No INRs! RNs Role Caring for Patients on Oral Anticoagulant Therapy

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Conflict of Interest

- No real or potential conflict to disclose

Objectives

- Oral Anticoagulation History
- Dabigatran
- Rivaroxaban
- Apixaban
- Selection of Anticoagulant
- How to Switch Between Anticoagulants
- Interruptions in Therapy (pre & post procedure)
- Nurses Role

Oral Anticoagulation History

- **Warfarin (Coumadin)**
  - *Warf* (Wisconsin Alumni Research Foundation) + *arin* (derived from coumarin)
  - Introduced in 1948 as pesticide for rats and mice
  - First Anticoagulant approved by FDA in 1954
  - Gold Standard for:
    - AF Stroke Prevention
    - Primary Treatment and Secondary Prevention of DVT and PE
  - Most widely used 'blood thinner' in the world

British Journal of Haematology 2008, 141, 757–763.

Warfarin Benefits

- ✓ Studied extensively
- ✓ Efficacy well established
- ✓ Much clinical experience
- ✓ Used in many indications
- ✓ Effects reversed by antidote
- ✓ Clearance not affected by renal function
- ✓ Low daily drug cost
- ✓ Pharmacodynamic profile is forgiving of missed dose or poor adherence

Warfarin Challenges

- Unpredictable anticoagulant effects
  - Variable dose response
  - Wide inter patient variation
  - Genetic variability
- Slow onset/offset of action
- Frequent lab monitoring
- Frequent dose adjustment
- Narrow therapeutic window (INR 2-3)
- Difficult to maintain therapeutic INR
  - TTR = Time in Therapeutic Range
- Many interactions
  - Drug-drug
  - Drug-food
  - Drug-disease
- ++ care coordination
  - Pt education
  - Pt provider communication
  - Burden on pt / health care team

Oral Anticoagulation History

- Novel Oral Anticoagulants (NOACs)

2010 **Dabigatran (Pradaxa ®)**
- Direct thrombin Inhibitor

2011 **Rivaroxaban (Xarelto ®)**
- Factor Xa Inhibitor

2012 **Apixaban (Eliquis ®)**
- Factor Xa Inhibitor

→ Target Specific Oral Anticoagulants (TSOAs) or Direct Oral Anticoagulants (DOACs)

