A Review of Novel Anticoagulation: Where We Are and Where We Are Going

Christopher Richter, Pharm.D.
Disclosures

• I have no relevant financial or non-financial relationships to disclose in relation to the content of this presentation.
Accreditation

University of Florida is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Experience

• UF Health Anticoagulation Clinic
  • August 2011 – present
  • Expanded clinic to include NOACs

• Have studied Coaguchek XS® in clinic setting
  • Developed a correction calculation for the point of care result to better reflect a venipuncture INR
Overview

• Review of coagulation physiology

• Review of NOACs (aka TSOACs)
  • Novel Oral Anticoagulants and Target Specific Oral Anticoagulants
  • Anticoagulation vs. no anticoagulation

• Appropriate place in therapy for NOACs

• The Future of anticoagulation
The Cascade We are Used To

- Intrinsic

Diagram with arrows indicating a cascade process.
The Cascade We are Used To

• AT III
  • Inhibits factor X and Thrombin

• Protein C and S
  • S activates C
  • C inhibits factors V and VIII
A Better Understanding

- \( V \) extrinsic meets intrinsic
- \( N \) found in plasma
- \( E \) balances for clot formation

Hypercoagulable Conditions

- Factor V Leiden
- Antiphospholipid Antibody Syndrome
- Protein C/S deficiency
- Antithrombin III deficiency
Novel Anticoagulants

- Direct vs Indirect Anti-Xa
- Direct Thrombin inhibition

[Diagram showing the inhibition of Xa and Thrombin with drugs such as Rivaroxaban, Apixaban, Edoxaban, Betrixaban, Dabigatran, TF/VIIa, VIIIa, IXa, Va, and fibrinogen/fibrin.]
Novel Anticoagulants

• Dabigatran
  • Half-life: 14-17 hours
    • 3-7% bioavailable

  • Almost completely excreted as unchanged drug
    • P-gp efflux transporter NOT CYP3A4 metabolite
    • Of the drug absorbed: 80% renal and 20% in feces

• NO reversal agent
Novel Anticoagulants

• Dabigatran
  • Non-valvular atrial fibrillation, CVA prophylaxis
    • 150 mg BID
  • CrCL 15-30 mL/min: dose reduce to 75 mg BID
  • CrCL less than 15 mL/min: do not use
  • CrCL 30-50 mL/min WITH 3A4 inhibitor: 75 mg BID
  • CrCL less than 30 mL/min WITH 3A4 inhibitor: do not use
Novel Anticoagulants

- Dabigatran
  - VTE/PE Treatment
    - 150 mg BID starting after 5-10 days of parenteral anticoagulant therapy
  - VTE/PE prophylaxis
    - 150 mg BID
Novel Anticoagulants

• Apixaban
  • Half-life: 8-15 hours
    • 66% bioavailable
  • 70% excreted unchanged (CYP3A4)
    • 25% renal, ~70% in feces

• REVERSAL: Prothrombin Complex Concentrates
Novel Anticoagulants

• Apixaban
  • Non-valvular atrial fibrillation, CVA prophylaxis
    • 5 mg BID
    • 2.5 mg BID (any 2 of these contraindications)
      • Age greater than 80 OR
      • SeCr greater than 1.5 mg/dL OR
      • Weight less than 60 kg
    • Can use in renal failure
  
• DVT/PE
  • 10 mg BID x 7 days, then 5 mg BID
Novel Anticoagulants

• Rivaroxaban
  • Half-life: 5-9 hours
    • 80% bioavailable

  • 50% excreted as unchanged drug (CYP3A4, 2J2)
    • 70% renal and 30% in feces

• REVERSAL: Prothrombin Complex Concentrates
Novel Anticoagulants

- Rivaroxaban
  - Non-valvular Atrial Fibrillation
    - 20 mg once daily
    - CrCl 15-50 mL/min: 15 mg daily
    - CrCL less than 50 mL/min WITH 3A4 inhibitor: do not use
  - VTE prophylaxis while having orthopedic surgery or acutely ill
    - 10 mg once daily
    - CrCL less than 30 mL/min: do not use
Novel Anticoagulants

• Rivaroxaban
  • VTE/PE treatment
    • 15 mg BID for 3 weeks post event, then 20 mg once daily
    • CrCL less than 30 mL/min: do not use
Novel Anticoagulants

• Edoxaban
  • Half-life: 10-14 hours
    • 62 % bioavailable
  • 50% renal elimination
  • REVERSAL: Prothrombin Complex Concentrates
Novel Anticoagulants

• Edoxaban
  • Atrial Fibrillation
    • 60 mg once daily
    • CrCL 15-50 mL/min: 30 mg once daily
Novel Anticoagulants

