Parenteral to Oral: Details on Dabigatran and Rivaroxaban
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Objectives
- Discuss the mechanism of action and indications for both dabigatran and rivaroxaban
- Identify and explain contraindications, adverse reactions and drug interactions, etc.
- Illustrate ways to determine appropriate candidates for dabigatran or rivaroxaban based on clinical trial results
- Address common misconceptions concerning these new medications

Thrombosis
- Underlying cause of many cardiovascular disorders
  - Unstable angina
  - Myocardial Infarction
  - Ischemic Stroke
- Several different treatment options available
- Current therapies vary based on pharmacodynamics and pharmacokinetics

Anticoagulants
- Unfractionated Heparin
- Dalteparin
- Enoxaparin
- Warfarin
- Argatroban
- Lepirudin
- Bivalirudin
- Rivaroxaban
- Apixaban
- Fondaparinux
- Dabigatran

Why do we need new drugs?
- Better protection with less adverse side effects
- Greater mortality benefit with the least risk
- “More selectivity is better than less selectivity”
- “Oral dosage forms are easier to administer than parenteral dosage forms”
- Limitations do exist for current therapies
Limitations in Standard of Care
- **UFH**: variable pharmacokinetics, does not inhibit fibrin bound thrombin, short duration, HITT
- **LMWH**: better kinetics, parenteral administration
- **VKA**: monitoring, dose adjustments, bridging with LMWH, variable response rates, etc
- **DTI**: limited use due to risk of bleeding, parenteral administration, limited indications
- **Factor Xa Inhibitor**: does not directly inhibit factor Xa or platelet bound Xa

“New Kids on the Block”
- **Dabigatran**
  - Direct Thrombin Inhibitor (DTI)
  - 75mg, 150mg capsule twice daily
- **Rivaroxaban**
  - Factor Xa Inhibitor
  - 10mg, 15mg, 20mg tablet once daily
- **Apixaban**: not currently FDA approved
  - Factor Xa Inhibitor
  - 5mg tablet twice daily

Dabigatran Etxilate
- Highly polar pro-drug that selectively, competitively and reversibly inhibits thrombin (DTI)
- Approved in Canada for postoperative thromboprophylaxis in hip and knee surgeries
- FDA approved for the treatment of non-valvular atrial fibrillation and secondary stroke/TIA prevention

Mechanism of Action
- Forms a salt bridge on the active site of thrombin inhibiting access, activation and thrombin-induced platelet aggregation
- Benefits:
  - Does not require a cofactor like heparin and is accessible to clot-bound thrombin
  - More selective than lepirudin or bivalirudin which also bind other thrombin substrate recognition sites

Kinetics
- Bioavailability: 3-7%
- Time to peak concentrations is delayed 2 hours by food intake, but food has no affect on bioavailability
- Metabolized by the liver and excreted (80%) in the urine
- Half life 12-17 hours; 15-18 hours for mild renal impairment; 28 hours for severe renal impairment

Kinetics
- 35% protein bound, partially dialyzable
- Must be stored in original container and is only good for 4 months after opening if stored properly
- Pellets void of their outer coating can increase bioavailability by 75% and risk toxicity. Patients should never open the capsule and sprinkle pellets on food or in beverages
Adverse Reactions
- Bleeding (8-33%), GI (<6%) Hematuria (1%)
- Dyspepsia (11% gastritis or abdominal discomfort)
- Anemia (1-4%)
- ALT increased (2-3%)
- Post-marketing: anaphylaxis, AST increased, epistaxis, intracranial hemorrhage, pruritus, rash, thrombocytopenia, and decreased hematocrit

Contraindications
- Hypersensitivity
- Active clinically significant bleeding
- Lesion at risk for re-bleeding
- Moderate to severe hepatic impairment
- Severe renal impairment
- Concomitant treatment with systemic ketoconazole, itraconazole, cyclosporine or tacrolimus (based on Canadian labeling)

Adjustments for Renal Impairment
- $\text{CrCl} > 30-50 \text{ ml/min}$ (moderate renal impairment) only consider dose reduction if patient is also taking dronedarone or oral ketoconazole
- $\text{CrCl} > 15-30 \text{ ml/min}$ (severe renal impairment) requires dose reduction to 75mg BID or potential avoidance due to increased bleeding
- $\text{CrCl} < 15 \text{ ml/min}$ should avoid dabigatran due to insufficient data and risk for bleeding