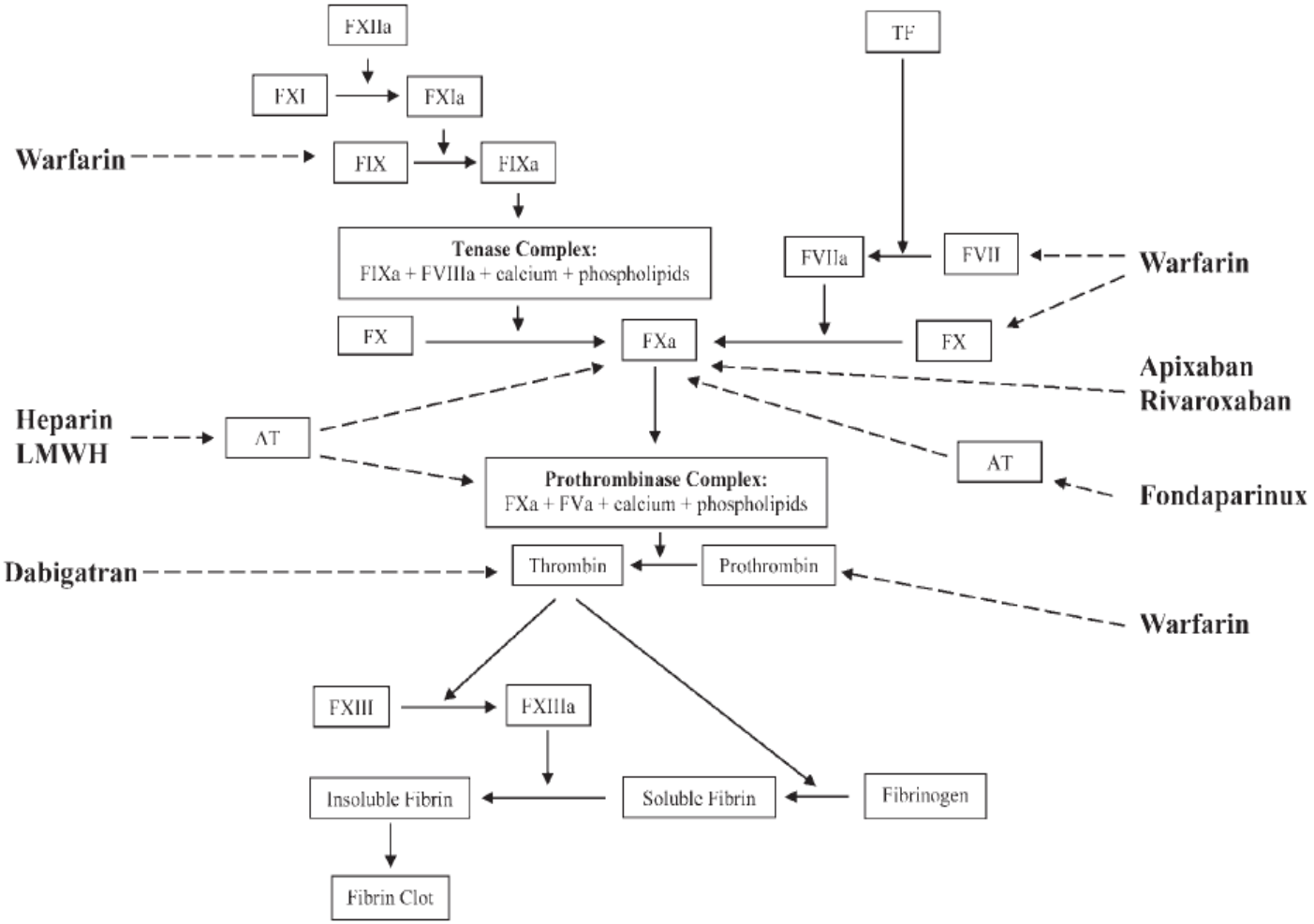
NOAC Advantages

- ✓ Quick onset / offset of action
  - ✓ Bridging with injectable anticoagulant not required
  - ✓ Easy peri-operative management
- ✓ Predictable kinetics and small inter-individual variation → fixed dosing regimens
- ✓ No routine lab monitoring
- ✓ Efficacious
- ✓ Relatively safe – less incidence of ICH

NOAC Disadvantages

- Increased cost
- Lack of antidote for reversibility and management of bleeds / urgent surgery
- Current lack of accurate monitoring in suspected toxicity cases
- Inability to use in patients with moderate-severe renal impairment or prosthetic heart valves
- Adherence concerns
  - Missed doses → ↑ risk for adverse event
  - NOACs with BID dosing may affect compliance
- Awaiting long term efficacy / safety data

Pharmacology



Ann Pharmacother 2011;45 epub ahead of print

Comparison Pharmacokinetic Properties

Property	Dabigatran	Rivaroxaban	Apixaban
Prodrug	Yes	No	No
Bioavailability	7%	>80%	50-66%
Cmax (hrs)	2-3	3	3
Half life (hrs)	11-17	5-13	8-15
Metabolism	Hepatic	Hepatic, mainly CYP 3A4	Hepatic, mainly CYP 3A4
Clearance	80% renal	66% renal	27% renal
Reversal: HD Antidote	 Yes No	 No No	 No No

Massicotte A. CPJ 2014; 147(1): 25-32
Popara TS, Lip GY. Best Practice & Research Clinical Haematology 2013; 26: 115-129
Gonsalves WI. Mayo Clin Proc May 2013:88(5):495-511

Dabigatran

Indication	Dose	Dose Adjustment
Prevention of stroke and systemic embolism in non-valvular AF	150mg PO BID	110mg PO BID if: • > 80 yrs old • > 75 yrs old + 1 bleeding risk factor • CrCl 30 – 49mL/min
Prevention of VTE in THR or TKR surgery	110mg initial dose then 220mg PO daily x 10 days (TKR) or x 28-35 days (THR)	75mg initial dose then 150mg PO daily (CrCl 30-49 mL/min)
Treatment / Prevention of DVT and PE	150mg PO BID following treatment with parenteral anticoagulant x 5-10 days	110mg PO BID if: • > 80 yrs old • > 75 yrs old + 1 bleeding risk factor •CrCl 30-49mL/min

