Out With the Old & In With the New?

A Review of Direct Oral Anticoagulants

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Disclosure

- I have no conflicts of interest to disclose
- I will not be discussing off-label use of medications

Objectives

- Chose an oral anticoagulant to initiate in a patient with non-valvular atrial fibrillation based on patient-specific characteristics
- Transition a patient from warfarin to a DOAC
- Assess the appropriateness of reversal strategies related to DOACs in patients with acute bleed

Nomenclature

NOACs: Novel Oral Anticoagulants

TSOACs: Target Specific Oral Anticoagulants

DOACs: Direct acting Oral Anticoagulants

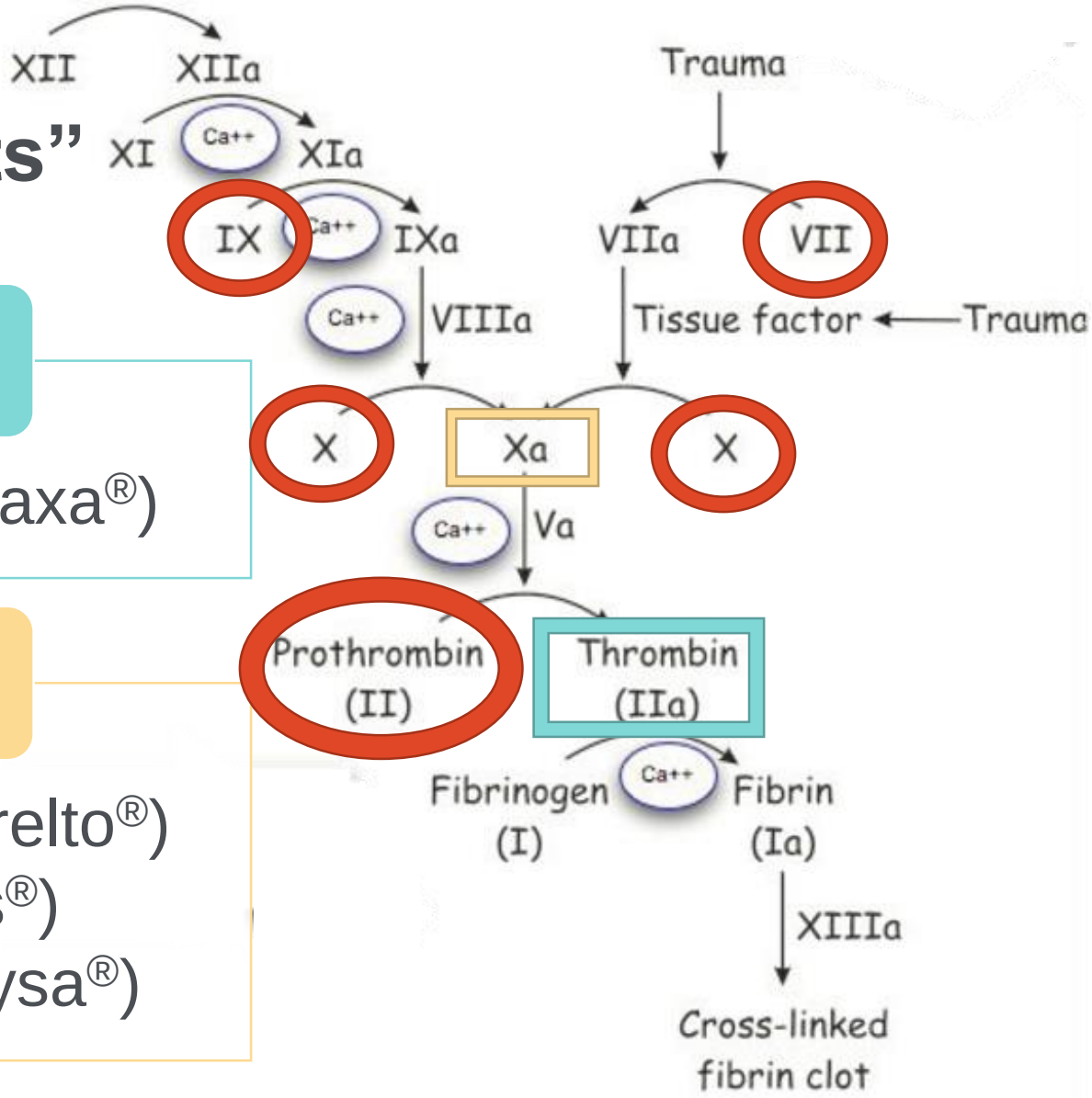
"New Anticoagulants"

