DOAC DO'S and DON'T'S

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GENERAL HEMATOLOGY
OHSU

DISCLOSURE

<u>Relevant Financial Relationship(s)</u>

Speaker's Bureau – none

Goals

- Drugs
- Diseases
- Dilemmas
- Do’s and Don’ts

The Drugs

- Anti-thrombin
  - Dabigatran
- Anti-Xa
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - (Betrixaban)

Dabigatran

- Oral Thrombin Inhibitor
- Bioavailability: 6.5%
- Onset of action: 2-3 hours
- Half-life : 12-14 hours
- Renal excretion: 80%
- Drug interactions: p-glycoprotein

Dabigatran

- **Atrial fibrillation: More effective than warfarin**
- **Venous thrombosis prevention: As effective as LMWH**
- **Venous thrombosis treatment: As effective as warfarin**

Dabigatran: Bottom Line

- Superior to warfarin in stroke prevention
- Effective in venous thrombosis treatment
- GI side effects 15%
- 1.3x increase risk of MI
- CrCl > 50
- Affects aPTT

Rivaroxaban

- Oral Xa Inhibitor
- Bioavailability: 80-100%
- Onset of action: 2.5-4 hours
- Half-life : 5-9 hours
- Renal excretion: ~66%
- Drug interactions: CYP 3A4+P-GP

Rivaroxaban

- **Atrial fibrillation: As effective as warfarin**
- **Venous thrombosis prevention: More effective than LMWH**
- **Venous thrombosis treatment: As effective and safer than LMWH/warfarin**

Rivaroxaban

- Approved 10mg daily for VTE prophylaxis in TKR and THR
- Approved 20mg daily for afib
  - 15mg if CrCl 15-50mL/m
  - Contraindicated < 15mL/m
- Approved for VTE
  - 15mg BID x 3 weeks
  - 20mg daily
  - 10mg chronic

Rivaroxaban: Bottom Line

- Effective in stroke prevention
- Superior in prevention of VTE
- Safer in treatment of VTE
- CrCl > 15 (15mg < 50)
- Once a day drug
  - BID x 3 weeks in acute VTE
- INR sensitive

Apixaban

- Oral Xa Inhibitor
- Bioavailability: 66%
- Onset of action: 1-3 hours
- Half-life : 8-15 hours
- Renal excretion: 25%
- Drug interactions: CYP 3A4 +P-GP

Apixaban

- Atrial fibrillation: More effective and safer than warfarin
- Venous thrombosis prevention: More effective than LMWH
- Venous thrombosis treatment: As effective and safer than LMWH/warfarin

Apixaban

- Approved 2.5 mg for VTE prophylaxis in TKR and THR
- Approved 5 mg BID for afib
  - 2.5mg if 2/3
    - Age > 80
    - Cr > 1.5
    - Weight < 60 kg
- Approved for VTE
  - 10 mg BID x 7 days
  - 5 mg BID
  - > 6 months 2.5 mg BID

Use Right Dose!

- Increasing data that under dosing DOACs lead to more thrombosis/stroke without change in bleeding
- Only dose adjust if indicated!

Apixaban: Bottom Line

- Superior in stroke prevention with less bleeding
- Superior in prevention of VTE
- Safer in therapy of VTE
- BID drug
- Does not affect INR/PTT

Edoxaban

- Oral Xa Inhibitor
- Bioavailability: 45%
- Onset of action: 1-1.5 hours
- Half-life : 9-11 hours
- Renal excretion: 33%
- Drug interactions: CYP 3A4
  - Multiple other pathways

Edoxaban: Bottom Line

- Effective in stroke prevention
- Safer in treatment of VTE
- Approved for CrCl < 95
- Once a day drug
- INR to monitor

The Diseases

- Joint replacement
- Atrial fibrillation
- Venous Thromboembolism

Joint Replacement

Drug	Thrombosis	Bleeding
Apixaban	Better	Equal
Dabigatran	Equal	Equal
Rivaroxaban	Better	Equal

Atrial Fibrillation

Drug	Stroke	Bleeding
Apixaban	Better	Safer
Dabigatran	Better	Equal
Edoxaban	Equal	Safer
Rivaroxaban	Equal	Equal

Warfarin ~ $4/month
DOAC ~ $300/month

ICH – Atrial Fibrillation

	Stroke		Intracranial Hemorrhage	
	Events/ 100 years	RR	Events/ 100 years	RR
Apixaban	1.19	0.79 (0.65-0.95)	0.33	0.42 (0.30-0.58)
Dabig 110	1.53	0.91 (0.74-1.11)	0.23	0.31 (0.20-0.47)
Dabig150	1.11	0.66 (0.53-0.82)	0.30	0.40 (0.27-0.60)
Edox 60	1.69	0.88 (0.75-1.03)	0.39	0.47 (0.34-0.63)
Edox 30	1.97	1.13 (0.97-1.31)	0.26	0.30 (0.21-0.53)
Rivaroxaban	1.76	0.79 (0.66-0.96)	0.49	0.67 (0.47-0.94)

