To Bleed or Not To Bleed: A New Look at Anticoagulation

Mid-Year Meeting
MPhA, MDASCP, MPhS
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Objectives
- To explain coagulation factors and risks.
- To better understand efficacy, safety and appropriate use of the newer oral anticoagulation agents
  - Dabigatran
  - Rivaroxaban
  - Apixaban
- To reinforce appropriate use and monitoring of warfarin.

Abbreviations List
- DVT: Deep Vein Thrombosis
- PE: Pulmonary Embolism
- VTE: Venous Thrombotic Event
- THR: Total Hip Replacement
- TKR: Total Knee Replacement
- ACS: Acute Coronary Syndrome
- CBC: Complete Blood Count
- FFP: Fresh Frozen Plasma
- PRBC: Packed Red Blood Cells
- CrCI: Creatinine Clearance
- NOACs: Novel Oral Anticoagulants

Coagulation
- Virchow’s Triad
  - Stasis
  - Vascular Injury
  - Hypercoagulability
- Rudolf Ludwig Karl Virchow (1859) developed the concepts of
  - Thrombosis
  - Embolism
- Coagulation Cascade

Risk Factors
- Age
- Gender
- Race / ethnicity
- Immobility
- Surgery
- Trauma
- Previous VTE
- Cancer
- Obesity
- Venous stasis
- Thrombophilic disorder

Anticoagulation 2015

Anticoagulation Update 2015

Anticoagulation Update 2015
Hypercoagulability: Higher Risk
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Antithrombin III deficiency
- Increased Factor XI
- Increased factor VII
- Hyperhomocysteinemia?
- Idiopathic

Reference: Chest 2014

Indications for Anticoagulation
- Treatment of DVT
- Treatment of PE
- Prophylaxis for DVT / PE
- Atrial fibrillation
- Acute coronary ischemic syndrome
- Prosthetic heart valves
- Post-surgical prophylaxis
- Prophylaxis post stent placement

Goals of Anticoagulation
- Prevent formation of a deep vein thrombus
- Prevent progression or propagation of existing thrombus
- Prevent a thrombus from becoming dislodged and forming an embolus
- Reduce risk of stroke secondary to thrombus

Getting Away from Warfarin
NOACs and You!
“Every Form of Refuge Has It’s Price”

“Lyin’ Eyes”, Eagles

What Do You Want in a New Anticoagulant?
- Safe
  - Especially bleed risk
  - Limited drug-drug interaction risks
- Effective
  - Rapid onset
  - Proven anticoagulant profile
- Convenient
  - Oral route
  - Limited or no monitoring

Some Universal Concerns
- Avoid use in patients with mechanical heart valves
- Sudden discontinuation of any agent may increase the risk for stroke
- Provide alternative anticoagulation
- All have bleeding risk
  - Always monitor
- All will require some monitoring
- Concerns about antidotes
Great First Concept; Really Bad Reality

- Ximelagatran (Exanta®, Astra Zeneca)
- Promising alternative to warfarin
- Direct thrombin inhibitor
- Reliable anticoagulation with BID dosing
  - Post orthopedic prophylaxis
  - Atrial fibrillation
- High risk for severe liver damage
- FDA pulled application 2006.

Pradaxa®

Dabigatran etexilate
Boehringer-Ingelheim

This is a general overview and may discuss some off-label and non-approved information.

Dabigatran

Initial FDA Approval: October 2010

Indicated for
- Reduction of risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- Treatment of DVT or PE in patients previously treated with a parenteral anticoagulant
- Reduction of risk for recurrence of DVT or PE in patients previously treated

Non-US approval for
- VTE prophylaxis following total hip and knee replacement

Dabigatran

Prodrug without anticoagulant activity that is converted in vivo to active dabigatran

Competitive, reversible, direct Factor IIa inhibitor

Inhibits thrombin, free and fibrin-bound, and thrombin-induced platelet aggregation
  - Acts to prevent effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI and XIII, and inhibition of thrombin-induced platelet aggregation.