Do not use if CrCl < 30mL/min

Available as 75mg, 110mg and 150mg capsule

Dabigatran

- **Side effects**
  - Bruising or bleeding
  - N/V/D, acid reflux, upset stomach, difficulty swallowing
  - Rash / itching, hives

- **Monitors**
  - Renal function: Scr, CrCl baseline and annually
  - Signs and symptoms of bleeding (CBC)
  - Weight
  - Interacting medications
  - Upcoming procedures
  - Compliance, affordability

Dabigatran

- **Special Information**
  - **Must take as ordered.**
  - If miss a dose – take as soon as remember. If < 6 h before next dose, skip missed dose then wait and take next dose at regularly scheduled time. Never double dose.
  - **Swallow whole** – do not crush, chew or open capsule; do not sprinkle pellets in food or mix in liquids
  - **Storage**:
    - **Stock bottles** – dispense original bottle to patient and must be used within 4 months following opening. Do not place capsules in dosettes.
    - **Blisters** – Keep capsule in foil blister until just prior to taking and peel back foil. Need to cut foil around each capsule and place capsule into dosette in its original blister foil.

Rivaroxaban

Indication	Dose
Prevention of stroke and systemic embolism in non-valvular AF	20mg PO daily **Dose Adjustment**: 15mg PO daily (CrCl 30-49mL/min)
Prevention of VTE in THR or TKR surgery	10mg PO daily x 14 (TKR); x 35 days (THR)
Treatment of VTE and prevention of recurrent DVT and PE	15 mg PO BID x 3 weeks then 20mg PO daily (up to 6 months)

Do not use if CrCl < 30mL/min

Available as 10mg, 15mg and 20mg tablets

Rivaroxaban

- **Side effects**
  - Bruising or bleeding
  - N/V/D, indigestion, upset stomach, constipation
  - ↓ general strength & energy

- **Monitors**
  - Renal function: Scr, CrCl baseline and annually
  - Liver function
  - Signs and symptoms of bleeding (CBC)
  - Weight
  - Interacting medications
  - Upcoming procedures
  - Compliance, affordability

Rivaroxaban

- **Special Information**
  - **Must take as ordered.**
  - **Take with food.**
  - May crush / mix with applesauce
  - If miss a dose – take as soon as remember:
    - **AF** – then take next tablet the following day. Never double dose.
    - **VTE**:
      - 15mg PO BID: do not take more than 2 x 15mg tablets on one day. May take 2 x 15mg tablets at same time to get a total of 2 tablets (30mg) on one day. Following day carry on as normal.
      - 20mg PO daily: then take next tablet the following day. Never double dose.

Apixaban

Indication	Dose	Dose Adjustment
Prevention of stroke and systemic embolism in non-valvular AF	5mg PO BID	2.5mg PO BID if any 2 of: • > 80 yrs old • < 60kg body weight • Scr > 133 umol/L
Prevention of VTE in THR or TKR surgery	2.5mg PO BID x 10 – 14 days (TKR) or x 32-38 days (THR)	

No dosing recommendation if CrCl < 25mL/min

Available as 2.5mg and 5mg tablet

Apixaban

- **Side effects**
  - Bruising or bleeding
  - Nausea
  - Anemia

- **Monitors**
  - Renal function: Scr, CrCl baseline and annually
  - Liver function
  - Signs and symptoms of bleeding (CBC)
  - Weight
  - Interacting medications
  - Upcoming procedures
  - Compliance, affordability

Apixaban

- **Special Information**
  - **Must take as ordered.**
  - If miss a dose – take as soon as remember then follow with second daily dose at regularly scheduled time. Never double dose.
  - Do not chew tablet
  - Take with food if have upset stomach

Interaction Type	Outcome	Dabigatran	Rivaroxaban	Apixaban
Pharmaco kinetic	**Increase** of at least 50% in anticoagulant plasma concentration	Amiodarone Dronedarone Ketoconazole Quinidine Verapamil	Clarithromycin Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole	Itraconazole Ketoconazole Posaconazole Ritonavir Voriconazole
Pharmaco kinetic	**Decrease** of at least 50% in anticoagulant plasma concentration	Carbamazepine Rifampin St. Johns Wort	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's Wort	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's wort
Pharmaco dynamic	Increased risk of bleeding	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics	ASA NSAIDs Platelet aggregation inhibitors Anticoagulants Thrombolytics