Potential for 10-12,000 less ICH in USA

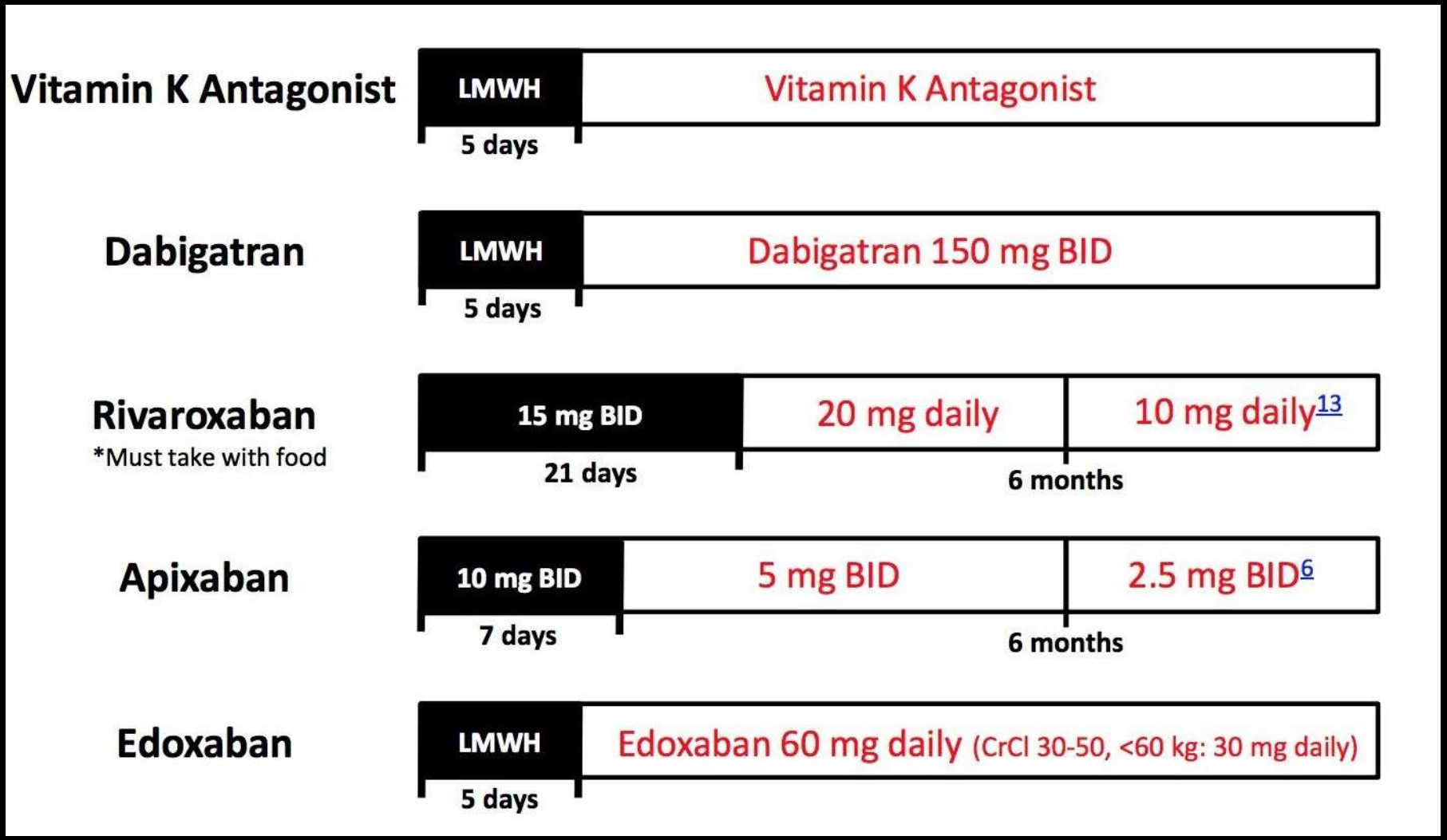
DOACs and VTE

- Robust randomized trial data for all new anticoagulants
- Now recommend over warfarin by new Chest Guidelines

Venous Thrombosis

Drug	Heparin First?	Thrombosis	Bleeding
Apixaban	No*	Equal	Safer
Dabigatran	Yes	Equal	Equal
Edoxaban	Yes	Equal	Safer
Rivaroxaban	No*	Equal	Safer

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily
Only “load” for acute VTE


Vitamin K Antagonist
LMWH
Vitamin K Antagonist
5 days
Dabigatran
LMWH
Dabigatran 150 mg BID
5 days
Rivaroxaban
*Must take with food
15 mg BID
20 mg daily
10 mg daily[13]
21 days
6 months
Apixaban
10 mg BID
5 mg BID
2.5 mg BID[6]
7 days
6 months
Edoxaban
LMWH
Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg daily)
5 days

DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

Blood 2014;124(12):1968-1975

Eur J Vasc Endovasc Surg. 2014 Nov;48(5):565-575.

Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - LMWH
  - Ximelagatran
  - Did not work for warfarin

Low Dose DOAC

- Two trials
  - Rivaroxaban 20mg vs 10mg
  - Apixaban 5mg vs 2.5 mg
- Start 6-12 months after VTE
- No difference in VTE or bleeding
  - Trend toward reduce major bleeding