Dabigatran

Bioavailability: 3 to 7%

Plasma concentration peaks within 1 to 2 hours

Half-life: 12 to 17 hours

Metabolism:
  - Liver microsomal carboxylesterases

Excretion:
  - Urine: 7%
  - Feces: 86%

Precautions

Hepatic
- Use cautiously in patients with moderate liver impairment
- Child-Pugh Class B or C
- Transaminases that are > 2 X upper normal limits
Precautions

Renal
- Cautious use for patients with creatinine clearance of 15 to 30 ml/ min
- Avoid use in patients with creatinine clearance ≤ 15 ml/ min
  - Lack of sufficient clinical evidence for safe and effective use
- Canadian labeling is more restrictive: avoid use if value is < 30
  - Best practice for most patients
  - 110 mg dose available in Canada

Cautions

- Higher bleed risk
  - Patient age over 75
    - Especially for those over 80
  - Patient weight less than 50 kg
  - Creatinine clearance < 50
- Beer’s List Drug
  - Limited RCT data for those 85 or older
- Acute coronary events
  - RE-LY Trial; Higher risk for MI/ ACS vs. warfarin

Adverse Events

- Bleeding – Up to 6% in trial populations
  - Frequent FDA/ BI information updates
- GI symptoms – Up to 16%
  - Dyspepsia
  - Diarrhea
- Joint Pain
- Fatigue
- Dizziness
- Dyspnea
- Peripheral edema

Drug-drug Interactions

- Other anticoagulants
- Antiplatelets
- P-glycoprotein inducers
  - Rifampin - AVOID combination with dabigatran
  - St. John’s Wort

Drug-Food Interactions

- Food has no effect on bioavailability
- Delays time to peak serum concentrations by about 2 hours
- Risk of GI distress may indicate need to give with or after meals

Drug-Drug Interactions

- P-glycoprotein Inhibitors
  - Amiodarone/ dronedarone
  - Clarithromycin
  - Cyclosporine
  - Diltiazem
  - Indinavir/ ritonavir
  - Itraconazole/ ketoconazole
  - Sirolimus/ tacrolimus
Monitoring Parameters

- Activated Partial Thromboplastin Time (aPTT)
  - Values > 2.5 X control; overly anticoagulated?
  - Sensitivity?
- Thrombin Time (TT)
  - Dilute TT may be more valuable
- Ecarin-based clotting time
- CBC with differential
- Always: creatinine clearance
- Serum dabigatran levels (Value?)
- PT/INR: PT can be affected

Monitoring Concerns

- Potential risk for bleeding higher than that discovered in RCT submitted for approval
- Serum level dose adjustment could lower risk of bleed by 30 to 40%
- No defined optimal therapeutic range
- 110 mg dose optimal to permit dose adjustment

BMJ July 2014

PT/ INR Monitoring

- Dabigatran can elevate PT and INR
- No direct clinical monitoring value
- Usually transient and more prevalent with initial dosing
- Switching from dabigatran to warfarin, check INR 2 days after dabigatran is stopped

Recovery

- No gold standard antidote
  - Idarucizmab under development
  - Discontinue the drug
  - Maintain adequate hydration/ diuresis
  - Dialysis: limited data, possible benefit
  - Consider transfusion
    - Fresh frozen plasma (FFP)
    - Packed red blood cells (PRBC)
    - Platelet concentrates

Dabigatran

- Dosing
  - 150 mg PO BID
- Renal Dosing
  - Creatinine clearance > 30 ml/ min: No change
  - Creatinine clearance 15 to 30 ml/ min
    - 75 mg PO BID with caution
  - Creatinine clearance < 15 ml/ min
    - Avoid use
- Hepatic Dosing: No recommendations

Dabigatran

- Dosage Forms:
  - Capsules: 75 and 150 mg
- Swallow intact; do not
  - Open
  - Chew
  - Sprinkle on food or mix with liquids
- Storage: Keep in original container
  - Bulk and unit-dose
  - No exceptions
- Use within 120 days of opening
Stopping Anticoagulation Prior to Elective Surgery

- Based in part on creatinine clearance
  - CrCl > 50: Safe at 1 to 2 days
  - CrCl < 50: 3 to 5 days
  - Unknown: Minimum of 3 days
- If spinal surgery, spinal block, or epidural catheter use is planned
  - Stop 5 days pre-op
- Extensive surgery: Allow 5 days

