Idarucizum–what!?! Keeping up with urgent anticoagulation reversal

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Disclosures

- No financial relationships to disclose
- Unapproved medications will be discussed
Objectives

- Evaluate common oral anticoagulants, including mechanism of action and FDA approved uses.
- Recognize indications for acute reversal of anticoagulation.
- Review historical and novel approaches to emergent anticoagulation reversal.
- Discuss safety and efficacy of newly approved tailored reversal agents.
Field Medicine Laws

- Air goes in and out
- Blood goes ‘round and ‘round
- Oxygen is good
- All bleeding will stop...eventually
Anticoagulation History

Warfarin (1954)
Anticoagulation History

- Warfarin (1954)
- Dabigatran (2010)
- Rivaroxaban (2011)
- Apixaban (2012)
- Edoxaban (2015)
Anticoagulation Mechanism
Anticoagulation Mechanism

Intrinsic Pathway

- XII → XIIa
- XI → Xla
- IX → IXa

Extrinsic Pathway

- VIIa → VII
- TF → VIIa

Common Pathway

- Xa
- II
- IIa

Medications and Inhibitors

- Warfarin
- Xa Inhibitors
- Dabigatran

Symbols:

- II = Thrombin
- I = Fibrinogen
- la = Fibrin
Which of the following terms is best and most safely used to describe the new group of oral anticoagulants?

- A. NOACs
- B. DOACs
- C. TSOACs
- D. SODAs
### Anticoagulation Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>Stroke prevention in NVAF</th>
<th>DVT/PE Treatment</th>
<th>VTE prevention post hip/knee surgery</th>
</tr>
</thead>
</table>

Oktay E. *Int J Card Acad.* 2015
Anticoagulation Indications

- Guideline recommendations
  - CHEST – Afib (2012)
    - Dabigatran > VKA (2B)
  - CHEST – DVT/PE (2016)
    - Non-cancer related
    - Dabigatran, Rivaroxaban, Apixaban, or Edoxaban > VKA (2B)
  - CHEST – Post surgical (THA, TKA) DVT Prophylaxis (2012)
    - Dabigatran, Apixaban, Rivaroxaban = VKA (1B)

You JJ, et al. CHEST. 2012
Kearon C, et al. CHEST. 2016
Anticoagulant Marketshare

Oktay E. Int J Card Acad. 2015
Bleeding Risk

- **2014 Meta-Analysis**
  - 12 RCTs, 102,607 patients
  - vs VKA — Decreased: major bleeding (RR 0.72), fatal bleeding (RR 0.53), intracranial bleeding (RR 0.43), and total bleeding (RR 0.76)

- **2015 Meta-Analysis**
  - 13 RCTs, 102,707 patients
  - vs VKA — Decreased: fatal bleeding (RR 0.53), all-cause mortality (RR 0.91)

Bleeding Risk

- Outcomes
  - Prospective, Observational – DOAC non-traumatic ICH
    - 28% mortality at 90 days
    - 65% of survivors had unfavorable functional outcomes
    - PCC administration (57%) – no significant effect on outcomes
  - Cohort Study – VKA associated ICH
    - 48.6% mortality at 30 days
    - 61% of survivors had major functional disability
  - Trauma Study – ICH
    - 38% vs. 8% mortality w/ pre-injury anticoagulation

Fang MC. Am J Med. 2007
Anticoagulation Reversal

- Indications/Considerations for reversal
  - **Serious or Major bleeding**
    - Potentially associated with significant blood loss requiring transfusions or bleeding into a critical space
  - **Urgent Surgery**
    - Unable to be delayed
  - Consider interval since last administration
    - \( \sim 5 \times \) half-lives to fully clear with normal renal function
      - 1-3.5 days depending on agent
    - Altered Pharmacokinetics with renal insufficiency
Anticoagulation Reversal

- **Specific Agents**
  - Vitamin K
  - Fresh Frozen Plasma
  - Prothrombin Complex Concentrate (PCC)
    - 3 Factor (3F-PCC) vs. 4 Factor (4F-PCC)
  - Idarucizumab