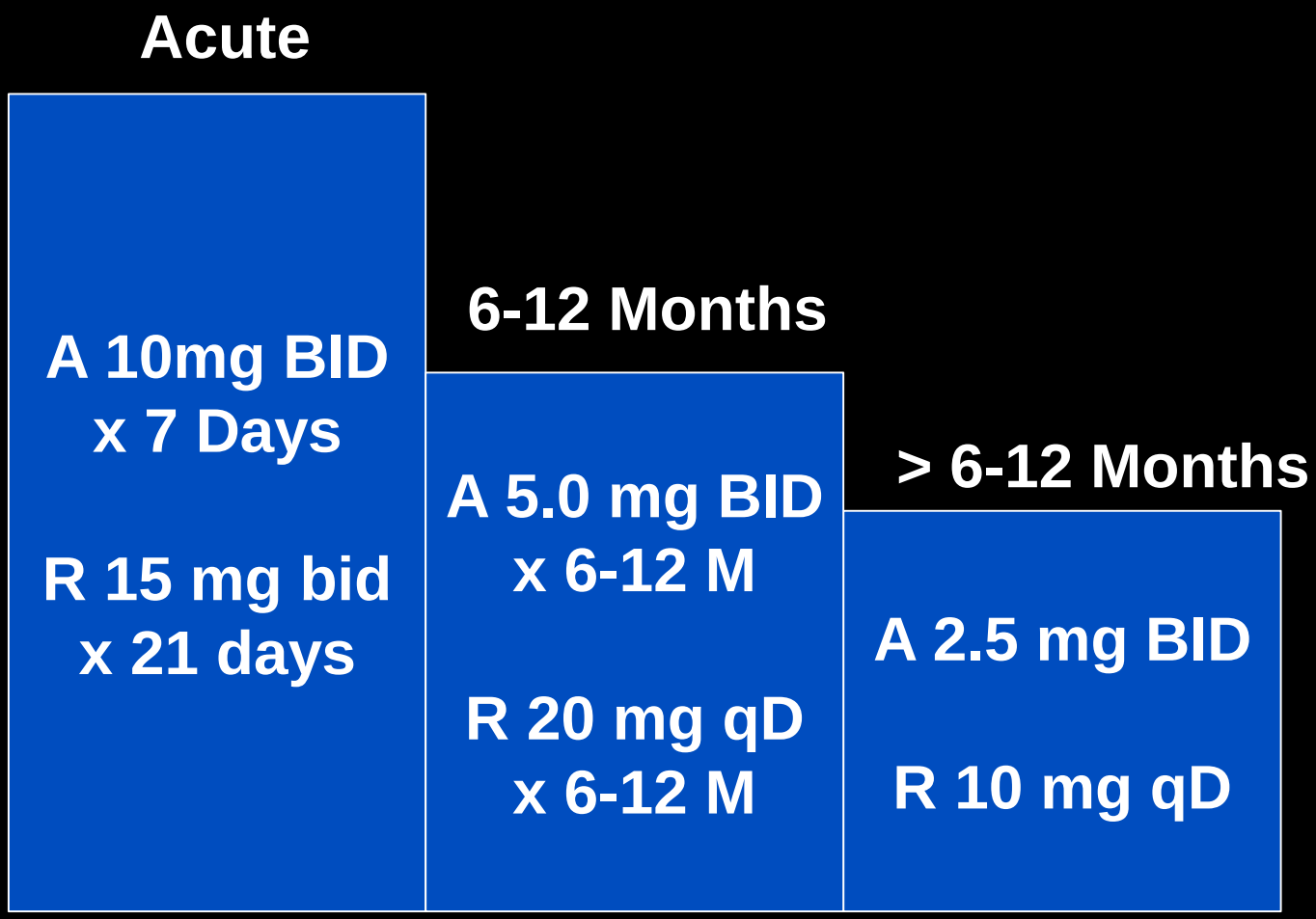
Low Dose DOAC

- Idiopathic or recurrent VTE
- After 6-12 months of therapy
- Not!
  - Cancer
  - APLA
  - Visceral thrombosis

Current Role of DOAC in DVT

- Initial therapy
  - Rivaroxaban, apixaban no heparin
- Long term therapy
  - Safer and easier
  - Uncomplicated thrombosis step down after 6-12 months

DOAC VTE Stepped Care



Direct Oral Anticoagulants

- Potential to be game changer
- Low dose for long term therapy good option
- But
  - Patients still need close follow-up
  - Still need to management anticoagulants

Dilemmas!

Who Must Stay on Warfarin

- Mechanical valves
- Weight < 50kg or > 140ish kg

Weight

- DOACs weight base
- Obesity
  - Atrial fibrillation: 140 kg
    - Increasing data for up to BMI 40
  - Venous disease: 140 kg
    - Chronic 160 kg
- Like with LMWH monitoring levels will allow greater use

Who Should get DOACs

- Venous thrombosis
- Older patients (> 75)
- Renal insufficiency
- Prior stroke or TIA
- Risk of bleeding
  - Apixaban

DOAC in Patients > 75

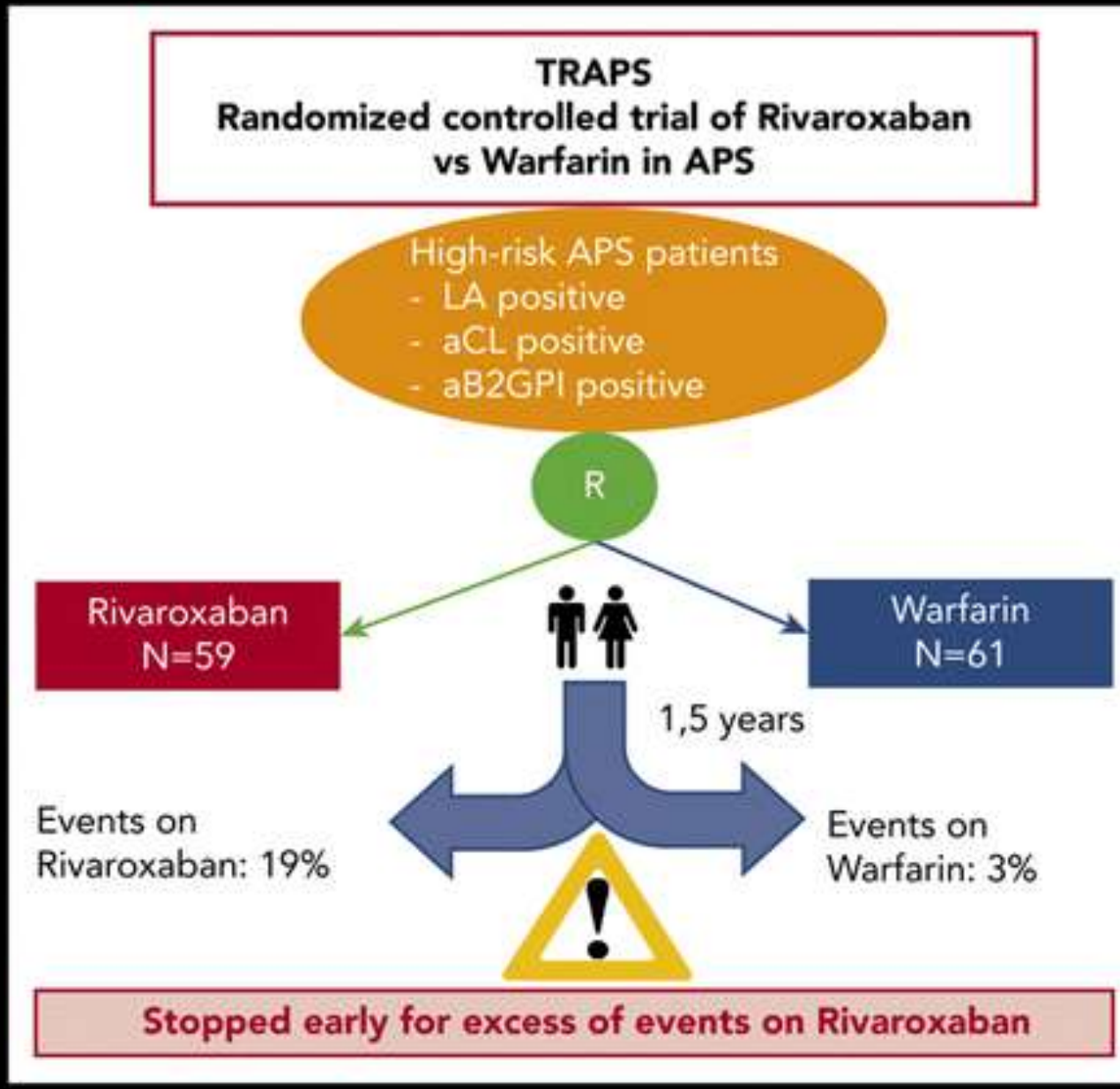
Outcomes	OR	CI
Bleeding	1.02	0.73-1.43
Stroke/embolism	0.65	0.48-0.87
VTE/Fatal PE	0.45	0.27-0.77

N = 25,031 in 10 RCT

JAGS 62:857, 2014

Thrombophilia

- Hereditary
  - No concerns
- Antiphospholipid Syndrome
  - Not for triple positive
  - Not for arterial disease


TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS
High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive
R
Rivaroxaban N=59
Warfarin N=61
1,5 years
Events on Rivaroxaban: 19%
Events on Warfarin: 3%
Stopped early for excess of events on Rivaroxaban

Pregnancy

- NO!
  - Will cross placenta
  - Secreted in breast milk
- LMWH remains anticoagulants of choice

History of GI Bleed

- Both rivaroxaban (1.5 HR) and dabigatran (1.6 HR) increase risk of bleeding but not apixaban (0.9 HR)
- Remember patients with GIB have <u>better</u> outcomes if placed back on anticoagulation

Monitoring

- Designed not to need monitoring
  - Many reference labs (UW)offer levels
- When to consider
  - Compliance
  - Drug failure
  - Renal diseases
  - Extremes of weight

Renal Disease

- Renal Function
  - All renally cleared:
    - Apixaban – dose reduced to 2.5 mg bid if
      - Creatinine > 1.5 plus age over 80 or weight < 60kg
      - Increasing dialysis data
    - Dabigatran – not for CrCl < 50
    - Rivaroxaban – 15mg CrCl 49-15
      - 10mg for dialysis
    - Edoxaban –30mg/day if CrCl 15-50

Apixaban: Dialysis

- Medicare dialysis patients
- Use of apixaban 5mg bid vs warf
  - Less bleeding
  - Less stroke
  - Less mortality
- Circulation. 2018;138:1519–1529

DOAC in Liver Disease

- Increasing data on safety in liver disease
  - Easier to use
  - Less bleeding
- Drug of choice
  - Apixaban ok in Childs B
- Exception Child C
  - Case by case basis

“Break-Through” Clots

- DOACs are not perfect
- Neither are patients…

“Break-Through” Clots

1. Is it a breakthrough clot?
   - New PE in first week ~ 5%
   - DVT can grow on therapy
   - New: new vessel or limb involved
   - PE after 2 weeks

“Break-Through” Clots

- 2. Was patient taking med?
  - Ideal: levels sent
  - Ok: INR/PTT check
  - Check DOAC dose
  - Ask patient
  - Check pharmacy

“Break-Through” Clots

3. Treatment
   - LWMH
     - If breakthrough LMWH raise dose 25%
   - Warfarin
     - Compliance concerns

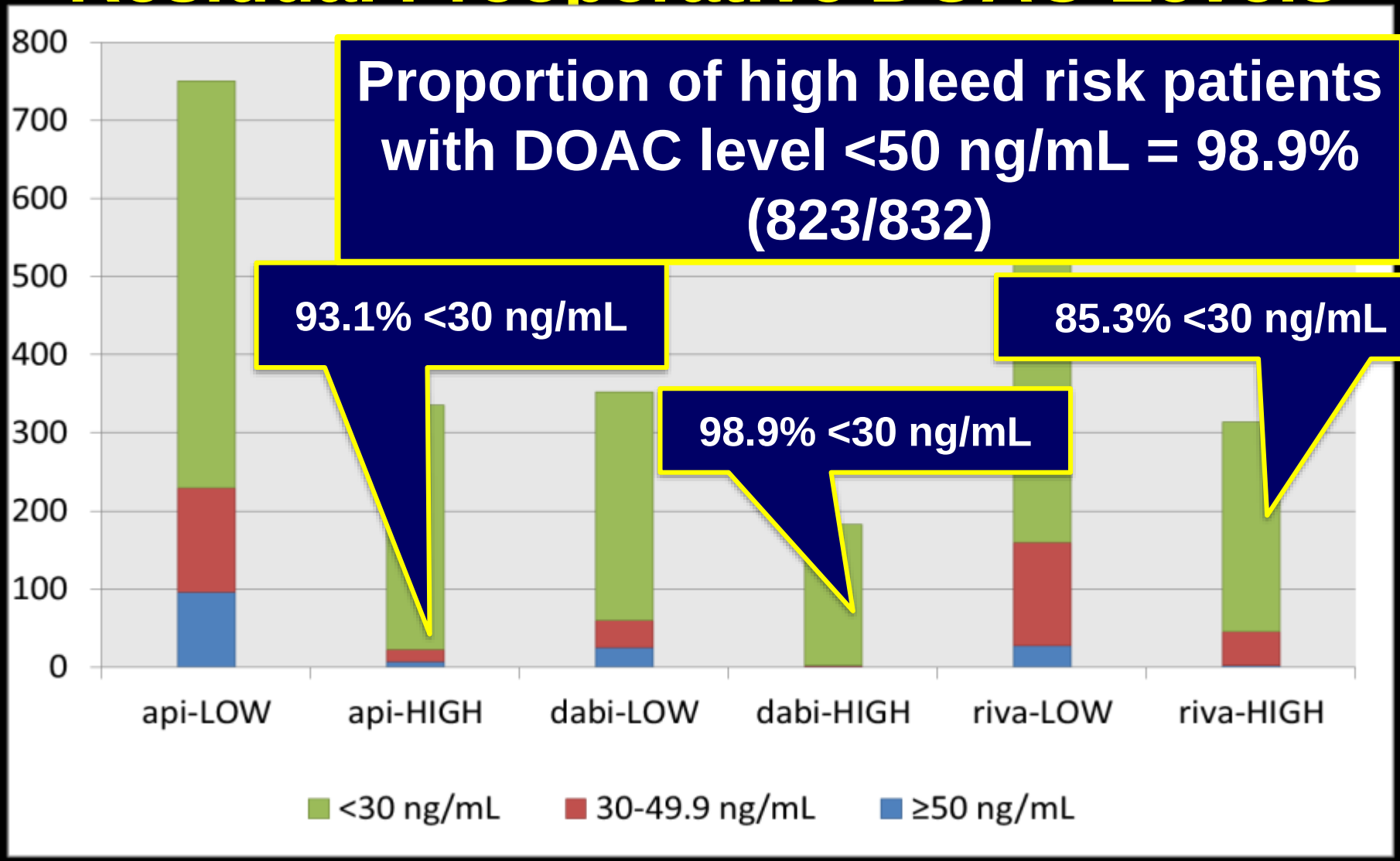
Surgery/Procedures

- Increasing data
- Need to know
  - Drug
  - Procedure
  - Renal function

DOACs and Surgery

Drug	Surgery	CrCl	-4	-3	-2	-1	Surgery
Apix	Major				Hold	Hold	Hold
	Minor					Hold	Hold
Dabig	Major	>50			Hold	Hold	Hold
		<50	Hold	Hold	Hold	Hold	Hold
	Minor	>50				Hold	Hold
		<50		Hold	Hold	Hold	Hold
Rivarox	Major				Hold	Hold	Hold
	Minor					Hold	Hold