Direct Thrombin Inhibitor

- Dabigatran (Pradaxa®)

Xa Inhibitors

- Rivaroxaban (Xarelto®)
- Apixaban (Eliquis®)
- Edoxaban (Savaysa®)



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Initial Selection of Agent

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Patient Case

- HPI: DW, a 77-year-old male, presents with fatigue, dizziness, and mild chest fluttering.
  - His 12-lead ECG reveals a narrow complex tachycardia with an irregularly irregular rhythm, with no discernible P waves consistent with new onset atrial fibrillation
- PMH: Well-controlled hypertension and diabetes (A1c = 7.0), GERD

Vitals:
BP: 150/82 mm Hg
HR: 130 (irregular)
Respiration rate: 17 bpm
Body temperature: 98.8º F
Room air oxygen saturation: 95%
Weight: 59 kg
BMI: 21 kg/m^2

Labs:
SCr: 2 mg/dL
CrCl: 27 mL/min
LFTs: WNL

Patient Case

- After treating DW with an appropriate rate control agent the decision is made to initiate long-term anticoagulation for stroke prevention.
- Which agent would you recommend?
  A. Warfarin
  B. Rivaroxaban
  C. Apixaban
  D. Edoxaban
  E. Dabigatran

J Am Coll Cardiol 2014;64:e1-76.
Chest 2012;141(Suppl 2):e44S-e88S.
Chest 2016;149:315-52.

Indications

DABIGATRAN (PRADAXA®)	RIVAROXABAN (XARELTO®)	APIXABAN (ELIQUIS®)	EDOXABAN (SAVAYSA®)	WARFARIN (COUMADIN®)
• non-valvular afib • VTE treatment* • VTE prevention post THR	• non-valvular afib • VTE treatment • VTE extended treatment • VTE prevention post TKR/THR	• non-valvular afib • VTE treatment • VTE extended treatment • VTE prevention post TKR/THR	• non-valvular afib • VTE treatment*	• non-valvular afib • VTE treatment • VTE extended treatment • VTE prevention post TKR/THR • Prosthetic heart valve

* After 5-10 days of parental anticoagulation

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Product information for Pradaxa. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. November 2015
Product information for Eliquis. Bristol-Myers Squibb Company. Princeton, NJ 08543. July 2016.
Product information for Xarelto. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560. March 2017.
Product information for Savaysa. Daiichi Sankyo, Inc. Parsippany, NJ 07054. September 2016

Efficacy: Trial Summary

- All DOACs have equal or better efficacy compared to warfarin
  - Dabigatran and apixaban = superior to warfarin in afib patients
  - Rivaroxaban and edoxaban = non-inferior vs. warfarin

	DABIGATRAN (PRADAXA®)	RIVAROXABAN (XARELTO®)	APIXABAN (ELIQUIS®)	EDOXABAN (SAVAYSA®)
Atrial Fibrillation	RE-LY	ROCKET-AF	AVERROES ARISTOTLE	ENGAGE-AF
VTE Treatment	RE-COVER I RE-COVER II	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	HOKUSAI-VTE
VTE Treatment (extended)	RE-SONATE RE-MEDY	EINSTEIN-DVT EINSTEIN-PE (Extension)	AMPLIFY-Extension	
Mechanical Valves	RE-ALIGN			

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N Engl J Med 2009;361:1139-51.
N Engl J Med 2011;365:883-91.