• Edoxaban
  • VTE/PE
    • Body weight greater than 60 kg: 60 mg once daily starting after 5-10 days of parenteral anticoagulation therapy
    • Body weight less than 60 kg: 30 mg once daily starting after 5-10 days of parenteral anticoagulation therapy
Reversal of Novel Agents

• Direct Anti-Xa Agents
  • Kcentra®
    • Possibly an accepted reversal agent
    • Not FDA approved
Kcentra®

• 4 factor PCCs discussed as best current option
  • Kinetic models show complete reversal of direct anti-Xa agents
• Kcentra®
  • 50 units/kg IV infusion
  • Study performed in Europe using Cofact®
    • Showed complete reversal based on prothrombin time
Andexanet alfa

- Binds to direct anti-Xa agents AND LMWH/fondaparinux activated ATIII
  - a decoy

- Phase 2 trial
  - 420 mg IV bolus of andexanet alfa plus 2 hour infusion
    - 2 minute post bolus 92% apixaban effect reversed
    - After 2 hour infusion 91% apixaban effect reversed

- Currently in Phase 3 trials
  - ANNEXA-A–R–E
Idarucizumab

• RE-VERSE AD trial (Phase 3)
  • 4-5 g IV Bolus
  • Expected completion 2017

• Dabigatran
  • Antibody against Dabigatran
    • Affinity 350 times greater than thrombin
Aripazine

• Dosing
  • 100-400 mg IV bolus

• Rivaroxaban, apixaban, edoxaban, dabigatran, UFH, LMWH and fondaparinux
  • Non-covalently binds to these agents and prevents activity

• Currently in Phase 2 trials
Scoring for Treatment

• CHADS2
• CHADS2-VASc
• HASBLED
CHA2DS2-VASc

• When is this more useful than CHADS2?
  • CHADS2 less than 2
    • Better management of low risk patients
# CHA2DS2-VASc

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<tr>
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• How do we use this?
  - HASBLED should be higher than CHADS2 or CHA2DS2-VASc

HAS-BLED

• H – HTN - 1
• Abnormal Hep/Ren Fxn - 1 or 2
• Hx of Stroke - 1
• Bleeding - 1
• Labile INR - 1
• Elderly > 65 - 1
• Drugs or EtOH - 1 or 2
HAS-BLED

• Hypertension
  • Systolic greater than 160 mm Hg

• Hepatic Dysfunction
  • Chronic Hepatic disease, documented abnormalities (bilirubin 2x upper normal limit, AST/ALT 3x upper normal limit)

• Renal Dysfunction
  • Chronic dialysis, transplant, SeCr of 200 mmol/L (2.3 mg/dL)

• Hemorrhagic Stroke
  • Sudden onset neurologic deficiency lasting greater than 24 hours caused by bleeding

• Bleeding
  • Any bleeding not from stroke requiring hospitalization and/or causing Hgb decrease greater than 0.2 g/dL and/or blood transfusion
Patient Case 1

- 70 year old female patient in anticoagulation clinic wishes to try a NOAC for therapy. Patient has been on warfarin (most recently 5 mg daily) for 5 years for a diagnosis of atrial fibrillation. Patient has no history of heart valve disorder. Patient has only significant other medical history for HTN (controlled at 130/85) and hypothyroidism. Patient is 50 kg with a serum creatinine of 1.0. Patient has historically been out of therapeutic INR range:
Patient Case 1

• What options are there for her anticoagulation?
Patient Case 2

- 65 year old male patient discharged the hospital after an acute DVT 2 weeks ago. Patient had a long road trip from Roanoke, VA to Gainesville, FL that is attributed to provoking the DVT. Warfarin therapy was started at discharge, and the patient would like to try a NOAC to decrease clinic visits. Past medical history is significant only for HTN and takes lisinopril 10 mg daily. He is 65 kg with a serum creatinine of 1.0. His INR today in anticoagulation clinic is 1.5.
Patient Case 2

• What options are there for his anticoagulation?
Are Novel Agents For Everyone?

• Indigent/Non-Compliant
  • NOACs are often cost prohibitive

• Factor V Leiden
  • Should we investigate this mutation more intensely and use of NOACs with this condition?
  • Anecdotal reports are present with patients on Anti-Xa agents having worsening DVT.
Questions for the Future

• Better for ATIII Deficiency?
  • Should we turn to NOACs in patients with ATIII Deficiency?
  • NOACs bypass ATIII mechanism of action utilized by injectable agents.
Questions for the Future

• Why not in heart valve patients?
  • It is one thing to know we should not use these agents in these patients, but what is the mechanism?

• Development of renally cleared Anti-Xa?
  • Easier dosing than current drugs with enzymatic interactions

• Should we develop application of HAS-BLED for DVT/PE Prophylaxis?
Thank You

• Any Questions?