Dabigatran Conversion

- From a parenteral anticoagulant
  - Start within 2 hours prior to next scheduled dose of the parenteral anticoagulant (LMWH, e.g.)
  - At the same time as discontinuation of a continuously administered parenteral drug (UFH infusion)
- To a parenteral agent
  - Creatinine clearance 15 to 30, wait 24 hours
  - Creatine clearance ≥ 30, wait 12 hours
  - My take: wait 24 hours

Conversions: Warfarin

- From dabigatran to warfarin
  - Stop dabigatran based on CrCl
    - >50, 3 day overlap
    - 30 to 50, 2 day overlap
    - ≤15 to 30, no to 1 day overlap
- From warfarin to dabigatran
  - Follow recommended dosing guidelines for warfarin use
  - Keep INR < 2 before restarting dabigatran

Significant Clinical Trials

- Non-valvular atrial fibrillation; effectiveness vs. warfarin
  - RE-LY
  - PETRO
- Total Hip Replacement
  - RE-NOVATE
- Total Knee Replacement
  - RE-MODEL

Xarelto®

Rivaroxaban
Janssen Pharmaceuticals

This discussion will include some off-label and other non-approved information

Rivaroxaban

- Initial FDA Approval: July 1, 2011
- Approved indications:
  - Prophylaxis for DVT/PE after TKR or THR
  - Reduce risk for stroke and systemic embolism in patients with nonvalvular atrial fibrillation
  - Treatment of DVT/PE & reduction of risk of recurrence of DVT/PE
- Direct, selective Factor Xa inhibitor by direct binding to active Factor Xa site
  - Prevents formation of thrombin
  - Compare to fondaparinux and indirect inhibition
Non-approved indications

- Trials underway for
  - Long-term prevention of Acute Coronary Syndrome in patients with history of ACS
  - Prevention of risk for stroke in patients with history of stroke of undetermined cause
  - Reduction of DVT/PE risk in patients with CAD
- Post hip fracture DVT prophylaxis
  - Positive European data
- Be alert for non-approved use

Pharmacokinetics

- Bioavailability: 60 to 80%
- Peak serum concentration: 1 to 4 hours
- Half-life: 5 to 9 hours
- Protein binding: 90%
- Excretion:
  - Renal, about 30%
  - Biliary/fecal
  - Hepatic: CYP450, 3A4

Pharmacodynamics

- Factor Xa inhibition: 20 – 61%
- Time to maximum Xa inhibition: 1 to 4 hours
- Duration of Xa inhibition: 5 – 12 hours
- Maximum PT prolongation: 1.3 – 2.6 times baseline
- Maximum aPTT prolongation: 1.5 X baseline

Precautions

- Renal Impairment
  - Avoid use if creatinine clearance (CrCl) is below 30 ml/min
  - Observe carefully if CrCl is 30 to 50 ml/min
- Hepatic Impairment
  - Avoid use for Child-Pugh B or C
- Age
  - RCT data shows benefit for those older than 75, BUT
  - For those over 65, assess CrCl prior to initiating therapy and monitor during
  - Special caution for those over 80
  - And for body weight < 55 kg

Monitoring Parameters

- Activated Partial Thromboplastin Time (aPTT)
  - Values > 1.5 to 2.5 times control may indicate overly aggressive anticoagulation
  - Pay attention before any planned surgical procedures
  - Sensitivity?
- Creatinine clearance
- Thrombin Time (TT)
- CBC with differential
- Anti Xa assay
- Bleeding

PT/INR Monitoring

- Rivaroxaban can affect PT and so elevate INR
- No direct clinical monitoring value
- Usually transient and more prevalent with initial dosing
- Switching from rivaroxaban to warfarin, check INR 2 to 3 days after rivaroxaban is stopped
Adverse Events

- **Bleeding**: Risk similar to enoxaparin comparator
  - Peri- and post-surgical
  - Retroperitoneal hemorrhage
  - Subdural, epidural hematomas
- **Pain**
  - Extremities
  - Musculoskeletal
- **Syncope**
- **Skin and subcutaneous tissue disorders**