Safety: Comorbidity Considerations

Patient Characteristic		Agent to Consider First
Renal Impairment	CrCl 30-15 mL/min	Warfarin, apixaban, or rivaroxaban
	CrCl <15 mL/min	Warfarin
Liver Impairment	Severe	Warfarin or LMWH
	Moderate	Warfarin, apixaban, or dabigatran
High Cardiovascular risk		Warfarin
Mechanical heart valves		Warfarin
High Stroke risk		Apixaban
High Bleed Risk/GI disease		Apixaban
Elderly		Apixaban
Obesity/History of Bariatric Surgery		Warfarin
Underweight		Warfarin, apixaban, edoxaban

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Clinical Resource, Comparison of Oral Anticoagulants. Pharmacist's Letter/Prescriber's Letter. May 2016
Am J Cardiovasc Drugs 2014;14:175-89
Thrombosis 2013;2013:640-723. Epub 2013 Dec 22.
Gastrointest Endosc 2013;78:227-39

Pharmacokinetics/Pharmacology

Characteristic	Warfarin	New agents
Bioavailability	99%	6-80% (some active drug in large bowel)
T-max	72-96 hours	2-4 hours
Half-life	40 hours	5-17 hours
Metabolism	Cytochrome P450	Biliary/Renal
Drug Interactions	Many	Not so many
Food Interactions	Yes	No
Genetic Variation	Major effects	Minor effects (?)
Monitoring	PT/INR	None
Reversal	Vit K/PCC/FFP	Idarucizumab, andexanet, PCC?

Am J Cardiovasc Drugs 2014;14:175-89
Chest 2008;133(Suppl 6):160S-98S
Circ J 2015;79:914-23.

Safety: DOAC Atrial Fibrillation Dosing

	DABIGATRAN (PRADAXA®)	RIVAROXABAN (XARELTO®)	APIXABAN (ELIQUIS®)	EDOXABAN (SAVAYSA®)
Dose	150mg BID	20mg daily with evening meal	5mg BID	60mg daily
Renal dose	CrCl 15-30 mL/min: 75mg BID. CrCl <15 mL/min: AVOID USE.	CrCl 15-50 mL/min: 15mg daily with evening meal CrCl <15 mL/min: AVOID USE.	2.5mg BID if at least 2 of the following: • age ≥ 80 • weight ≤ 60kg • SCr ≥ 1.5	CrCl > 95 mL/min: should NOT be used CrCl 15-50 mL/min: 30mg daily CrCl <15 mL/min: AVOID USE.
Comments	• CrCl < 30 excluded from RE-LY trial. • Use actual weight to calculate CrCl • Do NOT break, chew or opening capsule = 75% ↑ in absorption	• CrCl < 30 excluded from ROCKET-AF trial. • Use actual weight to calculate CrCl • MUST give w/ substantial meal	CrCl < 25 excluded from Aristotle trial	CrCl< 30 excluded from Engage-AF trial

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Compliance

- Consider warfarin
  - For patients who tend to miss doses
  - When cost is a potential adherence barrier
- Prescription Coverage of DOACs
  - Free trial and co-pay cards available for all of the DOACs
    - Co-pay cards
      - Only apply to commercially insured patients
      - NOT TO BE USED in Medicare/Medicaid/VA patients
  - Prior authorization is required on some and the co-pay can vary considerably

Am J Cardiovasc Drugs 2014;14:175-89

So should everybody get a DOAC?