- **Pipeline**
  - Andexanet alfa
  - Ciraparantag
Anticoagulation Reversal

- **Research/Evidence**
  - **Optimal**
    - “Real World” patients (bleeding, surgical emergencies)
    - Assessment of clinical outcomes (hemostasis, mortality)
    - Comparison with placebo
  - **Actual**
    - in vitro/animal studies
    - Healthy volunteers
    - Coagulation tests – as surrogate for clinical efficacy
  - **Unclear external validity**

Warfarin Reversal

- Pharmacokinetics
  - Class: Vitamin K Antagonist (VKA)
  - Dosing: Variable
    - Individualized based on patient
  - Onset: 24-72 hours
  - Full effect: 5-7 days
  - Half-life: 20-60 hours
- Monitoring
  - Protime/INR

Lexi-Comp Online Database
Warfarin Reversal

- **Reversal Agents**
  - **Vitamin K**
    - Promotes synthesis of clotting factors (II, VII, IX, X)
    - Sustains effects of factor products
  - **Fresh Frozen Plasma**
    - Replenishes clotting factors (II, VII, IX, X)
  - **Prothrombin Complex Concentrate (PCC)**
    - 3 or 4 Factor available
    - Replenishes clotting factors (II, IX, X +/- VII)
Warfarin Reversal

- Vitamin K

  - Routes of administration
    - PO: Onset 12-24 hours
    - IV: Onset 6-12 hours


Figure 1. Comparison of INR reduction in patients receiving intravenous versus oral vitamin K administration and no FFP. BL = baseline; FFP = fresh frozen plasma; INR = international normalized ratio.
Warfarin Reversal

- **Fresh Frozen Plasma**
  - IV administration
    - 20 ml/kg full dose
    - Requires cross-matching
  - Reversal of INR within 12-24 hours

- **Drawbacks**
  - Time delays for cross matching, thawing
  - Large volumes/infusion times
  - Risk of pathogen transmission
Warfarin Reversal

- Prothrombin Complex Concentrate (PCC)
  - 3 Factor (3F-PCC)
    - Requires FFP co-administration (Factor VII)
  - 4 Factor (4F-PCC)
    - Approved in United States since 2013
  - Most protocols dose based on INR values
    - Product standardized in Factor IX units
- Kinetics
  - Onset: 30 minutes
  - Duration 2-72 hours
Warfarin Reversal

- Prothrombin Complex Concentrate
  - Phase IIIb, Multicenter Trial
    - Pts w/ major bleeding on VKA therapy
    - 4F-PCC vs. FFP
  - Primary Outcome
    - 24 hour hemostatic efficacy (blinded assessment)
    - INR correction ($\leq 1.3$) at 0.5h after administration
  - Results ($n = 202$)
    - Median INR 3.9 vs. 3.6
    - Hemostasis at 24h achieved in 72.4% vs. 65.4% (NI)
    - INR correction at 0.5h in 62.2% vs. 9.6% (NI + Sup)

Warfarin Reversal

- Prothrombin Complex Concentrate

Results

Warfarin Reversal

- Prothrombin Complex Concentrate
  - Phase IIIb, Multicenter Trial
    - Pts on VKA therapy requiring urgent surgical procedures
    - 4F-PCC vs. FFP
  - Primary Outcome
    - Effective hemostasis
    - INR correction ($\leq 1.3$) at 0.5h after administration
  - Results ($n = 181$)
    - Baseline INR 2.9 vs. 2.9
    - Hemostasis in 90% vs. 75% (NI + Sup)
    - INR correction at 0.5h in 55% vs. 10% (NI + Sup)

Warfarin Reversal

- Prothrombin Complex Concentrate
- Results

Warfarin Reversal

- Prothrombin Complex Concentrate
  - INCH Trial (Germany)
    - Prospective, Randomized, Open-label
    - VKA associated ICH (Non-traumatic)
    - 4F-PCC vs. FFP
    - Primary Outcome – INR $\leq$ 1.2 w/in 3 hrs
  - Results, N = 50
    - INR Reversal - 67% vs. 9% (p = 0.0003)
    - 90 day Mortality – 19% vs. 35% (NS)
    - Hematoma growth $\geq$ 33%
      - 30% vs. 60% at 24 hours (p = 0.024)