Massicotte A, CPJ. Jan/Feb 2014, 147(1): 32

Cost and Coverage

	Dabigatran	Rivaroxaban	Apixaban
Cost / tablet or capsule	~$1.80	~$3.15	~$1.80
Cost for 1 month supply (AF stroke prevention)	~$117 150mg PO BID	~$105 20mg PO daily	~$117 5mg PO BID
Alberta Blue Cross Coverage?	Yes Step Therapy Special Authorization	Yes Step Therapy Special Authorization	Yes Step Therapy Special Authorization

Costs include drug price + dispensing fee

July 2014

ALBERTA BLUE CROSS®

Please complete all required sections to allow your request to be processed.

APIXABAN/DABIGATRAN/RIVAROXABAN
SPECIAL AUTHORIZATION REQUEST FORM

Patients may or may not meet eligibility requirements as established by Alberta Government sponsored drug programs.

PATIENT INFORMATION				COVERAGE TYPE:
PATIENT LAST NAME	FIRST NAME		INITIAL	☐ Alberta Blue Cross ☐ Alberta Human Services ☐ Other
DATE OF BIRTH: Year / Month / Day	ALBERTA PERSONAL HEALTH NUMBER			
STREET ADDRESS	CITY	PROV	POSTAL CODE	IDENTIFICATION/CLIENT/COVERAGE No:

PRESCRIBER INFORMATION			
PRESCRIBER LAST NAME	FIRST NAME	INITIAL	PRESCRIBER PROFESSIONAL ASSOCIATION REGISTRATION
			☐ CPSA ☐ ACO REGISTRATION NO. ☐ CARNA ☐ ADA+C ☐ ACP ☐ Other
STREET ADDRESS			PHONE: / FAX:
CITY , PROVINCE			
POSTAL CODE			FAX NUMBER MUST BE PROVIDED WITH EACH REQUEST SUBMITTED

***Note:** Rivaroxaban 10 mg is a benefit for the prophylaxis of venous thromboembolic events in patients who have undergone elective total knee replacement surgery. Coverage is restricted to two 14-day courses of therapy per patient per year. Rivaroxaban 10 mg is also a benefit for the prophylaxis of venous thromboembolic events in patients who have undergone elective total hip replacement surgery. Coverage is restricted to two 35-day courses of therapy per patient per year. Rivaroxaban 10 mg is not eligible for special authorization for coverage beyond these restrictions.

Section I Prevention of stroke and systemic embolism in Atrial Fibrillation (AF) patients

a) Indicate which drug is requested (check one box):

☐ Apixaban 2.5mg/ 5mg (e.g. Eliquis) ☐ Dabigatran 110mg /150mg (e.g. Pradaxa) ☐ Rivaroxaban 15mg /20mg (e.g. Xarelto)

b) Does the patient have non-valvular atrial fibrillation (AF)?

☐ Yes ☐ No

c) Please indicate if **warfarin** was used:

☐ Yes → If yes, please indicate if a **2 month trial of warfarin** was used:

☐ Yes

☐ No, please specify reason:_____

☐ No → If no, please elaborate:

a) If the patient has a contraindication to warfarin, provide information regarding the nature of the contraindication:

_____

b) If this patient is unable to monitor via INR testing services, please specify the reason:

Section II RIVAROXABAN 15mg/20mg (e.g. Xarelto) for treatment of deep vein thrombosis (DVT) without pulmonary embolism (PE)

Has the patient had a deep vein thrombosis (DVT)?

☐ Yes

→ If yes, please indicate if the patient has also had a pulmonary embolism (PE)? ☐ Yes ☐ No

☐ No

Section III APIXABAN 2.5mg (e.g. Eliquis) for prophylaxis of venous thromboembolism (VTE) following elective total hip or total knee replacement surgery

Has the patient had elective total **hip** replacement surgery?

☐ Yes ☐ No

Has the patient had elective total **knee** replacement surgery?

☐ Yes ☐ No

☐ **RENEWAL:** This product is eligible for step-therapy for the prevention of stroke and systemic embolism in AF patients only. A Special Authorization renewal request for this indication is required only if the patient has not made a claim for the drug product during the preceding 12 months.