Pros

- All of the NOACs were as good or better than warfarin from an efficacy and safety standpoint
- Monitoring is not required
- Potential for a decreased hospital stay for patients that would have required a bridge (rapid onset)
- No vitamin K related diet concerns

Cons

- Expensive
- Limited reversal options
  - Except dabigatran
- Compliance concerns about
  - Shorter $t_{1/2}$, missed dose = increase risk
- No coagulation test easily available to measure effect

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Int J Cardiol 2014;174:471-83.
Am J Cardiovasc Drugs 2014;14:175-89
Arch Intern Med 1998;158:1641-7

Patient Case

- Apixaban may be a good choice for DW based on his comorbidities and age, but his copay would be $538/month.
- Therefore, the decision has been made to initiate DW on warfarin 5 mg once daily with INR goal of 2-3.
- He is discharged from the hospital after achieving his INR goal and told to follow up with his INR clinic in 2-3 days.

Transitioning Between Agents

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Patient Case Continued

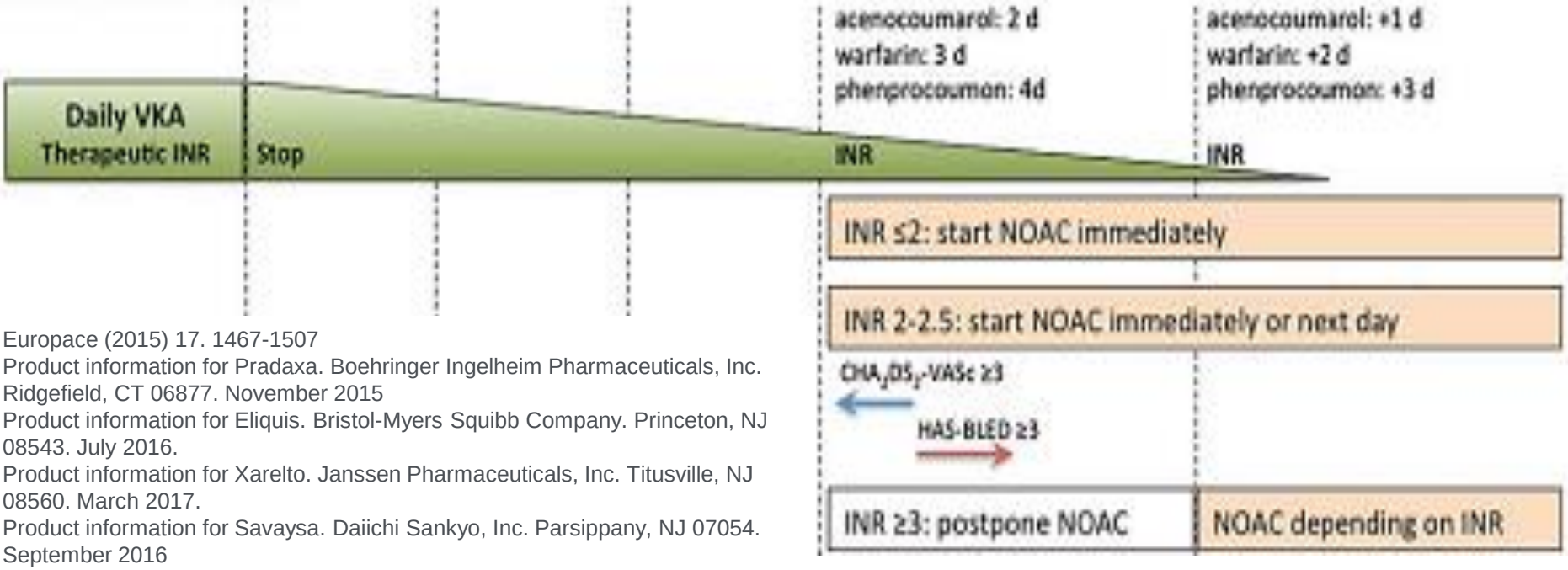
- DW returns to his primary care provider a couple of months later complaining of difficulty keeping his INR within goal and the inconvenience of visiting the INR clinic.
- He also has recently acquired a secondary private insurance which provides improved coverage for other anticoagulants.
- DW and his provider agree to start a DOAC.
- Today's INR = 1.9