Residual Preoperative DOAC Levels



PAUSE Trial

- Major bleeding: 0.9-1.85%
  - BRIDGE Trial/Meta: 1.3%/2.7%
- Arterial Thrombosis: 0.2-0.6%
  - BRIDGE Trial/Meta: 0.4%/0.9%

DOACs: Post Surgery

- Treat like LMWH
- Simple – restart next day
- Complex
  - Prophylactic dose
  - Full dose 48 hours or more

DOACs in Cancer

- Advantages
  - Few drug no food interactions
  - Short half-life
  - Not a shot
- Warfarin inferior to LMWH
  - Increase thrombosis
- Less than 33% of cancer patients on LMWH

Edoxaban Cancer

	Edoxaban (522)	LMWH (524)
Primary Outcome	67 (12.8%)	71 (13.5%)
rVTE	41 (7.9%)	59 (11.3%)
Major Bleeding	36 (6.9%)	21 (4.0%)

Bleeding increase in GI cancers
10% dalteparin drop out due to shots

N Engl J Med 2018; 378:615-624

Rivaroxaban Cancer

	Rivaroxaban (203)	LMWH (203)
rVTE	8 (4%)	22 (11%)
Major Bleeding	6 (3%)	9 (4%)
Relevant Bleeding	36 (17%)	11 (5.0%)

Bleeding increased in GI cancers

J Clin Oncol. 2018 Jul 10;36(20):2017-2023

Apixaban Cancer

	Apixaban (145)	LMWH (145)
rVTE	5 (3.1%)	20 (14.1%)
Major Bleeding	0 (0%)	3 (2.1%)
Relevant Bleeding	36 (17%)	11 (5.0%)

Presented at 2108 ASH, in press

Cancer

- 3 RCT: DOAC vs LMWH
- Recurrence: HR 0.48
- Bleeding: HR 1.54 (NS)
  - Mainly GI cancers
- DOAC can/should be use in cancer patients
  - Caution for upper GI cancers

Cancer

- DOACs now front line
- Reserve LMWH for break through thrombosis
- GI bleeding issue
  - Less with apixaban?

ELIQUIS HAS RISK OF
UNCONTROLLABLE BLEEDING & HEMORRHAGING

DOAC: Bleeding

- Analysis of all phase III trials
  - Venous thrombosis therapy
  - Atrial fibrillation
- N = 102,607 patients
- Chai-Adisaksopha Blood. 2014 Oct 9;124(15):2450-8

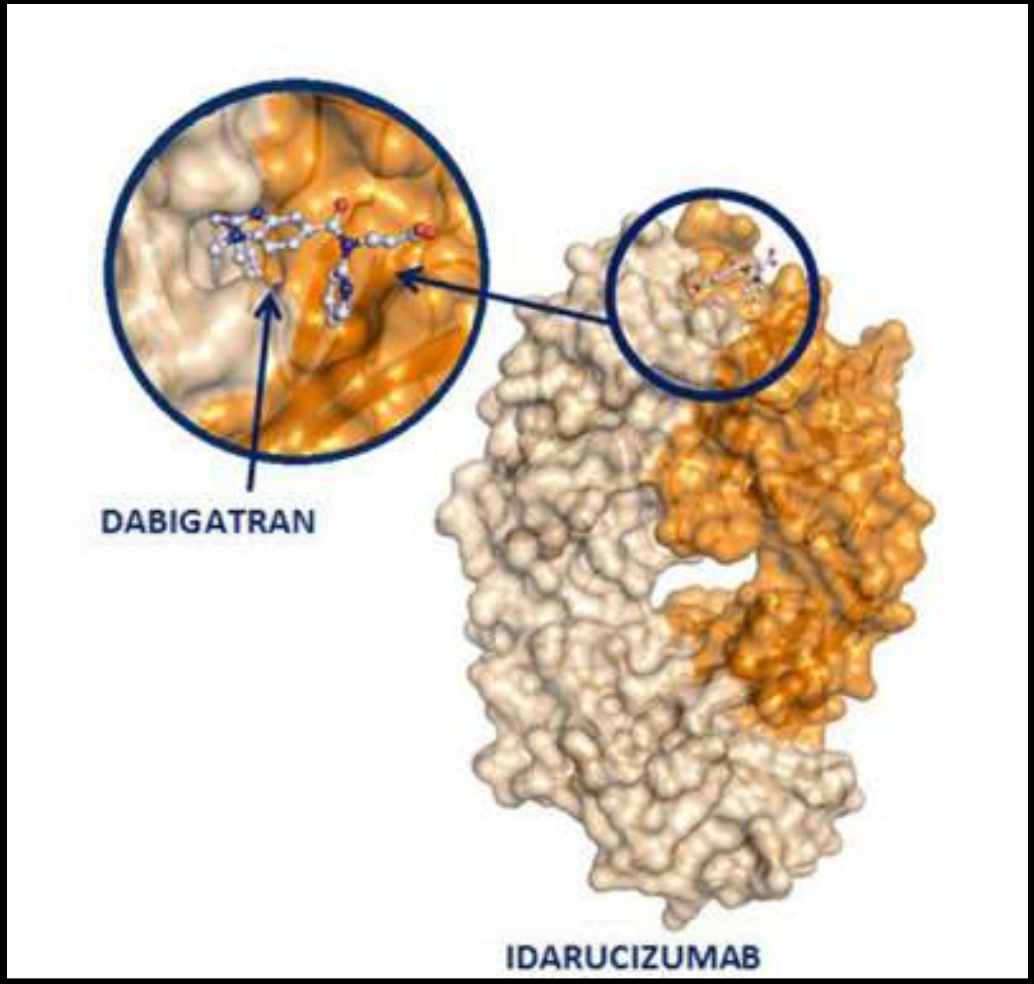
Results

- **Major** Bleeding RR = **0.72**
  - NNT = 156
- Fatal Bleeding RR = **0.78**
  - NNT = 454
- ICH RR = **0.76**
  - NNT = 185
- Total Bleeding RR = **0.76**
  - NNT = 18
- GI bleeding RR = **0.94**

