New Ways to Thin the Herd:
A Review of Current Guidelines and Direct Oral Anticoagulants (DOACs)

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Learning Objectives

1. Review and discuss DOACs with regard to mechanism of action, drug interactions, side effects, and indication as compared to warfarin.
2. Review clinical current guidelines concerning anticoagulation.
3. Discuss stratification of risk using CHA2DS2-VASc and HAS-BLED scoring systems for atrial fibrillation patients.
4. Identify the appropriate protocol to transition to and from DOACs in relation to warfarin, LMWHs, and surgical procedures.

2018 CHEST Guidelines Update

- ACCP Antithrombotic Therapy for Atrial Fibrillation
- Released November, 2018
- 60 recommendation statements in the areas of stroke risk, bleeding risk, antithrombotic therapy, and management of bleeding on oral anticoagulation
- New recommendations:
  - For patients who have one non-gender CHA2DS2-VASc risk factor, oral anticoagulation is suggested rather than no therapy, aspirin, or DAPT
  - When oral anticoagulation is recommended, use of a DOAC rather than dose adjusted warfarin. If can keep INR in range ≥ 70% of time warfarin can be continued or selected
  - Can use SAMe-TTR2 score to screen if warfarin is preferred
  - HAS-BLED score to identify modifiable risk factors in atrial fib patients

American College of Chest Physicians; 2018

Guideline Review:

- AHA/ACC/HRS Guideline for Management of Patients with Atrial Fibrillation, Executive Summary (2014)
- ACC Expert Consensus Decision Pathway for Periprocedural Management of Nonvalvular Atrial Fibrillation (2017)

Who Receives Anticoagulation?

- CHA2DS2-VASc is PREFERRED (AHA/ACC)
  - Broader score (0 to 9)
  - Women cannot achieve a score of “0” thus the new recommendation of non-gender designation
  - Better discrimination of stroke risk
  - More predictable with the lower risk category

Who Receives Anticoagulation?

- Recommended for:
  - Non-valvular Afib
    - CHA2DS2-VASc nongender score of 1 (males) and 2 (females)
  - Afib cardioversion with low TE risk or duration of <48 hours
  - Mechanical heart valves
  - Cardioversion candidates >48h and/or intermediate or high risk of CVA
  - Acute VTE/Prevention of VTE
  - Post arthroplasty

Who Receives Anticoagulation?

- Bleeding Risk Assessment with maximum score of 9
- HAS-BLED – Score of ≥ 3 potential high risk
  - HTN (SBP>160)
  - Abnormal Liver Function
  - Abnormal Renal Function
  - History of Stroke
  - History of Bleeding
  - History of fluctuation in INR
  - Elderly (>65yo)
  - Use Drugs that Promote Bleeding or ETOH abuse

CHEST 2010;138:1093-100.

“Old School“
Review of Warfarin Therapy

Rainbow of Warfarin

Please (Pink)
Let (Lavender)
Grandpa (Green)
Brown (Brown)
Bring (Blue)
Peaches (Peach)
To (Teal)
Your (Yellow)
Wedding (White)

Warfarin (Coumadin)

- Gold standard for comparison
- Remains the inexpensive option
- SAM-TRR2 score of ≥2 use DOAC
- Numerous drug and food interactions
- Compliance can be assessed
  - Narrow therapeutic window: INR 2-3
  - Mechanical mitral valve: INR 2.5-3.5
- Does not begin to work immediately
  - Half life of Vitamin K factors are reason
  - II, VII, IX, X

AES Question

AES Question 1

Which of the following does not require interruption of anticoagulation?

A. Spinal injections
B. Open cholecystectomy
C. Colonoscopy
D. Root Canal
E. None of the above

Therapy Interruption

- Certain procedures do not require interruption
  - Dental extraction of 1-3 teeth
  - Dental implant positioning
  - Periodontal surgery
  - Cataract or glaucoma intervention
  - Abscess incisions
  - Superficial Surgery
  - Colonoscopy/Endoscopy without surgery
  - Pacer, ICDs, ablations, angiography
    - BRUISE trial

Therapy Interruption

- Risk assessment:
  - Bleeding risk of procedure
  - Patient specific risks
    - CHA2DS2-VASc Score
    - HAS-BLED Score
  - Timing of VTE within last 3-12 months
  - Valve replacement with prosthesis and type
  - TIA and/or CVA within last 3 mos

AES Question

AES Question 2

When interrupting Warfarin therapy all patients must be bridged with LMWH?