Patient Case

- How should DW be transitioned to another anticoagulant?
  A. Stop warfarin and start DOAC in 2-3 days
  B. Reverse warfarin and start once INR = 1.0
  C. Stop warfarin and start DOAC today
  D. Stop warfarin and bridge the patient with parenteral anticoagulation until therapeutic

Transitioning from warfarin

- **Dabigatran**
  - d/c warfarin; start dabigatran when INR is < 2
- **Rivaroxaban**
  - d/c warfarin; start rivaroxaban when INR is < 3
- **Apixaban**
  - d/c warfarin; start apixaban when INR is < 2
- **Edoxaban**
  - d/c warfarin; start edoxaban when INR is < 2.5



Europace (2015) 17. 1467-1507
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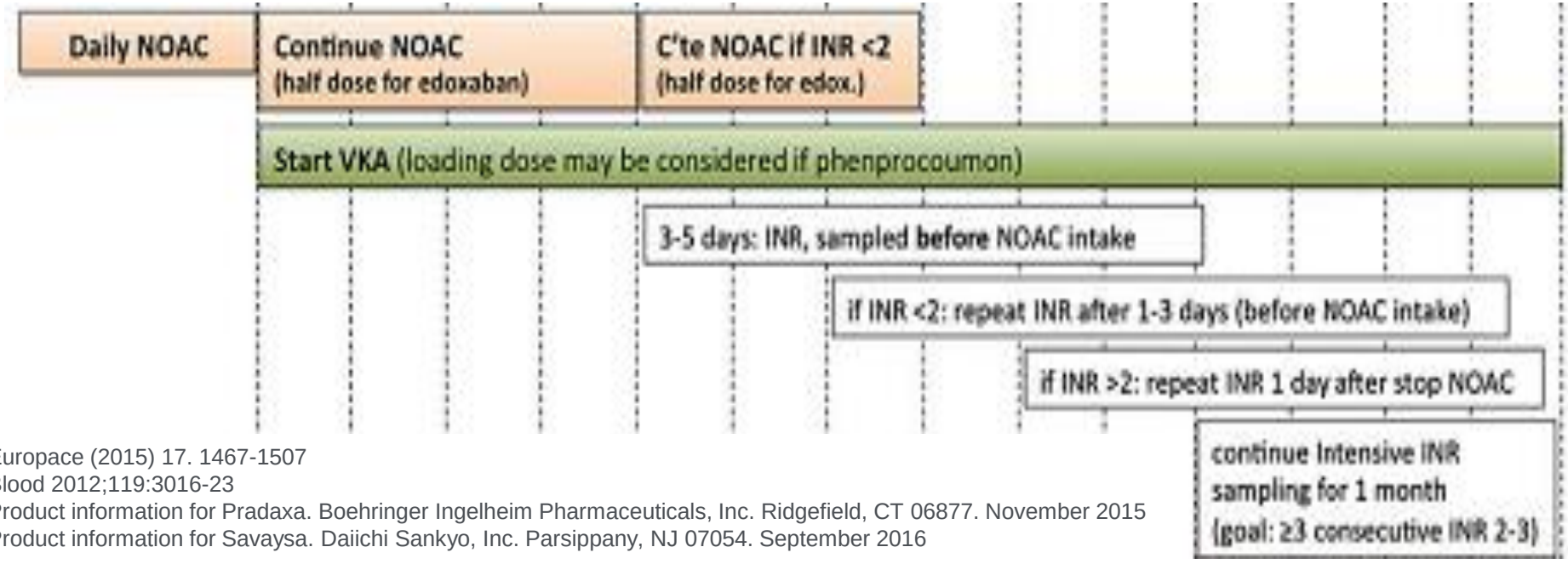
Transitioning to Warfarin