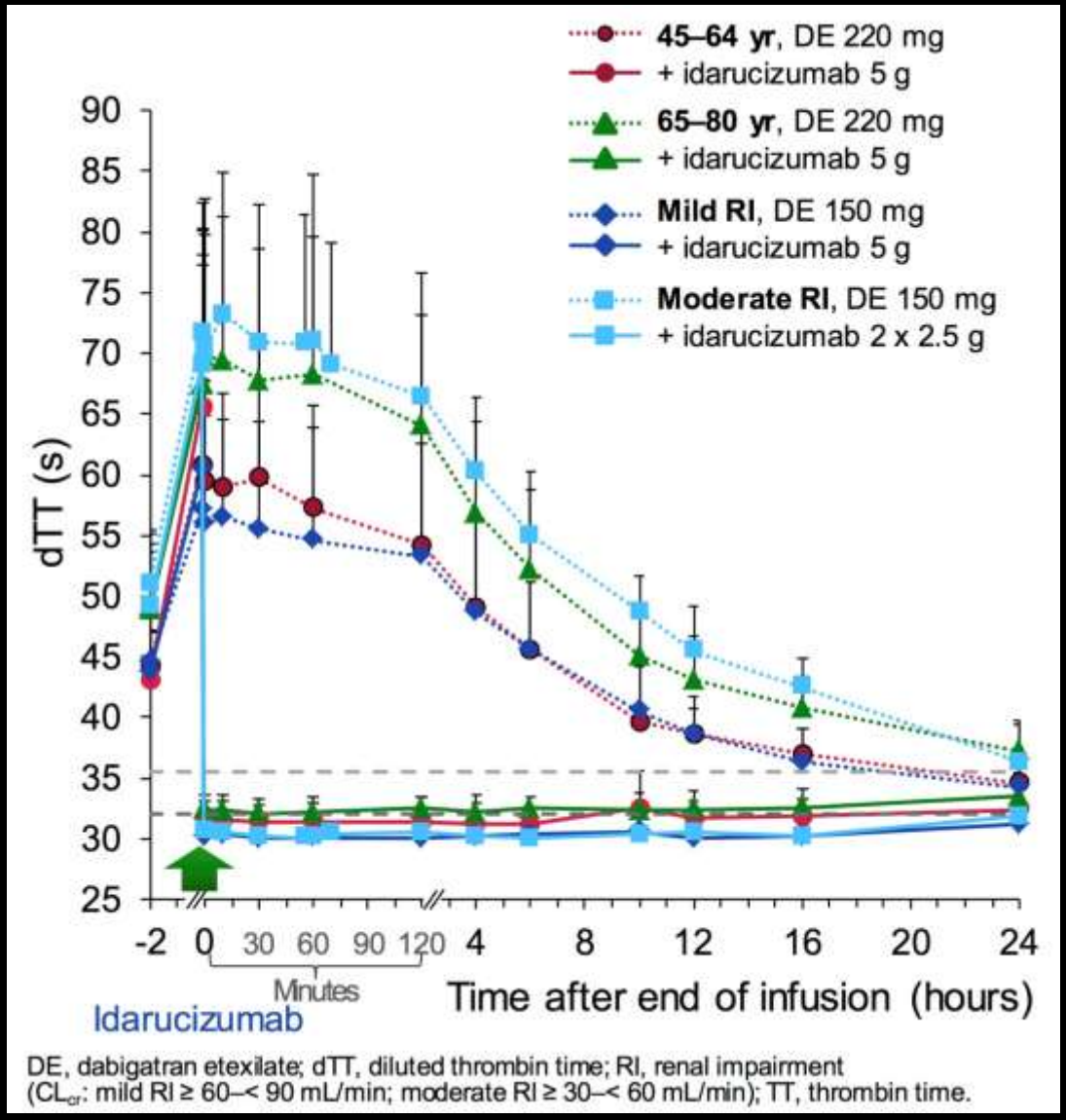
Irreversibility = Myth

- Less need to reverse
- No difference in outcomes in multiple studies with bleeding

Dabigatran Reversal



Idarucizumab



DE, dabigatran etexilate; dTT, diluted thrombin time; RI, renal impairment (CL_{cr}: mild RI ≥ 60–< 90 mL/min; moderate RI ≥ 30–< 60 mL/min); TT, thrombin time.

Idarucizumab

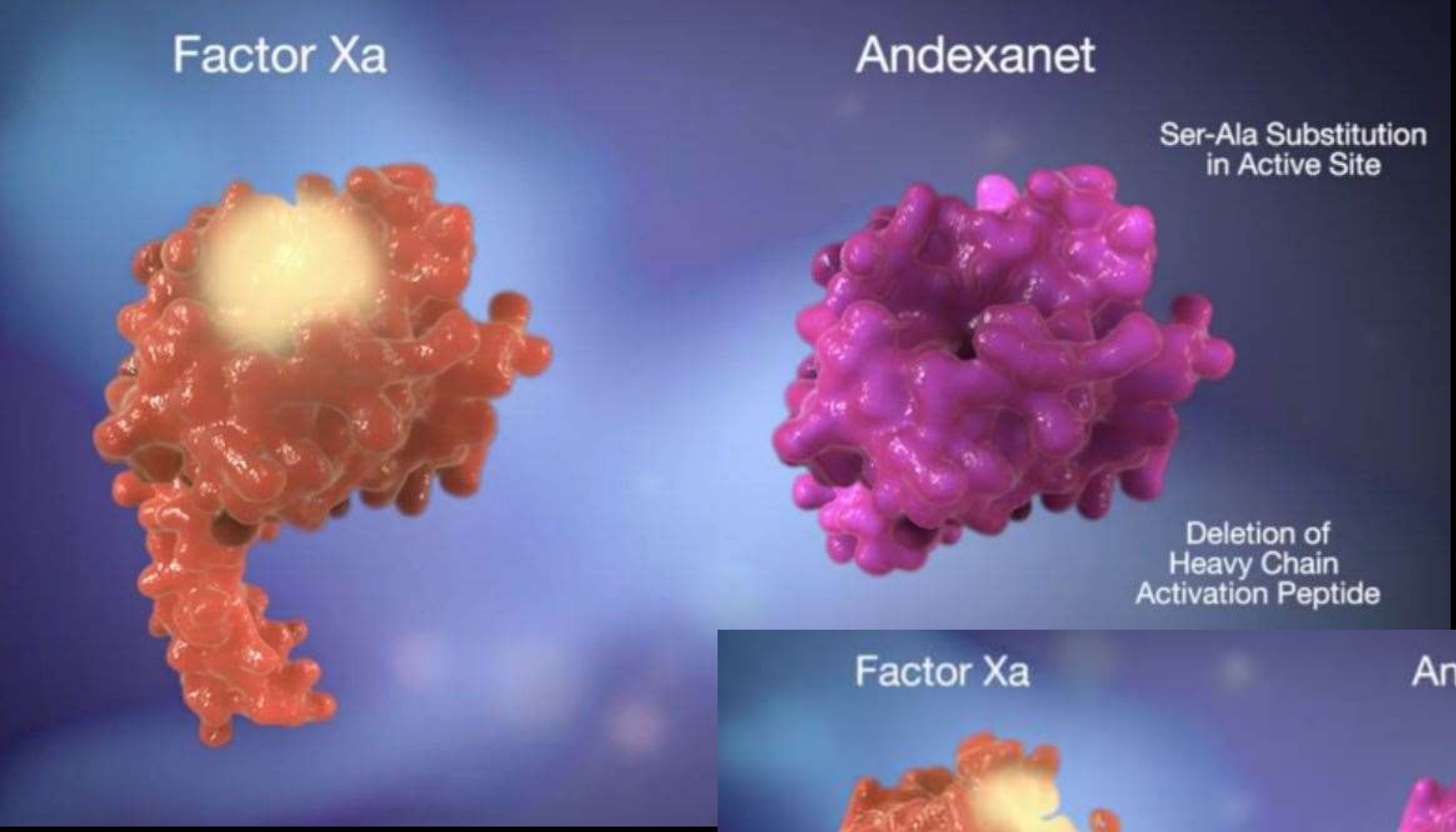
- Effective in ~ 98% of patients in reversing thrombin and Ecarin time
  - 24% with no drug on board
- 98% of patients could undergo emergency surgery
- ~ 2% of patients required redosing for bleeding
- 30 day thrombosis seen in ~ 5% patients