Drug-drug interactions

- **Other anticoagulants**
- **NSAIDs**
- **Aspirin**
- **Antiplatelets**
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®)
  - Ticagrelor (Brilinta®)

Drug-drug Interactions

- CYP450 3A4/ P-gp Inhibitors
  - Ketoconazole / Itraconazole
  - Ritonavir
  - Clarithromycin / erythromycin
  - Amiodarone / dronedarone
  - Carbamazepine / phenytoin
  - Felodipine
  - St. John’s Wart

Recovery

- No defined specific antidote in literature
- Not dialyzable
- Hold dosing
- Maintain adequate hydration/ diuresis
- Consider transfusions
  - Prothrombin Complex Concentrates
    - Kcentra® first of several
    - Combination of Factors II, VII, IX and X
  - Andexanet Alfa under investigation
  - FFP, PRBC
  - Possibly recombinant Factor VIIa

Rivaroxaban

- **Orthopaedic Surgery Prophylaxis**
  - **Dosing**
    - 10 mg PO once daily
  - May be given without regard to meals
    - Slowed absorption if given with food; no net clinical effect
  - Available as 10 mg tablet

Duration of Treatment

- **Post total knee replacement**
  - Clinical trials: 12 days
  - Recommend 2 weeks
- **Post total hip replacement**
  - Trials: 35 days
  - Recommend a full 6 weeks
- **Other hip/ other knee**
  - No approved use
  - Some European RCT data to support use
  - Similar durations
### Rivaroxaban – Atrial Fibrillation

- Creatinine clearance (CrCl) > 50 mL/min
  - 20 mg once daily – with evening meal
- CrCl 15 - 50 mL/min:
  - 15 mg once daily – with evening meal
  - Use with caution
- CrCl <15 mL/min
  - Avoid use
- Available as 15 and 20 mg tablets

### Rivaroxaban – DVT/ PE Treatment

- Always take at the same time each day and with a meal
- 15 mg PO BID x 21 days
- Then 20 mg PO once daily
- Extended treatment to prevent risk of recurrent VTE
  - 20 mg PO daily

### Stopping Anticoagulation Prior to Additional Surgery

- Safe to dose up to the day before planned surgery
- If spinal surgery, spinal block, or epidural catheter use is planned
  - Stop 3 to 5 days pre-op
- Extensive surgery: Allow 5 days

### Rivaroxaban Conversion

- From a parenteral anticoagulant
  - No approved technique
  - Start within 2 hours of planned dose of the parental anticoagulant (e.g., enoxaparin)
  - At the same time as discontinuation of a continuously administered parental drug (UFH infusion)
- To a parenteral agent
  - No specific guideline
  - Consider stopping rivaroxaban and starting parenteral agent in 4 to 6 hours

### Conversions: Warfarin

- From rivaroxaban to warfarin
  - Stop rivaroxaban
  - Start with recommended dose the next day
  - Check INR in 3 days
- From warfarin to rivaroxaban
  - Follow recommended dosing guidelines for warfarin use
  - Keep INR < 2 before restarting rivaroxaban
  - Suggest one additional INR

### Significant Clinical Trials

- Total Hip Replacement
  - RECORD-1; vs. enoxaparin
- Total Knee Replacement
  - RECORD-3; vs. enoxaparin
- Acute Coronary Syndrome
  - ATLAS; vs. aspirin or aspirin/ clopidogrel
- Atrial fibrillation
  - ROCKET; vs. warfarin
**Eliquis®**

Apixaban
Bristol-Myers Squibb/ Pfizer

This is a general overview and may discuss some off-label and non-approved information

**Apixaban**

- Initial FDA approval: 12/29/12
- Indications:
  - Reduce risk of stroke and system embolism in patients with nonvalvular atrial fibrillation
  - Prophylaxis of DVT/ PE post THR and TKR
  - Treatment of DVT/ PE and for reduction of risk of recurrent DVT/PE following initial treatment
- Other trials underway for
  - ACS

**Mechanism of action:**
- Reversible, selective site inhibitor of Factor Xa
- Active against both free and clot-bound Factor Xa
- Indirect inhibition of thrombin-induced platelet aggregation

