidence
- 6 healthy volunteers w ESRD
- 62% removed after 2 hours
- 68% removed after 4 hours

Rivaroxaban/apixaban too highly protein-bound for HD

Stangier, 2010

Reversal: PCC

Two preparations
- Kcentra® 4-factor PCC (II, VII, IX, X)
- Bebulin® 3-factor PCC (II, IX, X)



Reversal: Specific Agents

Human studies

Animal studies

Specific Antidotes

Reversal: Specific Agents

Human studies

Animal studies

Specific Antidotes

Reversal: Specific Agents

Human studies

- 5 studies, 2011-2013
- Healthy volunteers
- Anticoagulants: dabigatran, rivaroxaban, apixaban
- Reversal agents
  - PCC
  - aPCC
  - rFVIIa
- Outcome: clotting assays

Reversal: Human Studies

Erenberg, 2011

- Study design
  - N=12 subjects
  - Dabigatran or rivaroxaban po x 2.5 d
  - Treated with PCC bolus iv
  - Measured PT and ETP over 24 hours

Reversal: Human Studies

Erenberg, 2011

- Findings
  - PCC reversed PT, ETP in rivaroxaban treated patients
  - PCC did not reverse dabigatran

Reversal: Human Studies

Marlu, 2012

- Study design
  - N=10 men
  - Dabigatran or rivaroxaban po x 1
  - Collected blood samples
  - Treated blood (PCC, rFVIIa, aPCC)

Reversal: Human Studies

Marlu, 2012

- Findings
  - Dabigatran
    - rFVIIa most effective
  - Rivaroxaban
    - PCC most effective

Reversal: Human Studies

Khoo, 2013

- Dabigatran+aPCC
- Study design
  - N=8 subjects on dabigatran
  - Blood treated with aPCC

Reversal: Human Studies

Khoo, 2013

- Findings
  - aPCC reversed dabigatran

Reversal: Human Studies

Dinklaar, 2013

- Rivaroxaban+PCC
- Study Design
  - N=9 subjects
  - PCC added to rivaroxaban-treated samples
  - Coagulation assays performed

Reversal: Human Studies

Dinklaar, 2013

- Rivaroxaban + PCC
  - Findings – mixed results
    - PCC
      - Normalized thrombin generation
      - Did not normalize PT
    - Dose of PCC required depended on type of assay

Reversal: Human Studies

Korber, 2013

Rivaroxaban + PCC/rFVIIa

- Study design
  - N=10 subjects
  - Blood samples treated with rivaroxaban
  - Added PCC and rVIIa
  - Performed clotting assays

Reversal: Human Studies

Korber, 2013

Rivaroxaban + PCC/rVIIa

- Findings
  - PCC had no effect on clotting tests
  - rVIIa reversed PT and clotting factor time prolongation

Human Studies: Summary

Dabigatran

- Reversed with aPCC in 2/2 studies

Rivaroxaban

- Reversed with PCC in 3/4 studies

Human studies: Limitations

- Variable designs
- Healthy volunteers
- Reversal agents added to blood samples
- Clotting tests proxy for bleeding

Reversal: Specific Agents

Human studies

Animal studies

Specific antidotes

Reversal: Animal studies

- 6 studies, 2008-2013
- Anticoagulants:
  - Dabigatran
  - Rivaroxaban
  - Apixaban
- Reversal agents
  - PCC
  - rFVIIa
  - aPCC (FEIBA®)
  - Fibrinogen
  - FFP
- Outcomes
  - Clotting assays
  - Bleeding

Reversal: Animal Studies

Van Ryn, 2008

- Study Design
  - Rats infused w high dose dabigatran x 20 min
  - Reversed with rFVIIa and aPCC (FEIBA®) given iv
  - Bleeding measured 5 min after tail incision

Reversal: Animal Studies

Van Ryn, 2008

- Findings
  - Both agents reduced bleeding time
  - Neither agent reduced blood loss

Reversal: Animal Studies

Zhou, 2011

- Study Design
  - Mice were treated with dabigatran po
  - ICH induced
- Reversed with intravenous
  - PCC
  - Murine FFP
  - rFVIIa

Reversal: Animal Studies

Zhou, 2011

- Findings
  - N=96 mice
  - PCC prevented hematoma expansion
  - Murine FFP worked only with high dose dabigatran
  - rFVIIa did not prevent hematoma expansion

Reversal: Animal Studies

Godier, 2012

- Study Design (n=83 rabbits)
  - T=0 min, rivaroxaban iv
  - T=1 min, procoagulant iv (PCC, rFVIIa)
  - Hepatosplenic bleeding induced
  - T=15 min, total blood loss recorded