A. True

B. False

Warfarin - Bridging Therapy

- Low Risk:
  - CHA2DS2-Vasc score ≤ 4 with no previous CVA and/or TIA or SE
  - No bridge or consider low dose LMWH

- Moderate Risk:
  - CHA2DS2-Vasc score 5-6 or PMH of CVA/TIA and/or SE ≥ 3 mos
  - To Bridge or Not to Bridge
    - Do not bridge if HASBLED score ≥ 3 or no PMH of CVA/TIA or SE
    - Likely bridge if PMH CVA/TIA or SE with low HASBLED score

- High Risk:
  - CHA2DS2-Vasc score of ≥7
  - CVA/TIA and/or SE within last 3 months
  - Consider bridge therapy with parenterals

Doherty J. JACC 2017;69(7):1-23

Warfarin - Bridging Therapy

- If INR is 2-3
  - Start holding warfarin 5 days prior to procedure
  - Initiate LMWH 3 days prior to procedure (INR should be < 2.5)
  - Last dose of LMWH 24 h prior to procedure with INR check
  - Resume BOTH Warfarin and LMWH 12-24 h post
  - BUT If high risk for bleed resume LMWH 48-72 h post
  - INR and CBC Day 3, then on Day 5 start daily INRs until therapeutic
- If INR >4
  - Same as above but if INR >1.5 on Day 2 of hold consider oral vitamin K 2.5mg

Doherty J. JACC 2017;69(7):1-23

Direct Oral Anticoagulants (DOACs):

Direct Thrombin Inhibitor:

Dabigatran (Pradaxa)

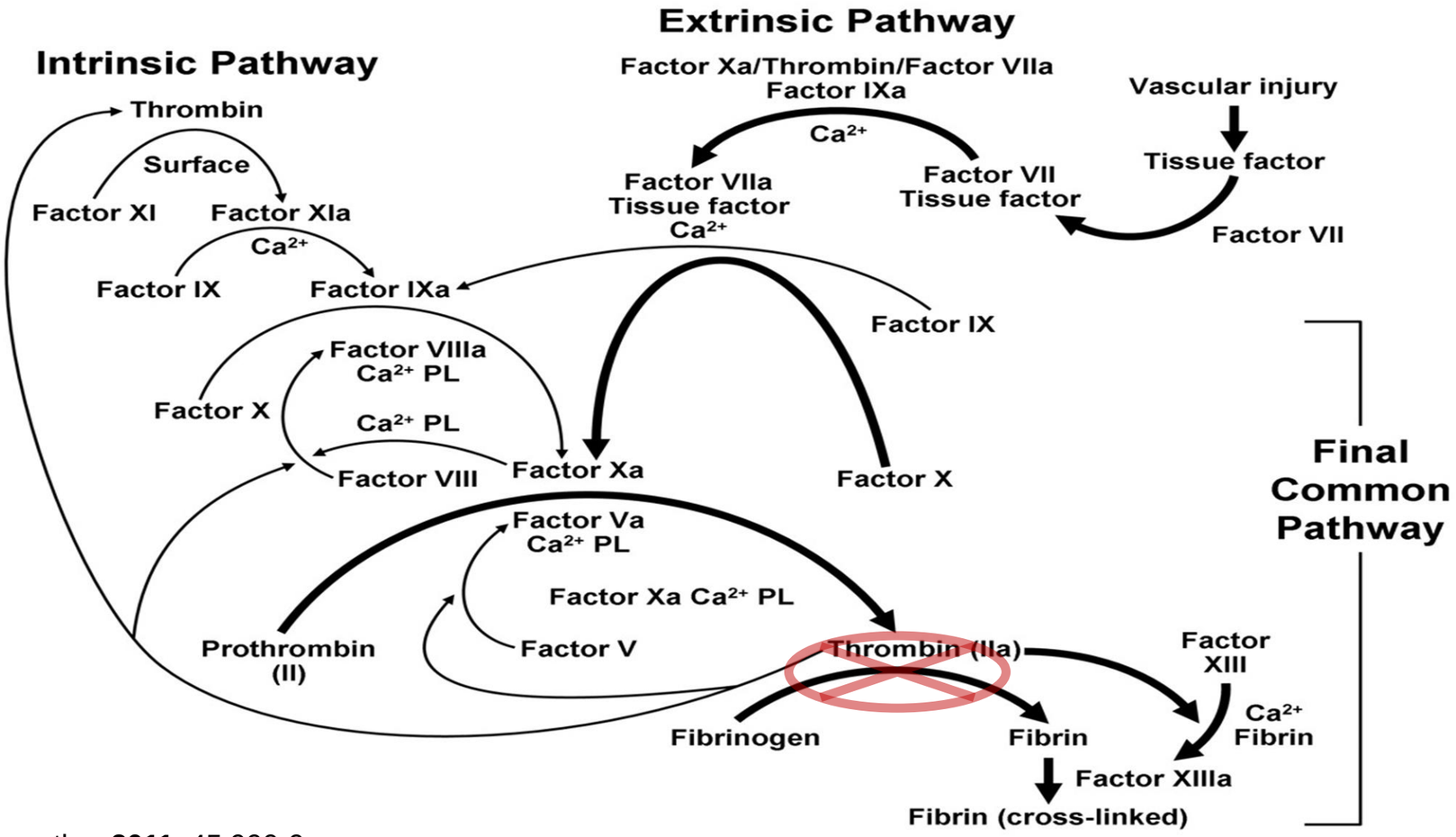
Dabigatran (Pradaxa)