Geriatric Considerations
- $> 65$ years old: Increased risk of bleeding is present in patients, especially in those with low body weight and/or renal impairment
- $> 80$ years old: Use with extreme caution; cases of hemorrhagic stroke have been reported post marketing. Consider avoiding dabigatran in this population due to unclear dosing recommendations, especially those at high risk of bleeding

Risk Evaluation and Mitigation Strategies (REMS)
- Boehringer Ingelheim is conducting an ongoing safety review of post-marketing hemorrhages
- Investigating if reports of bleeding are more common than expected
- Medication Guide for all patients receiving dabigatran

Drug Interactions
- Decrease Serum Concentrations
  - Antacids
  - Pg/ABCB1 Inducers
    - Rifampin, phenytoin, phenobarbital
  - Proton Pump Inhibitors
    - (May not be clinically significant)
  - Herbs: St John’s wort
Drug Interactions
Increase Serum concentrations:
- Pg/ABCB1 Inhibitors
- Prostacyclin analogs
- Quinidine
- Antiplatelets-clopidogrel (see product info)
- Amiodarone (consider decreasing to once daily)
- Verapamil
- Herbs: Alfalfa, Anise,

- Bilberry
- Dronedarone
- Ketoconazole
- NSAIDs
- Pentosan Polysulfate Sodium

Adjustments for Surgery
- Stop dabigatran 24 hours before surgery in patient with normal renal function
- Stop 2-4 days before surgery in patients with moderate to severe renal impairment
- Restart dabigatran single dose 1-4 hours after surgery in hemodynamically stable patients. Resume regular dose the following day

Conversion FROM Other Anticoagulants
- Initiate dabigatran at the time of discontinuation of heparin (continuous infusion)
- Discontinue parenteral anticoagulation at the time of dabigatran initiation
- Can initiate dabigatran ≤ 2 hours prior to the next scheduled dose of parenteral anticoagulation
- Initiate dabigatran after warfarin is discontinued and INR is < 2

Bridging with Enoxaparin
- There is no need to Bridging Dabigatran with Enoxaparin
- Increased risk for bleeding and related complications

Conversion To Parenteral Anticoagulants
- CrCl > 30 ml/min: initiate parenteral anticoagulants 12 hours after last dose of dabigatran
- CrCl < 30 ml/min: initiate parenteral anticoagulation 24 hours after last dose of dabigatran

Conversion To Warfarin
- CrCl > 50 ml/min: Initiate warfarin 3 days before stopping dabigatran
- CrCl 31-50 ml/min: Initiate warfarin 2 days before stopping dabigatran
- CrCl 15-30 ml/min: Initiate warfarin 1 day before stopping dabigatran
- CrCl < 15 ml/min: No recommendations provided
Monitoring
- No monitoring required
- Dabigatran does elevate the INR (1.2-1.8)
  - Should not be adjusted based on INR
  - aPTT should be compared to INR if overdose is suspected
- Complete blood count
- Hemoglobin/Hematocrit

Reversal agents
- No specific antidote for reversal
- Options: FFP, PRBC, surgical intervention
- 62-68% may be removed by hemodialysis
- Recombinant factor VIIa may be useful
- Prothrombin complex concentrate (PCC) does NOT reverse the anticoagulant effects of dabigatran

European Clinical Trials
- RENOVATE
  - Enoxaparin 40mg daily, VTE
- REMODEL
  - Enoxaparin 40mg daily, VTE shorter duration
- BISTRO (≥ 220mg BID)
  - Enoxaparin 40mg daily, VTE
- REDEEM
  - Placebo, clopidogrel + ASA; ACS
  **Dabigatran dose: 150-220mg

US Clinical Trials
- RELY
  - Warfarin; Atrial Fibrillation
- RECOVER
  - Warfarin; Venous Thromboembolism
- RESONATE
  - Placebo; Venous Thromboembolism
- REMOBILIZE (US and Canadian)
  - Placebo, Placebo
  - Enoxaparin 30mg BID

Atrial Fibrillation
- Standard of care: adjusted-dose warfarin
- Problems:
  - Monitoring burden
  - Frequent dosing adjustments
  - Drug/drug and drug/food interactions
- Superiority trial (150mg BID) to adjusted dose warfarin for stroke and VTE prevention

What about Risk of MI?
- Recent news Headline
- Decreases thrombin-induced platelet aggregation, but does not decrease platelet aggregation by arachadonic acid, adenosine diphosphate or collagen
- RELY perhaps skewed the meta-analysis
- Post-Hoc Analysis of newly identified events
- Statistically not significant, but caution in patients with high risk for coronary events
Rivaroxaban

- MOA: Highly selective, competitive, reversible factor Xa inhibitor
- FDA approval:
  - Secondary prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
  - Postoperative thromboprophylaxis for knee and hip replacements