Warfarin Reversal

- Prothrombin Complex Concentrate

  - Safety
    - 2016 Meta-Analysis
      - 4F-PCC vs. FFP (n = 388)
        - Possible thromboembolic events (14 vs. 14)(7.3% vs. 7.1%)
          - Treatment related in 8 vs. 5 patients
        - Fluid overload (4.7% vs. 12.7%)
        - Overall AE (60.2% vs. 62.9%)
    - Historical thromboembolic rates ~0-4.6%

Warfarin Reversal

- Prothrombin Complex Concentrate
  - Safety
    - Trial adverse effects
      - Constipation
      - Headache
      - Peripheral edema
      - Hypotension

Warfarin Reversal

- Reversal Algorithm
  - Major/Life Threatening Bleeding or Urgent Procedure
    - Discontinue warfarin
    - 4F-PCC + Vitamin K 5-10 mg
      - INR 2-3.9 - 25 units/kg (max 2500 units)
      - INR 4-6 - 35 units/kg (max 3500 units)
      - INR > 6 - 50 units/kg (max 5000 units)
  - Alternatives
    - 3F-PCC + FFP + Vitamin K
    - FFP 10-15 ml/kg + Vitamin K

Holbrook A, et al. CHEST. 2012
Dabigatran Reversal

- **Pharmacokinetics**
  - **Class:** Direct Thrombin Inhibitor (DTI)
  - **Dosing:** 150 mg twice daily
    - Reduced in renal impairment
  - **Half-life:** 12-17 hours
    - 15-34 hours in renal impairment
- **Monitoring**
  - TT, ECT*, dTT*, aPTT
    - *Quantifiable to dose-response, but not commercially available

Dabigatran Reversal

- Reversal agents
  - Idarucizumab
    - Humanized monoclonal antibody fragment (Fab)
    - ≥ 350x stronger affinity for dabigatran than thrombin
    - Small Vd ~8.9 L
    - Complex eliminated via renal catabolism

Dabigatran Reversal

- Idarucizumab
  - Phase I Trials
    - Healthy volunteers (n = 47)
      - Dabigatran BID x 3 days, followed by Idarucizumab or placebo
      - Dose-finding study
    - 98% reduction in dTT w/ ≥ 4g doses
    - Endogenous thrombin potential normalized w/in 30 minutes of infusion
    - Sustained effects x 72 hours

Dabigatran Reversal

- Idarucizumab
  - Phase III – RE-VERSE AD (Inter-rim analysis)
    - Multicenter, Prospective cohort study
    - Inclusion: Pts taking dabigatran
      - Group A – Overt, uncontrollable, or life-threatening bleeding
        - Physician determined reversal necessary
      - Group B – Need for urgent procedure w/in 8 hours

Dabigatran Reversal

- Idarucizumab
  - RE-VERSE AD
    - Enrollees given 2x 2.5g doses
    - Primary Endpoint – Max percentage reversal of a/c effect by dTT or ECT w/in 4 hours post administration
  - Secondary Endpoints
    - Time to bleeding cessation (Group A)
    - Intraoperative hemostasis (Group B)
    - Mortality

Dabigatran Reversal

- Idarucizumab

  - RE-VERSE AD
    - Preliminary Results (n = 90)
      - Group A – GIB (39%), ICH (35%)
      - Group B – Bone fractures, Cholecystitis, etc
      - Time since last dose 15.2 hrs (A), 16.6 hrs (B)
    - Median max percentage reversal – 100%
      - Evident on sample taken after 2.5 gm
    - dTT normalization 98% (A), 93% (B)
    - ECT normalization 89% (A), 88% (B)
      - Effects sustained at 12 & 24 hours for a majority of patients