**Peak plasma concentration**
- 3 to 4 hours

**Half-life**
- About 6 hours initial clearance
- About 12 hours after repeat dosing

**Plasma protein binding**
- About 87%

**Metabolism**
- Primarily via CYP3A4

**Excretion**
- Urine and feces
  - Renal: about 27% of total clearance

**Precautions**
- Avoid use if creatinine clearance is less than 15 ml/min
- Avoid use with severe hepatic impairment
- Always assess bleed risk

**Drug-drug Interactions**
- Substrate of
  - CYP3A4
  - P-glycoprotein
- Inhibitors increase effect
- Inducers decrease effect
- Anticoagulant/ antiplatelet agents
  - Rifampin
  - St. John’s Wort
Monitoring
- Serum creatinine and creatinine clearance
- PT/INR?
  - Apixaban does affect INR
  - Not reliable as sole monitor
- aPTT
  - Goal 1.5 to 2 times upper normal limit
- TT
- Anti-Xa assay
- CBC with differential

Recovery
- Andexanet Alfa (Annexa™) promising
- No established reversal protocol
- Not dialyzable due to high protein binding
- Stop dosing
- Hydration/diuretic use
- Use of antifibrinolytic or procoagulant reversal agents has not been evaluated
- Activated charcoal can reduce absorption

Apixaban Dosing
- Reduction of risk nonvalvular a fib.
  - 5 mg PO BID
- Prophylaxis post THR/TKR
  - 2.5 mg PO BID
  - 12 days for TKR; 35 days for THR
- Treatment of DVT/PE
  - 10 mg PO BID x 7 days, then
  - 5 mg PO BID
- Reduction of risk for DVT/PE recurrence
  - 2.5 mg PO BID after at least 6 months of treatment

Apixaban Dosing Adjustments
For patients with nonvalvular a fib
- Dosage adjustment:
  - 2.5 mg PO twice daily
  - Patients
    - 80 years of age or older
    - Body weight 60 kg or less
    - Serum creatinine of 1.5 or more
- May give without regard to meals

Apixaban Dosing Adjustments
- Drug-drug interaction risk
  - Concomitant with drugs that are strong dual inhibitors of CYP3A4 and P-gp
    - 2.5 mg PO BID
  - If already on 2.5 mg dose – avoid apixaban
  - Concomitant with strong dual inducers
    - Avoid use of apixaban
- Renal Compromise
  - Avoid use if creatinine clearance is below 15 ml/min

Stopping Apixaban Prior to Surgery
- Stop apixaban at least 48 hours before surgery or invasive procedures with high risk for bleeding
- Stop at least 24 hours before procedures with lower risk
- Any surgery lasting more than 1 hour should be considered high risk
- Recommend at least 3 days if spinal surgery is involved.
Apixaban Conversions

- **Warfarin to apixaban**
  - Start apixaban at next scheduled dose of warfarin
  - INR should be 2 or under
  - One additional INR check
- **Apixaban to warfarin**
  - Stop apixaban
  - Start warfarin with bridge prophylaxis as needed
  - PT/INR in 3 days
- **Apixaban and other anticoagulants**
  - Stop current regimen, begin apixaban at next scheduled dose.

Significant Clinical Trials

- **Atrial fibrillation**
  - ARISTOTLE: vs. warfarin
  - AVERROES: vs. aspirin
- **THR**:
  - ADVANCE 3.2
- **TKR**:
  - ADVANCE 2.2 AND APROPOS
- **ACS**:
  - APPRAISE
- **DVT**:
  - AMPLIFY & BOTICELLI
- **PE**:
  - AMPLIFY

Savaysa®

Edoxaban
- Daiichi-Sankyo

This is a general overview and will discuss some off-label and non-approved information

Edoxaban

- **FDA approval January 2015**
- **Indications**
  - Reduction of stroke and systemic embolism risk in patients with nonvalvular atrial fibrillation
  - Treatment of DVT or PE following 5 to 10 days of parenteral anticoagulation
- **As Lixiana® in Japan, indicated for VTE prevention after TKR/THR**