- Univalent, competitive, reversible direct thrombin inhibitor (DTI)
  - Binds to active site → inactivates fibrin-bound & unbound thrombin

- Thrombin Inhibition Prevents
  - Fibrinogen → fibrin
  - Positive feedback amplification
  - Platelet activation

Circulation 2005; 112:53-60.
Thromb Haemost 2010; 103:1116-27.
Thromb Haemost. 2011; 105:371-8.

Dabigatran: Mechanism of Action



Ann Pharmacother **2011**; 45:990-9.

Dabigatran: Pharmacokinetics

- Dabigatran etexilate (prodrug) + esterases → dabigatran (active)
  - Rapidly absorbed & hydrolyzed = peak plasma levels within 1.5 hrs
  - Acidic drug so can increase gastric irritation
- Plasma protein binding: ~35%
  - Few displacement interactions & dialyzable
- Predominant elimination pathway: RENAL (80%)
  - CrCl → most important factor for drug exposure
- Terminal half-life: 12-14 hrs

Circulation 2005; 112:53-60.
Thromb Haemost 2010; 103:1116-27.
Thromb Haemost. 2011; 105:371-8.

Dabigatran: Indications

- Nonvalvular afib (NVAF)
  - 150mg BID
  - Prevents 5 more CVAs per 1000 pts/yr than warfarin (RELY Trial)
- VTE prevention post hip
  - 110mg post op then 220mg/d x 10-35d
- Treatment of DVT and PE
  - Treat with a parenteral anticoagulant for 5-10 days then 150mg BID
  - Reduce the risk of recurrence of VTE 150mg BID
- Caution
  - >75yo
  - Poor renal function CrCl ≤30ml/min use 75mg BID
  - Underweight
  - H/O GI bleed- higher rate GI bleed vs warfarin
  - Weight >120kg

Dabigatran: Conversion

Warfarin to dabigatran	Stop warfarin and start dabigatran when INR < 2
Dabigatran to warfarin	• DC dabigatran 3 d after starting warfarin. •CrCl 31-50 ml/min: DC dabigatran 2 d after starting warfarin. •CrCl 15-30 ml/min: DC dabigatran 1 d after starting warfarin.
LMWH/Fondaparinux to dabigatran	•DC parenteral anticoagulant and give dabigatran 0-2 h before next parenteral dose would have been given
IV heparin to dabigatran	Administer 1st dose of dabigatran at time of discontinuation of IV infusion
Dabigatran to parenteral anticoagulant	•CrCl > 30 ml/min: Start parenteral anticoagulant 12 h after the last dose •CrCl < 30 mL/min: Start parenteral anticoagulant 24 h after the last dose

Dabigatran: Perioperative Management

Calculated CrCl ml/min	Low risk of bleed	High risk of bleed
>80	1 day	2 days
>50	1-2 days	3 days
30-50	2-3 days	4-5 days
15-29	3 days	5 days

Dubois et al. Thrombosis Journal 2017;15 (14):1-17
Doherty J. JACC 2017;69(7):1-23