Dabigatran Reversal

- Idarucizumab
  - RE-VERSE AD

Dabigatran Reversal

- Idarucizumab
- RE-VERSE AD

Dabigatran Reversal

- Idarucizumab
  - RE-VERSE AD
    - Secondary outcomes
      - Time to bleeding cessation – 11.4 hours (A)
      - Difficult to assess (ICH, GIB)
      - Achievement of normal intraoperative hemostasis – 92% (B)
      - Mortality 20% (18 patients)

Dabigatran Reversal

- **Idarucizumab**
  - **Safety**
    - **Trial Adverse Effects (>5%)**
      - Hypokalemia
      - Delirium
      - Constipation
      - Pyrexia
    - **Immunogenicity**
      - Not seen in trials
    - **Thrombotic Events**
      - 5 patients (1 within 72h of administration)

Dabigatran Reversal

- Idarucizumab
  - Unresolved Issues
    - Rebound anticoagulation at 12, 24 hours (REVERSE-AD)
      - No data between 4-12 hours post dose
      - More data on repeat dosing needed
    - No readily available coagulation assay
      - FDA reviewing commercially available dTT
    - Preliminary results
      - Awaiting finalized results from full trial to confirm
Dabigatran Reversal

- Reversal algorithm
  - Mild bleed
    - Discontinue drug
  - Moderate bleed
    - + hemodynamic support with fluids/blood/FFP
  - Major/Life-threatening bleed or Urgent Procedure
    - + Idarucizumab 5 gm x1 dose
- Alternatives
  - Hemodialysis (removes ~60% in 2-4 hours)
  - Consider activated charcoal if within 2-3 hrs
  - aPCC (50 units/kg) or 4F-PCC (50 units/kg)
fXa Inhibitor Reversal

- Oral fXa Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Dosing</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.5-5 mg BID</td>
<td>8-15 hours*</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>30-60 mg QD</td>
<td>10-14 hours*</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10-20 mg QD</td>
<td>5-9 hours*</td>
</tr>
</tbody>
</table>

*Prolonged in renal impairment

- Monitoring
  - Anti-Xa
    - Machine must be calibrated to specific agent
  - PTT, PT
fXa Inhibitor Reversal

- Reversal Agents
  - Prothrombin Complex Concentrate
    - 4F-PCC
    - Not a true reversal agent
fXa Inhibitor Reversal

- Prothrombin Complex Concentrate
  - Rivaroxaban
    - Circ 2011
      - Randomized, Double-blind, Placebo controlled, Cross-over
      - 12 healthy males – Rivaroxaban x 2.5 days (or dabigatran)
      - 50 units/kg 4F-PCC or Saline Placebo followed by a washout period and repeat treatment with the other agent
  - Results
    - PT Prolongation – completely reversed by PCC (p<0.001)
    - Endogenous Thrombin potential – normalized with PCC (p<0.001)

fxa Inhibitor Reversal

- Prothrombin Complex Concentrate
  - Apixaban
    - No data to support use
    - Rivaroxaban data used in surrogacy
fXa Inhibitor Reversal

- Prothrombin Complex Concentrate
  - Edoxaban
    - Single Center, Double-blind, 2-Way Crossover (n=93)

- Primary endpoint: Bleeding duration (BD) post punch biopsy
  - Punch biopsy 30 minutes post 4F-PCC or Placebo

- Secondary endpoints:
  - Bleeding volume (BV), Endogenous Thrombin Potential (ETP), Prothrombin Time (PT) change

fXa Inhibitor Reversal

- Prothrombin Complex Concentrate
  - Edoxaban
    - Results
      - BD – Full reversal in 50 units/kg
        - Partial/No reversal in 25/10 units/kg groups
      - BV and ETP – Full reversal in 50 units/kg
        - Partial/No reversal in 25/10 units/kg groups
      - PT – Partial response in all (50/25/10) groups

fXa Inhibitor Reversal

- Prothrombin Complex Concentrate
  - Edoxaban

Results

fXa Inhibitor Reversal

- **Reversal Algorithm**
  - **Mild Bleed**
    - Discontinue Drug
  - **Moderate Bleed**
    - + Hemodynamic support with fluids/blood/FFP
  - **Major/Life Threatening Bleed or Urgent Procedure**
    - + 4F-PCC 50 units/kg (max 5000 units)*
      - *Outcome benefits largely assumed due to limited literature support
  - **Alternatives**
    - aPCC (50 units/kg)
Pipeline Therapies