Dabigatran

- CrCl >50 ml/min: start warfarin 3 days before stopping dabigatran
- CrCl 30-50 ml/min: start warfarin 2 days before
- CrCl 15-30 ml/min: start warfarin 1 day before

Edoxaban

- ↓ dose 50%, initiate warfarin, and continue edoxaban until stable INR ≥ 2;measure INR at least weekly and just prior to edoxaban dose



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Blood 2012;119:3016-23
Product information for Pradaxa. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877. November 2015
Product information for Savaysa. Daiichi Sankyo, Inc. Parsippany, NJ 07054. September 2016

Transitioning to warfarin

Rivaroxaban

- D/c rivaroxaban and start a parenteral anticoagulant plus warfarin at the time of the next rivaroxaban dose
- D/c parenteral anticoagulant when INR reaches a therapeutic range

Apixaban

- D/c apixaban and start a parenteral anticoagulant plus warfarin at the time of the next apixaban dose
- D/c parenteral anticoagulant when INR reaches a therapeutic range

Europace (2015) 17. 1467-1507
Product information for Eliquis. Bristol-Myers Squibb Company. Princeton, NJ 08543. July 2016.
Product information for Xarelto. Janssen Pharmaceuticals, Inc. Titusville, NJ 08560. March 2017.

Patient Case

- Because DW's INR is < 2 today, he may start taking apixaban today.

Reversal

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Patient Case

- Six months later, DW is rushed in the ER with complaints of severe headache, nausea, vomiting, and some left sided numbness.
- He has been compliant with his apixaban. Last dose was this morning.
- Head CT reveals acute hemorrhage of the right temporal lobe

Patient Case

- What therapeutic strategy would you recommend to reverse the anticoagulant?
  A. Activated charcoal and dialysis
  B. Vitamin K and blood products
  C. 4 factor PCC
  D. Idarucizumab

What to do if a patient bleeds?

- When was there last dose?
  - DOACs have a relatively short half live (around 12 hours)
  - Reversal may not be needed if it has been > 24 hours.
- How severe is the bleeding?
  - Mild, moderate, life-threating
- Are there any lab test that can help tell if the drug is on board?
  - aPTT, dilute TT, ECT, INR?
- Is there something that will reverse the effects?
  - Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity, dialysis?, PCC?, others?

Table 4 Interpretation of coagulation assays in patients treated with different NOACs and range of values at trough (P5–P95) in patients with normal function and the standard dose, as measured in clinical trials

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Plasma peak level	2 h after ingestion	1–4 h after ingestion	1–2 h after ingestion	2–4 h after ingestion
Plasma trough level	12 h after ingestion	12 h after ingestion	24 h after ingestion[36]	24 h after ingestion
PT	Cannot be used	Can be prolonged but no known relation with bleeding risk[37]	Prolonged but variable and no known relation with bleeding risk[36,38] Range at trough: NA	Prolonged but no known relation with bleeding risk Range at trough: 12–26 s with Neoplastin Plus as reagent; local calibration required
INR	Cannot be used	Cannot be used	Cannot be used	Cannot be used
aPTT	Range (P10–P90) at trough D150: 40.3–76.4 s Range (P10–P90) at trough D110: 37.5–60.9 s At trough: >2 × ULN may be associated with excess bleeding risk[39]	Cannot be used	Prolonged but no known relation with bleeding risk[36]	Cannot be used
dTT	No data from RE-LY trial on range of values At trough: >200 ng/mL ≥65 s: may be associated with excess bleeding risk[39,40]	Cannot be used	Cannot be used[41]	Cannot be used
Anti-FXa chromogenic assays	Not applicable	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 1.4–4.8 IU/mL	Quantitative[41]; no data on threshold values for bleeding or thrombosis Range at trough: 0.05–3.57 IU/mL[a]	Quantitative; no data on threshold values for bleeding or thrombosis Range at trough: 6–239 μg/L
ECT	Range (P10–P90) at trough D150: 44.3–103 Range (P10–P90) at trough D110: 40.4–84.6 At trough: ≥3 × ULN: excess bleeding risk[39]	Not affected[37]	Not affected	Not affected
ACT	Rather flat dose response. No investigation on its use. Limited utility	No data. Cannot be used	No data. Cannot be used	Minor effect. Cannot be used

Routine monitoring is not required. Assays need cautious interpretation for clinical use in special circumstances, as discussed in the text.