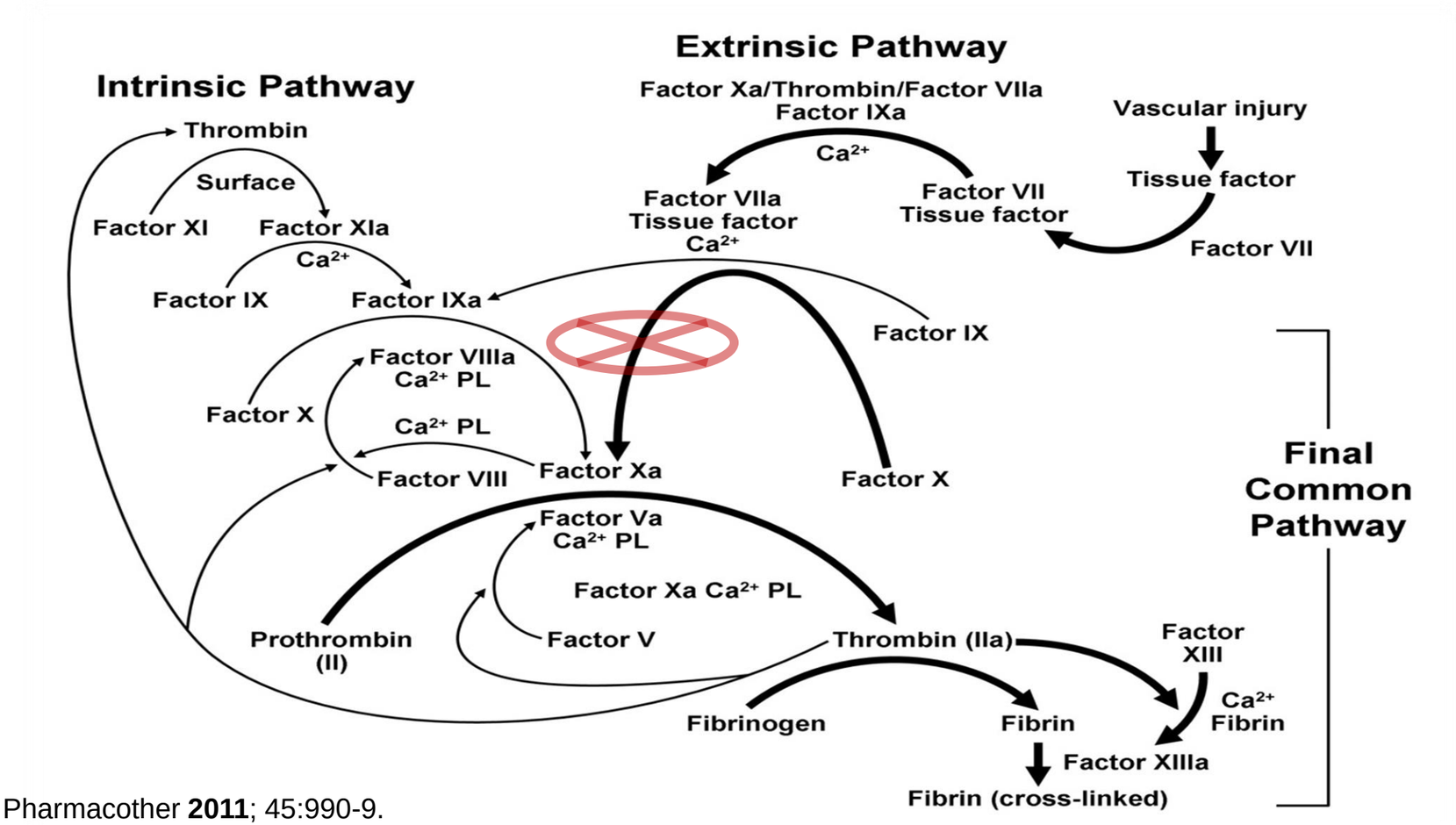
Idarucizumab (Praxbind)

- Humanized monoclonal antibody fragment that binds dabigatran
- Indication:
  - Immediate reversal of dabigatran for urgent/emergent situations
- Dosing:
  - 5 g dose → 2.5 g/50 mL boluses x 2 within 15 minutes
  - Re-dosed based on continued bleeding
- Efficacy:
  - RE-VERSE AD trial showed 90-100% immediate reversal within 4 hours
  - Dabigratran can be restarted 24 h after the reversal dose given
- Safety:
  - Anaphylactic reactions
  - Thrombosis risk increases
  - Other side effects were generalized
- Cost:
  - $3500/5 g dose

Direct Oral Anticoagulants (DOACs): Factor Xa Inhibitors:

Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Edoxaban (Savaysa)
Betrixaban (Bevyxxa)

Mechanism of Action of Factor Xa Inhibitors



Ann Pharmacother **2011**; 45:990-9.