- Andexanet alfa
- Ciraparantag
Andexanet alfa

- Modified recombinant factor Xa (FXa)
  - Decoy protein
  - Similar binding affinity to native FXa
  - No interference with endogenous anticoagulation
  - Half-life ~ 1 hr

Early trials – Phase II

- Healthy volunteers, Small size
- Andexanet alfa dose ranging
  - 90 mg bolus to 800 mg bolus + 8 mg/min infusion
- Apixaban –
  - 420 mg Andexanet bolus reduced Anti-Xa activity by 90%
- Rivaroxaban
  - 720 mg Andexanet bolus reduced Anti-Xa activity by 81%
- Edoxaban
  - 800 mg Andexanet bolus reduced Anti-Xa activity by 73%
- Some enoxaparin data as well

Andexanet alfa

- **ANNEXA – Phase III**
  - Double blind, Placebo controlled
  - Healthy volunteers
    - Age 50-75
  - Two part study
    - (A) – Apixaban 5 mg BID x 3.5 days
    - (R) – Rivaroxaban 20 mg QD x 4 days
  - Intervention
    - Andexanet alfa vs. Placebo
    - Bolus vs. Bolus + Infusion

ANNEXA

Primary Outcome
- Percentage change in anti-Xa activity from baseline* to nadir after Andexanet

Secondary Outcomes:
- Proportion with ≥ 80% anti-Xa reduction from baseline*
- Change in unbound inhibitor concentration from baseline*
- Change in thrombin generation from baseline*

*baseline prior to reversal/placebo administration

ANNEXA

Results (post bolus)
- Apixaban (N = 65), Rivaroxaban (N = 80)
- Anti-Xa activity reduction
  - (A) 94% vs. 21%
  - (R) 92% vs. 18%
- ≥ 80% Reduction in Anti-Xa activity
  - (A) 100% vs. 0%
  - (R) 98% vs. 0%
- Unbound fXa Inhibitor reduction
  - (A) 9.3 ng/ml vs. 1.9 ng/ml
  - (R) 23.4 ng/ml vs. 4.2 ng/ml
- Thrombin generation full restoration
  - (A) 100% vs. 11%
  - (R) 96% vs. 7%

Andexanet alfa

- ANNEXA

- Results

**C** Apixaban Study, Andexanet Bolus plus Infusion

- End of bolus
- End of infusion

- Placebo (N=8)
- Andexanet (N=23)

**D** Rivaroxaban Study, Andexanet Bolus plus Infusion

- Placebo (N=13)
- Andexanet (N=26)

Andexanet alfa

- ANNEXA
- Results

**C** Apixaban Study, Andexanet Bolus plus Infusion

- **D** Rivaroxaban Study, Andexanet Bolus plus Infusion

Andexanet alfa

- ANNEXA-4 – Phase III (Inter-rim Analysis)
  - Prospective, Open-Label, Single Group
  - Acute major bleeding
    - Within 18h of fXa Inhibitor administration
      - Rivaroxaban
      - Apixaban
      - Edoxaban
      - Enoxaparin

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- **ANNEXA-4**
  - **Intervention – Andexanet alfa**
    - **Bolus + 2h Infusion**
      - 400 mg/480 mg
        - Apixaban
        - Rivaroxaban > 7h post admin
      - 800 mg/960 mg
        - Enoxaparin
        - Edoxaban
        - Rivaroxaban ≤ 7h post admin

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- ANNEXA-4

  - Primary Outcome
    - Percentage change in anti-Xa activity from baseline*

  - Secondary Outcomes:
    - Rate of “good” or “excellent” hemostasis at 12h post infusion
      - Independent adjudication committee
      - Predetermined criteria