PT, prothrombin time; aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; INR, international normalized ratio; ACT: activated clotting time; ULN, upper limit of normal.

[a](P2.5–P97.5) for edoxaban.

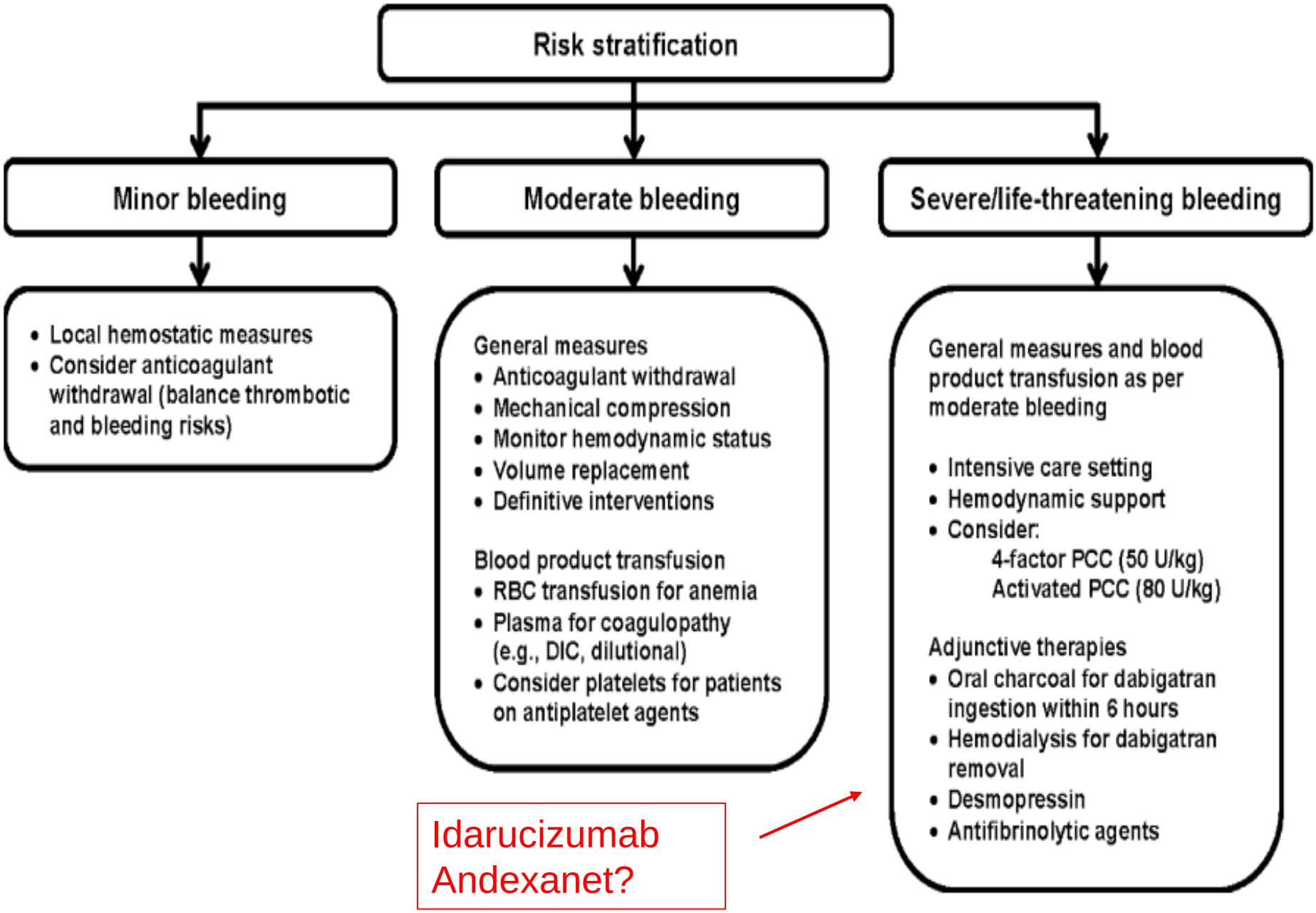

Fig. 3 Management of DOAC-associated bleeding

Patient Case

- As DW was taking apixaban when the stroke occurred, he was given 4 factor PCC for reversal and appropriate hemodynamic support.

Conclusions

- Patient characteristics and cost are the primary drivers in the selection of oral anticoagulation
- Transition from warfarin to DOACs relatively simple
- There are still some concerns about what to do with patients that bleed on these agents but that issue is improving

Questions?

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Holding prior to surgery

Bleeding Risk	DABIGATRAN (PRADAXA®)	RIVAROXABAN (XARELTO®)	APIXABAN (ELIQUIS®)	EDOXABAN (SAVAYSA®)
Moderate or high risk	2 days prior (CrCl >50) 4 days (CrCl 30-50) 6 days (CrCl ≤30)	At least 24 hours prior to procedure	48 hours prior to procedure	At least 24 hours prior to procedure
Low risk	24 hrs prior (CrCl >50) 2 days (CrCl 30-50) 4 days (CrCl ≤30)	At least 24 hours prior to procedure	At least 24 hours prior to procedure	At least 24 hours prior to procedure

Transitioning to/from a parenteral anticoagulant

Conversion from a parenteral anticoagulant:

- Initiate NOAC at the time of the next scheduled dose of the parenteral anticoagulant (e.g., enoxaparin) or at the time of discontinuation for a continuously administered parenteral drug (e.g., IV heparin); discontinue parenteral anticoagulant at the time of NOAC initiation.