Benefits over conventional treatment

- More than 10,000 fold selectivity for factor Xa compared with fondaparinux
- Attaches to prothrombinase complex and clot associated factor Xa
- Only has indirect effects on tissue factor mediated platelet aggregation unlike dabigatran

Dosing

- Secondary stroke prophylaxis
  - 20mg once daily
  - Duration: similar to previous treatments
- Post-operative Prophylaxis (Knee and Hip)
  - 10mg once daily starting 6-10 hours post surgery
  - Duration: 2-5 weeks respectively

Kinetics

- Kinetics are linear up to 15mg of Xarelto
  - 10mg tablet is 80-100% bioavailability
  - 15mg and 20mg tablets are 66% bioavailability
  - Dissolution limited absorption and decreased bioavailability
  - Take 15mg-20mg tablets with food (100% bioavailability)
- Highly protein bound (92%) Not dialyzable
- Half-life: 5-9 hours and 11-13 hours in the elderly
  - Could be problem in noncompliant people
- 66% excreted in the urine; 28% in the feces (21% metabolized to inactive ingredients)

Adverse Reactions

- Bleeding (21%-total) (6%-major)
- Thrombocytopenia (3%)
- Peripheral edema (2%)
- Headache (5%)
- GGT increased (7%), LFT (3%)

Post-marketing: Agranulocytosis, alkaline phosphate and LDH elevation, hematoma, xerostomia, Stevens-Johnson syndrome, peripheral edema

Contraindications

- Current bleeding (especially major)
- Risk factors: Bacterial endocarditis, congenital bleeding disorders, vascular retinopathy, thrombocytopenia, stroke, severe uncontrolled hypertension, renal impairment, recent major surgery
- Disease related contraindications: Avoid in moderate to severe hepatic impairment
- Concomitant use with DTIs, Heparin, LMWH, aspirin, and VKA should be avoided. Clopidogrel should be used cautiously
Adjustments

- Location of absorption is important!
  - Decreased AUC and Cmax was observed in the small intestine (Avoid rivaroxaban in feeding tubes located in the small intestine or colon)

- Renal Impairment Adjustments
  - Cr_cl >50 ml/min: 20mg once daily
  - Cr_cl 15-50 ml/min: 15mg once daily
  - Cr_cl <15 ml/min: avoid use (also avoid in hemodialysis)

Black Box Warning

- Increased risk of stroke with discontinuation of rivaroxaban in patient with Afib. Consider the addition of alternative anticoagulation therapy when discontinuing for reasons other than bleeding
- Spinal or epidural hematomas, including subsequent paralysis, may occur with neuraxial anesthesia or spinal puncture who are on rivaroxaban.

Renal Impairment Adjustments

- Cr_cl >50 ml/min: 20mg once daily
- Cr_cl 15-50 ml/min: 15mg once daily
- Cr_cl <15 ml/min: avoid use (also avoid in hemodialysis)

Geriatric Considerations

- Mean AUC was 41% greater in patients over 75 years of age
- Rivaroxaban’s half life increased to 11-13 hours in elderly patients

REM'S

- Janssen Pharmaceuticals to submit ongoing post-marketing safety analysis
- Patient Medication Guide & Communication Plan
- Inform patients/physicians that discontinuing rivaroxaban without adequate alternative anticoagulation may increase risk of stroke
- Inform patients to take 15 and 20mg tablets with evening meal

Drug Interactions

- Avoid Use: St John’s wort, other anticoagulants (Clopidogrel should only be used if risk outweighs benefits)
- Decreased Serum Levels:
  - Pg/ABCB1 Inducers
  - St. John’s wort
  - Deferasirox
  - Tocilizumab
- Increases Serum Levels:
  - Deferasirox
  - Macrolide antibiotics
  - NSAIDs
  - Diltiazem, Verapamil
  - Prostacyclin Analogs
  - Pg/ABCB1 Inhibitors
  - Grapefruit juice
  - Salicylates
  - Iodine I 131, Tositumomab
  - Pentosan Polysulfate Sodium
Conversion from Heparin, Enoxaparin or Warfarin

- Initiate rivaroxaban at the time of heparin discontinuation
- Discontinue current enoxaparin therapy and initiate rivaroxaban ≤ 2 hours prior to next regularly scheduled does of enoxaparin
- Bridging is not recommended
- Discontinue warfarin and initiate rivaroxaban as soon as INR falls to < 3

Conversion to Heparin, Enoxaparin or Warfarin

- Initiate heparin or enoxaparin 24 hours after discontinuation of rivaroxaban
- Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuation of rivaroxaban