Perioperative Management

Calculated CrCl	Low Risk of Bleed	High Risk of Bleed
>50	1 days	2 days
>30	1-2 days	3-4 days
<30	2 days	4 days

Dubois et al. Thrombosis Journal 2017;15 (14):1-17
Doherty J. JACC 2017;69(7):1-23

Rivaroxaban (Xarelto)

Rivaroxaban (Xarelto): Indications

- Nonvalvular afib (NVAF)
  - 20mg/d with evening meal
- VTE prevention post hip or knee replacement
  - 10mg/d x 35 d for hip and 12 d for knee
- Treatment of DVT and PE
  - 15mg BID with food x 21 days then 20mg/d x 3-6 mos.
  - 10mg/d if needed to reduce recurrence of VTE
- CV risk reduction in CAP or PAD
  - 2.5mg BID with ASA 81mg but DO NOT do this!

Rivaroxaban: EBM

- ROCKET AF Trial
  - Nonvalvular afib (NVAF)
  - Comparable to warfarin in high CVA risk pts
  - Lower rate of hemorrhagic CVA
  - Higher rate of GI bleed
- EINSTEIN-DVT EINSTEIN-PE Trials
  - Comparable to warfarin/enoxaparin?
  - Bleed risk similar
- Prevention of VTE post hip and knee replacement
  - Prevents 4 more VTEs vs LMWH
  - Causes 9 more serious bleeds/1000 pt x 14 d
- CV risk reduction in CAD or PAD
  - COMPASS trial: recently added new indication

Rivaroxaban: Cautions

- Use Caution:
  - Elderly and underweight
  - H/O GI bleed- higher rate GI bleed vs warfarin
  - CrCl ≤50ml/min need dose adjustment
  - Avoid if CrCl< 15 mL/min
  - Significant hepatic disease (Child-Pugh B or C)
  - Weight >120kgs

Rivaroxaban: Pharmacokinetics

- Rivaroxaban is rapidly absorbed after administration
  - Peak plasma levels within 2-4 hrs
- Pharmacogenomics: hepatic oxidation → CYP3A4
  - Avoid concomitant use with strong CYP3A4 inhibitors/inducers
- Plasma protein binding: ~93%
  - Some data that 10-15mg/d could be used
  - Bioavailability 80-100%
- T 1/2: 5-13 hrs
- Renal (66%) and fecal/biliary (33%) elimination

Rivaroxaban: Conversion

- From Warfarin
  - Initiate Rivaroxaban when INR $\leq$ 3
- To Warfarin
  - Initiate warfarin and LMWH 24 h after last dose of Rivaroxaban
- From LMWH
  - Initiate ≤ 2h prior to the next regularly scheduled dose of LMWH
- To LMWH
  - Initiate 24h after the last dose of Rivaroxaban

Apixiban (Eliquis)

Apixiban: Indications

- NVAF
  - 5 mg BID
  - 2.5 mg BID if 2 or more of the following met:
    - Age ≥ 80 years old
    - Weight ≤ 60 kg
    - Scr ≥ 1.5 mg/dL
- Treatment and prevention of VTE
  - Initial 10mg BID x 7 d then 5mg BID x 3-6 mos
  - Extended timeline reduce to 2.5mg BID
- Hip and Knee post op
  - 2.5mg BID x 12 days Knee or 35 days hip
- Dosing considerations:
  - Caution >120 kgs
  - Do not use in severe liver impairment or CrCl ≤ 25ml/min

Apixaban: EBM

- AMPLIFY and AMPLIFY-EXT
  - Non-inferior to warfarin
  - Superior with adverse effects like major bleeding
- ARISTOTLE results
  - 3 more CVAs prevented per 1000 pts/yr
  - Avoids 10 major bleed per 1000 pts/yr
  - Prevents 4 deaths per 1000 pts/yr
  - Demonstrated superiority against Warfarin
  - Less bleeding noted vs. Dabigatran