Conversion to a parenteral anticoagulant:

- Discontinue NOAC and initiate continuous infusion (or e.g. SQ enoxaparin) at the time the next dose of NOAC would have been taken.*

* If the patient has worsening renal insufficiency a longer hold time may be needed

Idarucizumab (Praxbind®)

- Monoclonal antibody fragment (Fab)
  - binds to dabigatran and its metabolites with higher affinity (350x) than to thrombin → neutralizing the anticoagulant effect
- Dose
  - 5g IV (2x 2.5g/50mL vials)
- Data
  - RE-VERSE AD
    - 1º endpoint: maximum % reversal of anticoagulant effect of dabigatran within 4 hours
    - 2º endpoint: median time to cessation of bleeding
- Cost: $3,500 per treatment (2 vials)

What about the other NOACs?

- Andexanet Alfa
- Andexanet is designed to reverse the anticoagulant effects of factor Xa inhibitors
  - It is currently under an accelerated review by the FDA with a decision expected this Fall
  - ANNEXA-A and ANNEXA-R trials

- Aripazine (PER977):
- Universal reversal agent for oral direct thrombin and factor Xa inhibitors, UFH, LMWH, and fondaparinux
  - Currently only phase II trials underway

Acute Ischemic Stroke & rtPA

- Current AHA/ASA guidelines recommended exclusion criteria:
  - Current use of anticoagulant with INR > 1.7 or PT > 15s
  - Current use of direct thrombin inhibitor or direct factor Xa inhibitors with elevated sensitive laboratory tests (aPTT, INR, plt count, ECT, TT, ot appropriate factor Xa activity assays)
- Poorly studied
- May need to rely on elimination half-life
  - May be prolonged in patients with renal impairment