PRESCRIBER 'S SIGNATURE	DATE	Please forward this request to:
		Alberta Blue Cross, Clinical Drug Services **10009-108 Street NW, Edmonton, Alberta T5J 3C5** FAX: **780-498-8384** in Edmonton • **1-877-828-4106** toll free all other areas

ONCE YOUR REQUEST HAS SUCCESSFULLY TRANSMITTED, PLEASE DO NOT MAIL OR RE-FAX YOUR REQUEST.

Selection of Anticoagulant

Patient Characteristic	NOAC or Warfarin Preferred?	Comment
Age < 80	NOAC	Lower dosage if CrCl < 50 mL/min
Age > or = 80	NOAC (if CrCl > 50mL/min)	Lower dosage or Apixaban
CrCl > 50 mL/min	NOAC	
CrCl 30-50 mL/min	NOAC	Lower dosage or Apixaban
CrCl < 30 mL/min	Warfarin	
TTR > 65%	Warfarin	
TTR < 65%	NOAC	
Compliance issue	Warfarin?	
Cost / drug insurance issues	Warfarin	

Patient Characteristic	NOAC or Warfarin Preferred?	Comment
Severe liver disease	Warfarin?	*NOAC Contraindication
Severe renal disease	Warfarin	*NOAC Contraindication
Mechanical heart valves Rheumatic heart disease	Warfarin	*NOAC Contraindication
Valvular atrial fibrillation (AF)	Warfarin	*NOAC Contraindication
New non-valvular AF	NOAC	
- Active / recent major bleeding - Recent acute stroke / systemic embolism	Warfarin	*NOAC Contraindication
Pregnancy / Breastfeeding	Warfarin	*NOAC Contraindication
P-glycoprot or CYP 3A4 drugs	Warfarin	*NOAC Contraindication

Patient Characteristic	NOAC or Warfarin Preferred?	Comment
Recent CAD with PCI and/or dual antiplatelets	Warfarin	Temporary situation?
Recent GI bleed	Warfarin	Apixaban
Risk of GI bleed Risk of dyspepsia	Warfarin NOAC	Apixaban Apixaban or Rivaroxaban
Documented warfarin failure (stroke on warfarin)	NOAC	Dabigatran 150mg PO BID or Apixaban
Documented non-hemorrhagic warfarin ADR	NOAC	
Documented warfarin allergy	NOAC	
Barriers to lab monitoring	NOAC	
HAS BLED 0-4	NOAC	No active GI bleeding
HAS BLED > 4	Warfarin	Consider apixaban

How to Switch Between Anticoagulants

From	To	How to switch
Heparin	NOAC	Start NOAC at the time of heparin discontinuation
LMWH / fondaparinux	NOAC	Stop LMWH / fondaparinux and start NOAC ≤ 2 hr before next scheduled LMWH/fondaparinux dose
Warfarin	NOAC	Stop warfarin and start dabigatran/apixiban when INR < 2.0 Stop warfarin and start rivaroxaban when INR < 2.5
Dabigatran	Warfarin	CrCl > 50ml/min: start warfarin 3 days before stopping dabigatran CrCl 31-50ml/min: start warfarin 2 days before stopping dabigatran CrCl 15-30ml/min: start warfarin 1 day before stopping dabigatran CrCl <15ml/min: no recommendations provided
Rivaroxaban Apixaban	Warfarin	Start warfarin with rivaroxaban/apixaban until INR ≥ 2.0 and then stop rivaroxaban/apixaban (INR testing should be done just before rivaroxaban/apixaban dose)
NOAC	Parenteral anticoagulants	Stop NOAC and start parenteral anticoagulant 12 hours after last apixaban/dabigatran dose and 24 hours after last rivaroxaban dose
NOAC	Different NOAC	Administer new agent when next dose is due