Apixaban: Pharmacokinetics

- Apixaban is rapidly absorbed after administration
  - Peak plasma levels within 3-4 hrs
  - Take with or without food and can crush
- Pharmacogenomics: CYP3A4 metabolizes and substate of P-gp
  - Avoid concomitant use with strong CYP3A4 inhibitors/inducers
- Plasma protein binding: ~87%
  - NOT dialyzable
  - Bioavailability 50%
  - Dialysis: Recent trial concluded more effective and safer vs warfarin
- T 1/2: 12 hrs
- Renal (27%) and fecal/biliary (73%) elimination

Apixaban: Conversion

- From Warfarin
  - Initiate when INR <2
- To Warfarin
  - Initiate LMWH and warfarin when next dose of Apixaban is scheduled
- From LMWH
  - Start Apixaban at the next regularly scheduled LMWH dose
- To LMWH
  - Start LMWH at the next regularly scheduled Apixaban dose

Edoxaban (Savaysa)

Edoxaban: Indications

- Afib
  - 60mg daily with CrCl >50 and ≤95ml/min
  - 30mg daily with CrCl 15 to ≤50ml/min
- VTE
  - Parenteral anticoagulant for 5-10d then
  - >60kg use 60mg/d
  - ≤60kg use 30mg/d
  - CrCl 15 to 50 ml/min use 30mg/d

Edoxaban: EBM

- ENGAGE AF-TIMI 48 Study
  - Approval 2015
  - Non-inferior to warfarin in afib pts
    - INFERIOR if CrCl ≥95ml/min
  - Superior with adverse effects like major bleeding
    - 6 fewer bleeds per 1000 patients/yrs
- Hokusai VTE Study
  - About as effective as Warfarin
  - Less bleeding noted
    - 18 fewer bleeds per 1000 patients/yr

Edoxaban: Pharmacokinetics

- Edoxaban is rapidly absorbed after administration
  - Peak plasma levels within 1-2 hrs
  - Take with or without food and can crush
- Pharmacogenomics: conjugation and oxidation via CYP3A4
  - May need dose reduction with 3A4 inhibitors
  - Dose reduction with Pgp inhibitors for VTE treatment
- Plasma protein binding: ~55%
  - NOT dialyzable – only 7% removed
  - Bioavailability 62%
- T ½: 10-14 hrs
- Renal (50%) and fecal/biliary (50%) elimination route
  - Do not use if CrCl <15 and >95ml/min

Edoxaban: Conversion

- From Warfarin
  - Initiate when INR <2.5
- To Warfarin
  - Reduce dose by ½ and start warfarin with weekly INR checks
  - Start LMWH and warfarin at the time of the next scheduled dose of Edoxaban
- From LMWH
  - Start Edoxaban at the next regularly scheduled LMWH dose
- To LMWH
  - Start LMWH at the next regularly scheduled Edoxaban dose

AES Question

AES Question 3

Which of the following is considered to have the best balance of efficacy and safety in atrial fibrillation?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. All the above

Betrixaban (Bevyxxa)

Betrixaban: Indications

- VTE prevention in acutely ill medical, non-surgical patients with moderate or severely limited mobility plus other VTE risk factors
  - 160mg x 1 then 80mg/d with food x 35-42 days
  - 80mg x 1 then 40mg with foods if CrCl 15-30ml/min
- No data on switching to/from other anticoagulants

Betrixaban: EBM

- APEX Trial
  - Betrixaban vs. Enoxaparin for prevention of VTE in acute medically ill patients (Multicenter)
  - 2 separate cohorts studied:
    - Overall for entire study betrixaban-treated patients had lower rates of symptomatic VTE than those receiving enoxaparin
    - Rates of major bleeds similar
    - But higher rate of clinically relevant non-major bleeding with betrixaban

Betrixaban: Pharmacokinetics

- Pharmacogenomics: minimal CYP involvement
- Drug Interactions: P-gp inhibitors can increase concentration ie amiodarone, azithromycin
- Betrixaban is rapidly absorbed after administration
  - Peak plasma levels in 3-4 hours
  - Bioavailability: 34%
  - No data in ESRD and Hemodialysis
- T 1/2: 19-27 hours
- Urine (11%) and Feces (85%) elimination
- Pricing: $450

Betrixaban: Perioperative Management

Calculated CrCL	Low Risk of Bleed	High Risk of Bleed
>30	4 days	4 days
<30	Do not use	Do not use

Cohen AT et al. New Engl J Med 2016; 375:534-44.