Reversal: Animal Studies

Godier, 2012

- Findings
  - Neither rFVIIa nor PCC reduced total blood loss

Reversal: Animal Studies

Pragst, 2012

- Study Design (n=28 rabbits)
  - T=0 min, dabigatran iv
  - T=5 min, PCC infusion
  - T=10 min, kidney incision

Reversal: Animal Studies

Pragst, 2012

- Findings
  - PCC reduced blood loss, bleeding time
  - Dose dependent

Reversal: Animal Studies

Perzborn, 2013

- Study Design – rats
  - T=0 min, rivaroxaban iv
  - T=5 min, bleeding induced
  - T=6 min, reversal iv (PCC, aPCC, rFVIIa)

Reversal: Animal Studies

Perzborn, 2013

- Findings – rats
  - n=7-12/group
  - All agents reduced bleeding time
    - PCC
    - aPCC
    - rFVIIa

Reversal: Animal Studies

Perzborn, 2013

- Study Design – baboons (n=7)
  - T=0 min, rivaroxaban infusion
  - T=30 min, reversal agent
  - Experimental forearm incision
  - Bleeding time measured

Reversal: Animal Studies

Perzborn, 2013

- Findings
  - aPCC and rVIIa both reduced bleeding time
    - aPCC – from twice normal to normal
    - rFVIIa – from 2.5 normal to 1.7 normal

Reversal: Animal Studies

Martin, 2013

- Study design
  - T=0, simultaneous apixaban bolus and reversal agent bolus
  - T=20 min hepatosplenic section
  - T=30 min, blood loss measured

Reversal: Animal Studies

Martin, 2013

- Findings
  - rFVIIa partially corrected bleeding time
  - PCC, rFVIIa, fibrinogen did NOT reverse blood

Summary of Animal Studies

Dabigatran

- PCC reversed dabigatran in 3/3 animal studies

Rivaroxaban and Apixaban

- PCC, aPCC, rFVIIa reversed rivaroxaban in 1/3 studies

Animal Studies: Limitations

- Wide variability in study design
  - Different doses
  - Different species
  - Different outcomes (coagulation assays, bleeding time, blood loss)
- Human clotting factors behave differently in non-humans

Reversal: Specific Agents

Human studies

Animal studies

Specific antidotes

Reversal: Specific Antidotes

- r-Antidote (PRT064445)
- aDabi-Fab
- PER977

Reversal: Specific Antidotes

r-Antidote (PRT064445)

- Antidote for rivaroxaban
- Recombinant protein
- Binds Xa inhibitor site
- Reduced blood loss in animal models
- Not tested in humans

Lu, 2013

Reversal: Specific Antidotes

aDabi-Fab

- Monoclonal antibody
- Antidote for dabigatran
- Reversed anticoagulant assays in rats

Schiele, 2013

Reversal: Specific Antidotes

PER977

- Small synthetic molecule
- Directly binds Xa and IIa
- Reverses dabigatran, rivaroxaban, apixaban

Laulicht, 2012

Summary Specific Antidotes

- Three promising agents
- None FDA-approved in humans yet

Roadmap for today

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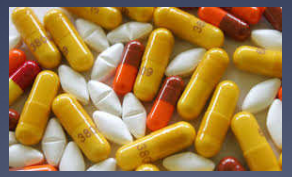
- **UCSF guidelines**

UCSF Guidelines

UCSF Guidelines

Caveat:

No proven reversal agents or antidotes



UCSF Guidelines

General Principles

- Discontinue drug
- Hemostasis
- Hemodynamic support
- Reverse other antithrombotic drugs

UCSF Guidelines

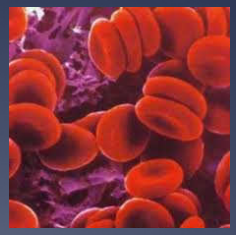
Consider

- Hemodialysis (dabigatran only)
- Activated charcoal

UCSF Guidelines

If other measures fail

- Assess thrombotic risk
- In past 6 wks
  - MI
  - CVA, TIA
  - DVT/PE
  - Severe PVD



UCSF Guidelines

If all measures fail

- aPCC (FEIBA®) to reverse dabigatran
- PCC (Kcentra®) to reverse rivaroxaban/apixaban

FEIBA® and Kcentra® Cautions

- Increase risk of thromboembolism
- Reversal is OFF-LABEL
  - Weigh risk/benefit
- Blood products
- Kcentra® contains heparin

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