Edoxaban

**Mechanism of action:**
- Highly specific, direct inhibitor of Factor Xa
- Active against both free and clot-bound Factor Xa

Edoxaban

**Boxed warnings:**
- Less effective for AF patients with CrCl > 95 ml/min
- Increased risk of stroke in these patients
- Premature discontinuation increases risk for ischemic events
Edoxaban
- Peak plasma concentration
  - 1 to 2 hours
- Half-life
  - About 6 hours initial clearance
  - Reported at 10.7 hours after repeat dosing
- Plasma protein binding: 40 to 59%
- Excretion: Via active secretion into the kidney
  - 60% detected in feces; 40% in urine

Precautions
- Avoid use if creatinine clearance is less than 15 ml/min
- Cautious use with severe hepatic impairment
- Remember boxed warnings
- Always assess bleed risk

Drug-drug Interactions
- Substrate of
  - CYP3A4
  - P-glycoprotein
- Inhibitors increase effect
- Inducers decrease effect
- Anticoagulant/ antiplatelet agents
- Rifampin a special concern
- St. John’s Wort

Monitoring
- Serum creatinine and creatinine clearance
- PT/ INR?
  - Edoxaban will affect INR
  - Not reliable as sole monitor
- aPTT
  - No stated goal; anticipate max of 2X UNL
- TT
- Anti-Xa assay
- CBC with differential

Recovery
- No established reversal protocol
- Andexanet Alfa may be of value, but not assessed
- Value of dialysis is not known, potential value
- Stop dosing
- Hydration/ diuretic use
- Activated charcoal can reduce absorption

Dosing
- Same regardless of indication
- 60 mg once daily
- Dose reductions
  - CrCl 15 to 50 ml/ min; 30 mg once daily
  - CrCl < 15 ml/min; avoid use
  - Patients with P-gp inhibitors; 30 mg once daily
- AF treatment, avoid use if CrCL > 95 ml/ min
- Tablets: 60 mg, 30 mg, 15 mg
Stopping edoxaban prior to surgery

- Stop edoxaban at least 24 hours before surgery or invasive procedures.
- Consider at least 48 to 72 hours for higher risk
  - Any surgery lasting more than 1 hour should be considered high risk
  - Recommend at least 3 days if spinal or orthopedic surgery is involved.

Transitions to edoxaban

- From warfarin: Stop warfarin; start edoxaban when INR is 2.5 or less
- From NOAC: Stop current drug; start edoxaban when next scheduled dose is due
- From LMWH: Stop LMWH; start edoxaban when next LMWH dose is due
- From UFH: Stop infusion; start edoxaban in 4 hours

Transitions from edoxaban

To warfarin:
- From 60 mg dose, reduce to 30 mg and start warfarin immediately
- From 30 mg dose; reduce to 15 mg and start warfarin immediately
- Alternatively: Stop edoxaban, add a parenteral AC and warfarin. D/C parenteral AC when INR is stable at 2 or less

Transitions from edoxaban

To another NOAC
- Stop edoxaban and start alternative NOAC when next edoxaban dose is due

To a LMWH or UFH
- Stop edoxaban and start the chosen agent at the time the next edoxaban dose is due

Significant Clinical Trials

- ENGAGE-AF-TIMI
  - Atrial fibrillation indication
  - Cautions about CrCl
- Hokusai-VTE trials
  - DVT/ PE treatment indications

The Flood Yet To Come

- Betrixaban: Portola, Merck
- YM150: Astellas
- AZD0837: AstraZeneca
- LY517717: Lilly
- Letaxaban: Takeda
- Darexaban: Astellas (Development discontinued)
- Eribaxan
Potential Candidates for NOACs

- Intolerance of warfarin
  - I’m not taking rat poison
  - My father died on warfarin
  - I had bleeding problems before
- Compliance/ adherence concerns
  - Consistency with dosing
  - Interactions
  - Lab compliance
  - Needlephobia – avoid LMWH

We Owe It All to Wisconsin

- Cattle bled after eating sweet clover
- Recovered after eating soybean greens
- Wisconsin Alumni Research Foundation
  - A dicumarol molecule
  - Coumarin responsible for bleeding
  - Warfarin (Coumadin®), DuPont
- Rat Poison in 1948
- Approved as drug 1954

Difficulties with Warfarin

- Narrow therapeutic index drug;
- Highly variable dose response
- Drug-drug, drug-food, and drug-disease state interactions;
- Lab control difficult to standardize;
- Variances in PT/INR based on sample;
- Genetic variances; and
- Problems with patient compliance and adherence and communication between the patient and health care professionals.