Monitoring

- Routine monitoring is not required
- Complete blood count
- Renal and Liver Function tests
- Low body weight or extreme obesity might require closer of PT which correlates well with rivaroxaban concentrations (INR)
- Prolongs aPTT, HepTest, and The Russell viper venom time

Reversal Agents

- Overdose: Activated Charcoal is effective
- Prothrombin complex concentrate (PCC)
  - Study results and clinical results may not be the same; use caution
- Not dialyzable
- Recombinant Factor Xa may be useful but expensive and no sufficient data

Supporting Clinical Trials

- European Trials:
  - EINSTEIN
    - Enoxaparin + VKA; VTE
  - ATLANTIS ACS TIMI 46
    - Placebo; ACS patients taking ASA or clopidogrel plus aspirin for prevention of coronary events
  - RECORD 1-4
    - Enoxaparin; VTE

- US Trials
  - ROCKET AF
    - Warfarin; Stroke prophylaxis in Aflb
  - MAGELLAN
    - Enoxaparin; VTE prophylaxis in medically ill patients
**Atrial Fibrillation**
- Non-inferior to warfarin for stroke prophylaxis
- Similar major and non-major bleeding rate as warfarin
- Lower intracranial and fatal bleeds compared to warfarin
- Mean age 73 years old with CHADS2: 3.5

**Post-operative Thromboprophylaxis**
- Found to be non-inferior to standard therapy
- Decreased risk of bleeding compared to standard therapy
- May be a safe alternative

**Acute Coronary Syndrome**
- Death from cardiovascular causes was decreased in the rivaroxaban group compared to standard therapy (low dose aspirin plus clopidogrel)
- Intracranial hemorrhage was increased compared to placebo
- Issue: 2.5mg was used in the ATLAS ACS 2 TIMI 52 study which is not an available formulation
- At this time the effect in combination with P2Y12 inhibitors is not known.

**Heparin-induced Thrombocytopenia**
- Dabigatran and Rivaroxaban do not interact with platelet factor 4 (PF4) or anti PF4/heparin Antibodies in vitro
- Currently argatroban and lepirudin are recommend over other non-heparin anticoagulants including the new oral anticoagulants
- More studies are needed to evaluate this further

**Apixaban**
- Factor Xa Inhibitor
- Not FDA approved yet; FDA to answer later this month
- Clinical Trials:
  - APROPOS, ADVANCE and ADOPT - VTE
  - APPRAISE - Acute Coronary Syndrome
  - ARISTOTLE, AVERROES - Atrial Fibrillation

**Rivaroxaban’s competitor**
- Apixaban was found to be superior to adjusted dose warfarin for the prevention of stroke and systemic embolism
- Evidence is not as promising for acute coronary syndrome
Preferred Treatment
- Dabigatran was found to be superior to warfarin and Rivaroxaban was non-inferior to warfarin
- Based on clinical trials Dabigatran is the preferred treatment
- Rivaroxaban is used when patients cannot take dabigatran due to GI intolerance or for lower risk patients CHADS2 (0-2)
- Warfarin is still a viable option for some patients

Which one is Best?
- Insurance companies are pushing heavily for and covering these new anticoagulants
- Clinical trials are only relative to a limited defined patient population
- Essential to assess Risk vs. Benefits for each patient
- There is still a lot unknown about these new drugs

Use Caution with Extrapolation
- Extrapolation from study to study can be dangerous
- Different patient populations for each study
- Different definitions of bleeding for each study
- Take care in determining whether your patient correlates with these populations

How do we choose?
- What limitations are present in the patient?
- What are the patient’s risk factors for bleeding?
- Does the patient have severe renal dysfunction?
- Does the patient have valvular heart disease?
- How old is the patient?
- How compliant is the patient?

Some things to think about...
- Severe renal impairment or non-valvular heart disease; warfarin is still preferred due to lack of studies
- Non-compliance; Dabigatran is given twice daily and there is a black box warning about stopping Rivaroxaban; The products may not be better than adjusted dose warfarin

How do we choose?
- Why are we thinking about switching?
- What reasons do you have for wanting them on either of these medications?
- Sensitive patients may have unknown reactions to these new anticoagulants
- Warfarin is cheap
- “If it ain’t broke, don’t fix it”
The Bottom Line

- Patient Assessment is key in deciding which drug is best for each patient
- Counseling is a must to ensure successful treatment no matter which drug is chosen
- Monitoring for any adjustments needed
- Ultimate goal should be safety of our patients

References

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