Interruptions in Therapy – Preop

Drug (Half Life)	Renal Function	Low Bleeding Risk Surgery (2–3 drug half lives between last dose and surgery)	High Bleeding Risk Surgery (4–5 drug half lives between last dose and surgery)
Dabigatran T ½ = 14h	Normal / mild impairment (CrCl > 50mL/min)	Last dose 2d before sx (skip 2 doses)	Last dose 3d before sx (skip 4 doses)
T ½ = 15–18 h	Mod impairment (CrCl 30–50mL/min)	Last dose 3d before sx (skip 4 doses)	Last dose 4–5d before sx (skip 6–8 doses)
Rivaroxaban T ½ = 9 h	Normal / mild impairment (CrCl > 50mL/min)	Last dose 2d before sx (skip 1 dose)	Last dose 3d before sx (skip 2 doses)
	Mod impairment (CrCl 30–50mL/min)	Last dose 2d before sx (skip 1 dose)	Last dose 3d before sx (skip 2 doses)
Apixaban T ½ = 9h	Normal / mild impairment (CrCl > 50mL/min)	Last dose 2d before sx (skip 2 doses)	Last dose 3d before sx (skip 4 doses)
T ½ = 17–18h	Mod impairment (CrCl 30–50mL/min)	Last dose 3d before sx (skip 4 doses)	Last dose 4d before sx (skip 6 doses)

Adapted from Douketis JD. Current Pharm Design 2010;16(31) & Blood 2012;120(15)

Resumption of Therapy – Post

Drug	Low Bleeding Risk Surgery	High Bleeding Risk Surgery
Dabigatran	Resume day after sx (24h postop) 150mg PO BID	Resume 2-3 days after sx (48-72h postop) 150mg PO BID*
Rivaroxaban	Resume day after sx (24h postop) 20mg PO daily	Resume 2-3 days after sx (48-72h postop) 20mg PO daily**
Apixaban	Rseume day after sx (24h postop) 5 mg PO BID	Resume 2-3 days after sx (48-72h postop) 5mg PO BID**
*For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran 110-150mg PO daily on the evening after surgery and on the following day (first postop day) after surgery		
**Consider a reduced dose (Rivaroxaban 10mg PO daily or Apixaban 2.5mg BID) in patients at high risk for thromboembolism		

Spyropoulos AC et al Blood 2012;120(15)

RN Role

1. **Selection of Oral Anticoagulant**

- NOAC Patient Evaluation
  - Appropriate approved indication for use?
  - Lack of clinical conditions / drug interactions that preclude use?
  - Adequate resources / insurance coverage?
    - Has patient been on warfarin prior?
  - Adequate renal function?
    - Appropriate dose selection
  - Adequate liver function?
  - Compliance history?

RN Role

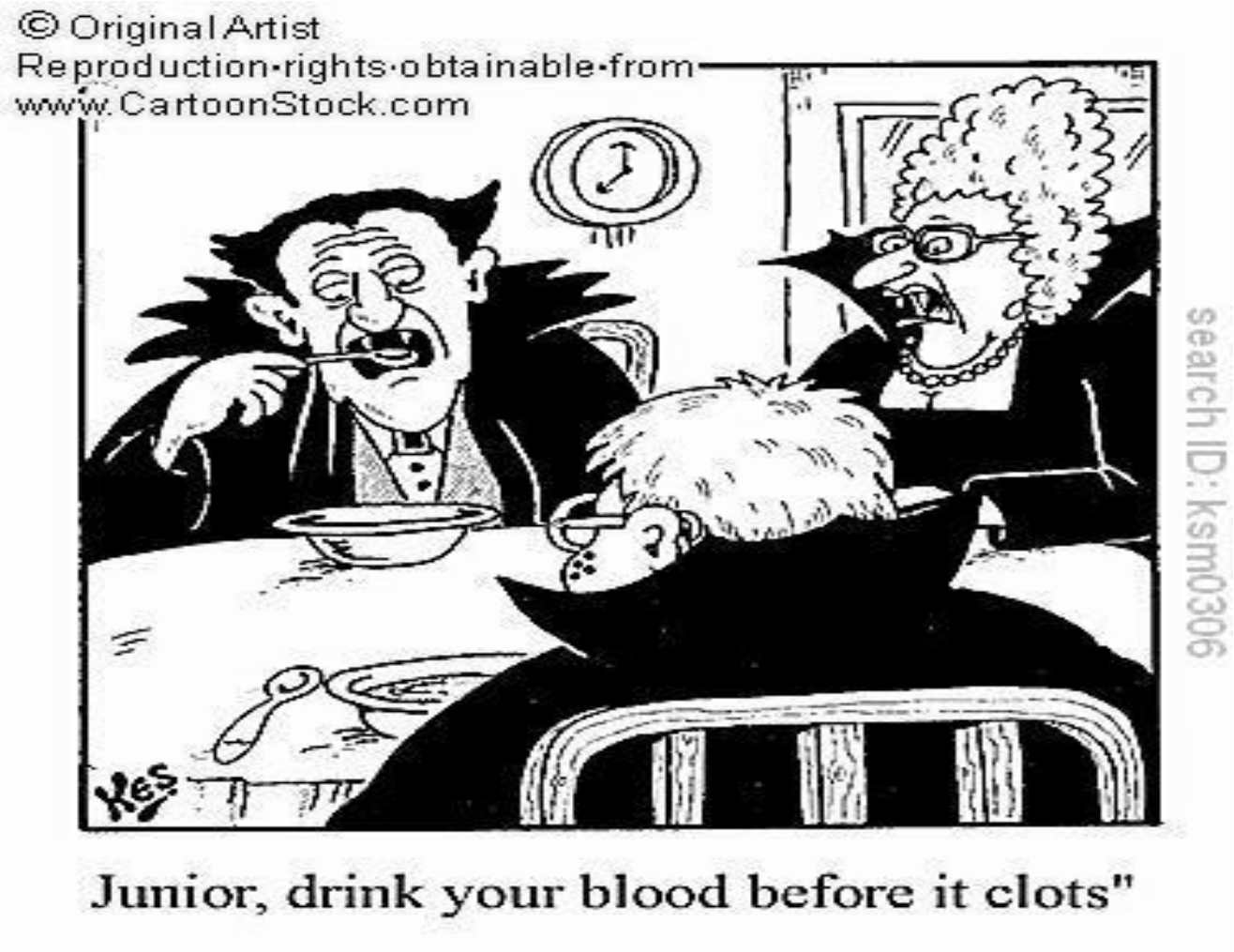
- Switching Between Agents
- ABC Special Authorization form