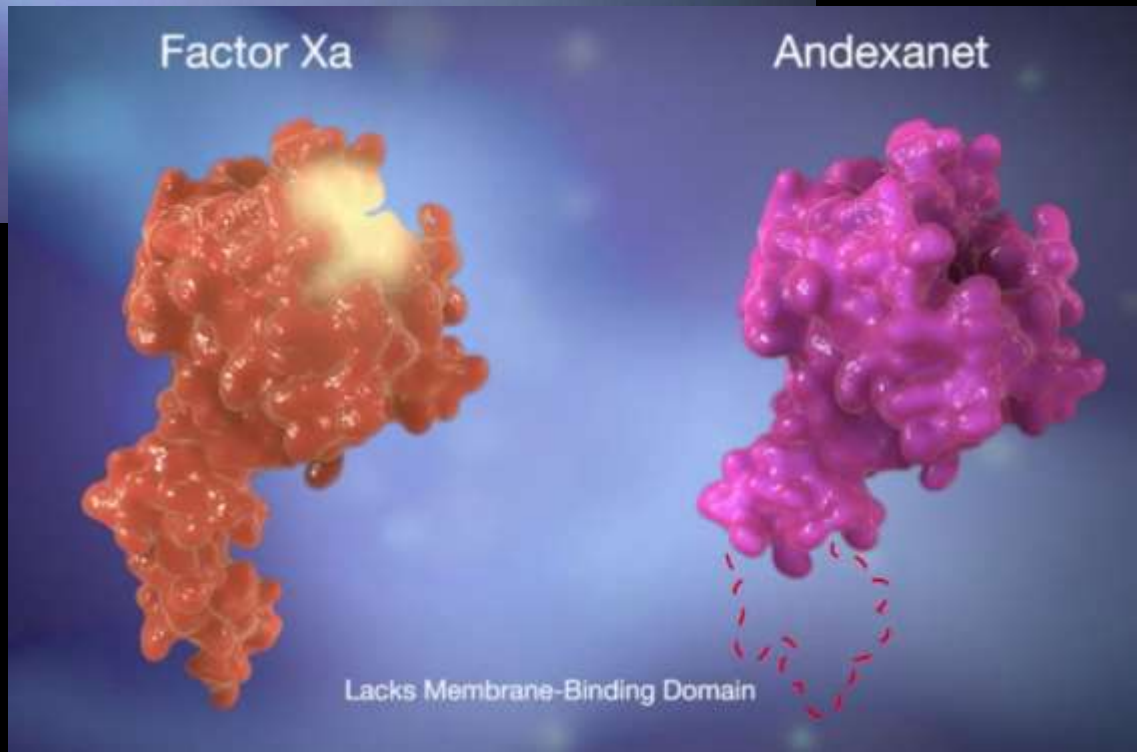
Our Protocol

1. Indication: ICH for patient on dabigatran
2. Baseline thrombin time and aPTT
   - Not to screen for use but to assess drug use
3. Five grams administered as 2.5 grams bolus one right after other
4. Consider for emergency surgery if TT/aPTT elevated

Andexanet - PRT064445

- “R-antidote”
- Recombinant fXa derivative
  - Catalytically inactive
  - Lacks the Gla-domain
- Reverses both direct and indirect Xa inhibitors