*baseline prior to andexanet administration

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- ANNEXA-4

- Results (N = 67)
  - Average Age: 77
  - Mechanisms
    - GIB – 53%
    - ICH – 43%
  - Efficacy Population (N = 47)
    - Rivaroxaban – 26
    - Apixaban – 20
    - Enoxaparin - 1

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- ANNEXA-4
  - Results (Efficacy Population)
    - Anti-Xa activity reduction (Rivaroxaban)
      - Decreased by 89% post bolus
      - Decreased by 86% post infusion
    - Anti-Xa activity reduction (Apixaban)
      - Decreased by 93% post bolus
      - Decreased by 92% post infusion

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- ANNEXA-4
  - Results

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

- ANNEXA-4
  - Results (N = 47 – Efficacy Population)
    - Hemostatic Efficacy “Good” or “Excellent” 12h post administration
      - Overall – 79%
      - Rivaroxaban – 81%
      - Apixaban – 75%
      - Enoxaparin – 100% (1 patient)
    - Mortality: 15%

Connolly SJ, et al. NEJM. 2016
Andexanet alfa

Safety

- Adverse Effects (all mild)
  - Constipation
  - Dysgeusia
  - Urticaria
  - Flushing

- No neutralizing antibodies detected

- Transient increases in D-Dimer and Prothrombin fragments 1 and 2

Andexanet alfa

- **Safety**
  - **Thromboembolism**
    - **ANNEXA**
      - No documented cases
    - **ANNEXA-4**
      - 18% overall rate
        - MI (1)
        - Stroke (5)
        - DVT (7)
        - PE (1)
      - Only 4 cases within 72 hours
        - No anticoagulation resumed

Andexanet alfa

- Unresolved Issues
  - Optimal dosing/duration
    - Repeat dosing?
  - Validation/Confirmation of results
    - ANNEXA-4 final analysis
  - Prothrombotic significance in patients
    - Elevated D-Dimer, Prothrombin fragments
    - ANNEXA-4 – thromboembolism risk?
Ciraparantag

- **Reversal effects**
  - Strong, non-covalent bonds
    - UFH
    - LMWH
    - Fondaparinux
    - Apixaban
    - Edoxaban
    - Rivaroxaban
    - Dabigatran
  - Inhibits further activity once bonded

Ciraparantag

- Phase I Trial
  - Double blind, Placebo controlled
  - 80 healthy volunteers
    - Edoxaban 60 mg x1 followed by Ciraparantag or placebo after 3 hours

- Results
  - Edoxaban increased WBCT by 37% over baseline
  - Ciraparantag ≥ 100 mg reversed effects to within 10% of baseline value within 10 minutes
    - Effect sustained x 24 hours
    - Placebo group ~12-15 hours to achieve reversal

Ciraparantag

- Phase I Trial
  - Healthy pts, placebo controlled
    - Ciraparantag reversal in pts on Edoxaban x 2 days
      - 25, 50, 100, 300, or 600 mg – single dose
    - Edoxaban reinitiated on Day 4, followed by a second reversal with Ciraparantag
  
- Results
  - Ciraparantag ≥ 100 mg completely reversed WBCT effects within 60 minutes
  - Re-anticoagulation successful at 24h

Safety

- Trial Adverse Effects
  - Flushing
  - Taste distortion
  - Headache

- No pro-coagulant effects reported

Ciraparantag

- Unresolved Issues
  - Validity in real patients
    - All studies in healthy volunteers – Phase III needed
  - Re-anticoagulation interference
    - Prolonged duration of action
    - Affects all anticoagulants
  - Monitoring effects
Summary

- Oral anticoagulation market is changing
- Anticoagulation has risks
  - Require rapid, effective reversal strategies
- Reversal is not a benign therapy
  - Pts are pro-thrombotic at baseline
- Reversal agents/strategies
  - Best available – despite evidence limitations
  - Additional agents on the horizon
Questions?


Laulicht B, Bakhru S, Steiner S, et al. PER977 (ciraparantag) reverses edoxaban anticoagulation at steady state and has no effect on re-anticoagulation at the next scheduled dose. *Eur Heart J.* 2015;36:859-60.