2. **Education**
   - Drug information
   - Cost / drug insurance coverage
   - Importance of drug adherence
   - Situations which may need interruption in therapy

RN Role

3. **Monitoring NOAC**
   - Renal / Liver function
   - Labs: Scr/CrCl, LFTs, CBC
   - Existence of drug interactions
     - Did patient start any new meds?
   - Occurrence of adverse drug reactions?
   - Development of contraindications?
   - Question about upcoming procedures / surgery / dental work?
   - Ability to maintain medication therapy (cost?)
   - Barriers to adherence
   - Patient satisfaction with therapy
4. **Guidance for Interruption in Therapy**

Questions?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www.CartoonStock.com
search ID: ksm0306
Junior, drink your blood before it clots"

NOACs Phase III Clinical Trials

Population Studied	Dabigatran Trials	Rivaroxaban Trials	Apixaban Trials
VTE Prevention, Orthopedic Surgery	RE-NOVATE RE-NOVATE II RE-MODEL RE-MOBILZE	RECORD 1 RECORD 2 RECORD 3 RECORD 4	ADVANCE I ADVANCE II ADVANCE III
VTE Prevention, Medically Ill	Not studied	MAGELLAN	ADOPT
Stroke Prevention, Atrial Fibrillation	RELY RELY-ABLE (RE-ALIGN)	ROCKET AF	ARISTOTLE AVERROES
Secondary Prevention, ACS	Not studied	ATLAS II	APPRAISE II
VTE Treatment	RE-COVER RE-COVER II RE-MEDY RE-SONATE	EINSTEIN DVT EINSTEIN PE EINSTEIN EXT	AMPLIFY AMPLIFY-EXT

Management of Patient Bleeds on Dabigatran

	Minor Bleeding	Moderate Bleeding	Major Bleeding
Testing	• CBC, INR/PTT • Creatinine	• CBC, INR/PTT • Creatinine • Fibrinogen • Type and Screen • Thrombin Time	• CBC, INR/PTT • Creatinine • Fibrinogen • Crossmatch • Thrombin Time
Supportive Therapy	• Local therapy	• Local therapy / site control • Transfusion • Surgery / Intervention	• Local therapy • Transfusion • Surgery / Intervention • Consider plt transfusion if antiplatelets agents in use
Drug Dosing	• Hold Dabigatran	• Hold Dabigatran • Hold antiplatelet agents	
Reversal / Removal	None	• Consider charcoal** < 2-4 hrs post dose • Consider dialysis	
Procoagulant Agents	None	• Tranexamic acid (10mg/kg IV or 25mg/kg PO)*	• Consider PCC 25-50u/kg or FIEBA 50 IU/kg •If no PCC/FIEBA → tranexamic acid (10mg/kg IV)*