Adapted from ACCP 2014

Warfarin (Coumadin®)

- Vitamin-K antagonist:
  - Depletes Vitamin K-dependent factors
  - II, VII, IX, and X
- Slow onset of effectiveness
  - 3 to 5 days or more
- A real nemesis
  - Clinically
  - Operationally
  - Reliability

Warfarin and Other Drugs

- Worry just a bit about most of them
- Antibiotics and gut flora
- Rifampin
- FAB 4
  - Fluconazole and similar
  - Amiodarone & dronedarone
  - Bactrim
  - Fluoroquinolones (and metronidazole)
Warfarin and Diet
- Dark green leafy vegetables
- Cranberry juice
- Grapefruit juice
- Ethanol
- Green tea
- Suggest moderation and no major swings in diet rather than complete avoidance
- Remember the farmers in Wisconsin

Warfarin Adverse Events
- Bleeding
- Bruising
- Skin Necrosis
- Loss of Appetite
- Chills
- Fatigue
- Paresthesias
- Exacerbated by drug-drug interactions

International Normalized Ratio: INR
- Monitored with prothrombin time
- INR Standardizes prothrombin time using International Sensitivity Index (ISI)
- PT Ratio = (Individual PT / mean normal PT)
- INR = (PT Ratio)^ISI
- ISI Range is 1.0 to 3.2

INR Target Ranges
- ACCP: Stroke Prevention in Atrial Fibrillation
  - Any high risk factor or > 1 moderate risk factor
    - INR 2.5, Range 2 - 3
  - One moderate risk factor
    - INR 2.5, Range 2 - 3; Aspirin 325 mg daily alternative
- AGS:
  - Atrial Fibrillation
    - 2 - 3
  - Bioprosthetic heart valve
    - 2 - 3
  - Mechanical heart valve
    - 2.5 - 3.5
  - Post MI
    - 2.5 - 3.5

Warfarin Dosing Adjustments
- No well-accepted, evidence-based guidelines
- Initial dosing of 5 to 10 mg
  - Avoid higher “loading” doses
  - Lower dose for those 80 or with other risk factors
- Rough benchmark
  - 10% dose adjustment = INR change of 0.5 to 0.7 weekly
  - 15% dose adjustment = INR change of 1 weekly
- Monitor INR 3 - 5 days after dose adjustments
  - Can be less frequent with long term dosing
  - Monitor more frequently if drug interaction risk
  - Benefit can exist when INR is in target range more than 55% of the time

Recovery: Warfarin
Based on INR and bleeding
- INR 3.5 to 5: no significant bleeding
  - Hold 1 (or 2) Doses
  - Decrease dose by 10 to 20%
- INR 5 to 9: no significant bleeding
  - Hold 2 doses
  - Redraw INR
  - Decrease dose by 10 to 25%
  - Low dose Vitamin K option
- INR > 9
  - Hold dosing
  - Vitamin K 2.5 to 5 mg
  - If bleeding, Vitamin K 5 mg slow IV, consider FFP

Adapted from ACCP
Brand vs. Generic

- “It Don’t Matter To Me”
- Extensive literature review and meta-analysis: no clinically significant difference in outcomes
  - 11 studies; over 40,000 patients
- Nonetheless: Check INR after for any switch
- Stick with the one that you start with

Resources

- American College of Chest Physicians
  - www.chestnet.org
- Annals of Pharmacotherapy
  - www.theannals.com
- American Geriatrics Society
  - www.americangeriatrics.org
- National Institutes of Health
- Merck Manual of Geriatrics
  - www.merck.com

Thank you

“I was curious. Since I am not a cat, that was not dangerous.”

Gregory House; House, MD

Curious? Are there any questions?