Andexanet Alfa (Andexxa)

- First antidote
  - Rivaroxaban (Xarelto) and Apixaban (Eliquis)
  - Off label for Edoxaban (Savasya) and Betrixaban (Bevyxxa)
- Available as “limited drug launch” in 2018
- Fully available early 2019
- MOA:
  - 1) directly binds to/sequesters rivaroxaban and apixaban
  - 2) inhibits Tissue Factor Pathway Inhibitor (TFPI)→ increase in thrombin generation
- Dosing:
  - 400-800 mg IV bolus→4-8 mg/min infusion (up to 120 minutes)
  - Dose depends on when last dose of Xa inhibitor given

Andexanet Alfa (Andexxa)

- ANNEXA-4 trial:
  - Decreased anti-Xa activity by an average of 89% after bolus→infusion
  - 4 hours post infusion:
    - Decrease in 39% (rivaroxaban) and 30% (apixaban)
  - Thrombotic event in 18% of patients during 30 day follow up
    - Factor Xa can rebound after the end of infusion
  - Effective hemostasis in 79% of patients
  - Cost: 100mg is $3,300 each

NEJM 2016; 375:1131-1141.

New(ish) Info from Clinical Trials

- Meta-analysis of DOACs vs. warfarin (*BMJ)*
  - Report: DOACs superior in terms of stroke prevention/all cause mortality, but higher incidence of severe ADR
    - HOWEVER! All dependent on time in therapeutic INR range for warfarin
    - Bottom line: DOAC's safety profile ~ warfarin…if monitored appropriately
  - Specific risk for DOAC ADR's
    - Rivaroxaban: increased risk of GI/intracranial bleed
    - Apixaban: lowest risk of bleeding for DOAC's
- Rivaroxaban vs. Rivaroxaban + Aspirin
  - COMPASS Trial in NEJM 2017:377(14):1319-1330.
  - Margin of benefit is small
  - For combined tx: Need to treat 71 pt x 2 years to prevent 1 CVA, MI, or CV death

New(ish) Info from Clinical Trials

- DOACs used for VTE prevention in cancer patients
  - Edoxaban and Rivaroxaban have head to head studies showing lower rate of VTE vs LMWH
    - HOKUSAI-VTE Cancer study
    - Select-D trial
  - Meta-analysis published in 2018 concluded overall DOACs were more effective in reducing VTEs however DOACs were associated with significantly increased risk of major bleeds (Li A., Thrombosis Research (2018), https://doi.org/10.1016/j.thromres.2018.02.144)
  - NCCN has moved Rivaroxaban higher on recommendation list

New(ish) Info from Clinical Trials

- Apixaban
  - Considered to be DOAC of choice overall due to superiority and less bleed risk (Article, Lean Toward Eliquis for the Best Balance of Effiacy and Safety in Atrial Fib. Pharmacists Letter, June 2018).
  - Recently suggested as oral anticoagulation of choice in ESRD on hemodialysis (June 28:[Epub ahead of print]
    - 5mg BID dose significantly less CVE/SE vs low dose and warfarin
    - Significantly lower risk of death
    - Significantly lower risk of major bleeding

Barriers to Practice

- Attempting to keep up with literature that contradicts guidelines
- Drug pricing continues to rise
- Third party payors may dictate which DOAC they prefer but may not be optimal choice for patient
- No routine office visit or lab to assess nonadherence with DOACs
- Afib with Mitral valve stenosis or cardiomyopathy requires warfarin
- Warfarin issues:
  - Requires bridge therapy
  - Food interactions
  - Slow onset of action
  - Titration can tricky especially with CYP 2C9

Best Practice Recommendations

- Review literature routinely, ever changing!!
- More information than ever on evolution of where DOACs fit vs traditional therapy
  - DOAC now class of choice?
  - Some DOACs show superiority and better safety
  - Some DOACs have increased bleeding risk especially GI bleeds
- Expansion of indications to optimize use by patients
  - Cancer patients using oral therapy vs LMWH
- Use warfarin
  - Nonadherent due to longer half life and INR checks
  - Prosthetic heart valve
  - ESRD/Hemodialysis?
  - Cost is an issue

1. C
2. B
3. C

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