Management of Patient Bleeds on Rivaroxaban / Apixaban

	Minor Bleeding	Moderate Bleeding	Major Bleeding
Testing	• CBC, INR/PTT	• CBC, INR/PTT • Fibrinogen • Type and Screen • Anti Xa level	
Supportive Therapy	• Local therapy	• Local therapy • Transfusion • Surgery / Intervention	• Local therapy • Transfusion • Surgery / Intervention • Consider plt transfusion if antiplatelets agents in use
Drug Dosing	• Hold Rivaroxaban / Apixaban • Hold antiplatelet agents	• Hold Rivaroxaban / Apixaban • Hold antiplatelet agents	
Reversal / Removal	None	• Consider charcoal** (no evidence for effectiveness) • Not dialyzabe	
Procoagulant Agents	None	• Tranexamic acid (10mg/kg IV or 25mg/kg PO)*	• Consider PCC 25-50u/kg or rFVIIa 90 mg/kg •If no PCC/rFVIIa → tranexamic acid (10mg/kg IV)*

Measurement of anticoagulant Effect

	PT (INR)	aPTT	Fibrinogen	Thrombin Time	Ecarin Clotting Time
Dabigatran	↑	↑ ↑	↔ thrombin based test fibrinogen may be falsely low	↑ ↑ ↑	↑ ↑ ↑
Rivaroxaban Apixaban	↑ ↑	↑	↔	↔	↔

- Dose, time since dosing, laboratory parameters will affect test result

Why Decreased Intracranial Bleeding with Newer Agents?

- Tissue factor (TF) transmembrane receptor for factor VIIa in the brain → hemostatic protection
- TF-VIIa complexes primary cellular initiators of coagulation
- Warfarin blocks vitamin K dependent factors II, VII, IX, X → suppress TF-VIIa complexes
- Newer agents preserve hemostasis in the brain

Circulation 2011;123(21):2363-2372.

Why Potential Increased Risk MI Dabigatran?

- RE-LY, REMEDY and meta analysis showed dabigatran to be associated with an increased risk of myocardial infarction or ACS
- Due to better risk reduction with warfarin compared to dabigatran rather than true increased risk with dabigatran
- Mechanism unknown
  - Related to increase in inflammation with direct thrombin exposure
- No reports with Direct Xa inhibitors
- Select warfarin or another NOAC for high risk or past history of CAD

G Connolly Practical issues, limitations and periprocedural mgt of the NOACs J Thromb Thrombolysis
C Ricchetti and L Shea Target Specific Oral Anticoagulants US Pharmacist

Why Potential Increased Risk MI Dabigatran?

- PETRO study (N=502) duration 12 weeks
  - dabigatran 50 mg, 150 mg or 300 mg bid, ASA 81 mg or 325 mg or no ASA vs warfarin
    - nonvalvular atrial fibrillation
  - randomized trial with blinded outcome adjudication
  - after 12 weeks
    - Increased excretion of thromboxane

warfarin	dabigatran 100 mg/d	dabigatran 300 mg/d	dabigatran 600 mg/d
+ 4%	+ 31%	+ 17%	+ 23%
p=0.32	p=0.019	p=0.028	p=0.0004

    - suggest possible platelet activating effect?
      - potential for paradoxic increase in thrombotic risk

Am J Cardiol 2007;100(9):1419-1426.

Dabigatran Genetic Polymorphism

- CES1 gene single-nucleotide polymorphism rs2244613
  - blunts biotransformation of dabigatran etexilate to dabigatran
  - associated with 15% drop in dabigatran trough levels
- Clinical Outcomes associated with rs2244613 in Re-LY

End point	OR (95% CI)	p
Ischemic stroke or systemic embolism	0.70 (0.33-1.47)	0.34
Any bleeding	0.67 (0.55-0.82)	0.00007
Major bleeding	0.66 (0.43-1.01)	0.06
Minor bleeding	0.70 (0.57-0.85)	0.0004

European Society of Cardiology 2012 Congress; August 29, 2012, Munich, Germany.