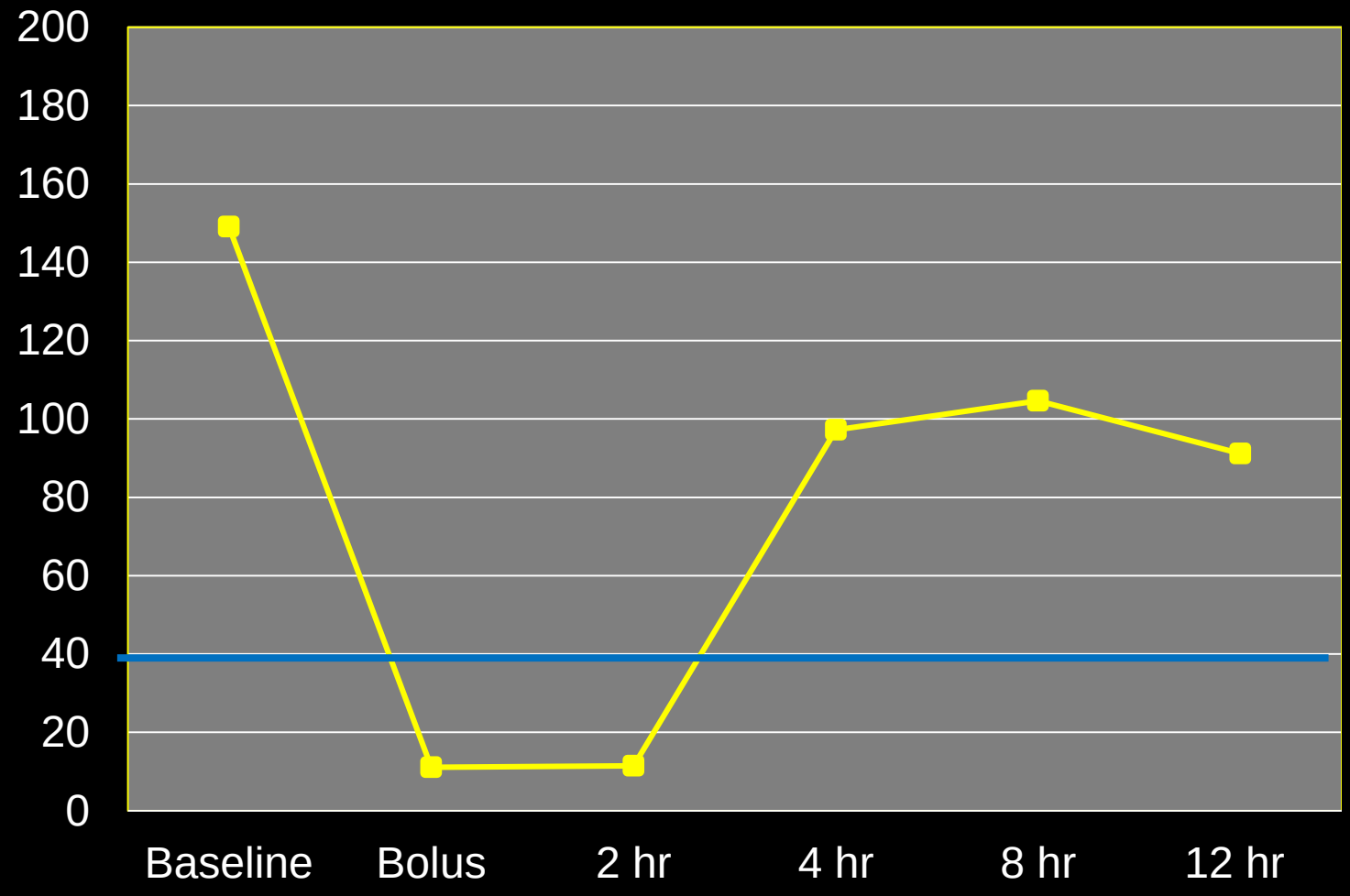

Factor Xa
Andexanet
Ser-Ala Substitution
in Active Site
Deletion of
Heavy Chain
Activation Peptide


Factor Xa
Andexanet
Lacks Membrane-Binding Domain

However….

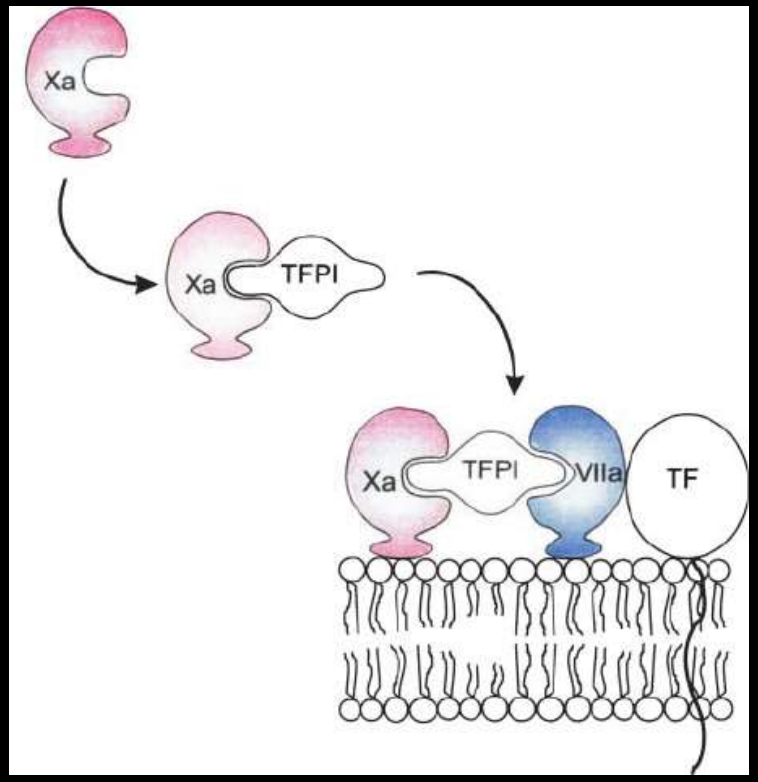
- Short duration
- Thrombosis rate ~ 10%
- Expensive
  - $25-50,000
- Limited availiblity

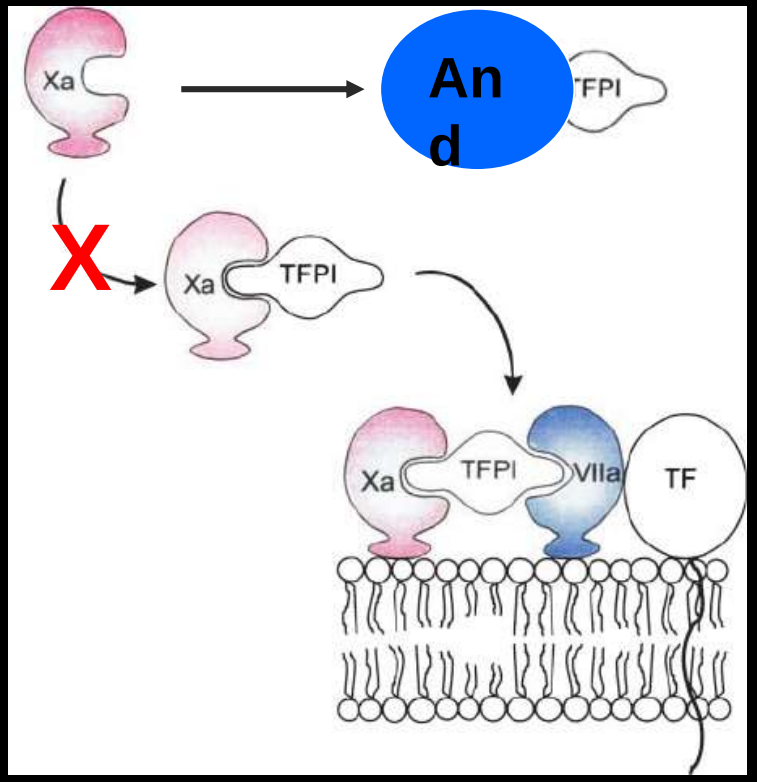
APIXABAN


200
180
160
140
120
100
80
60
40
20
0
Baseline
Bolus
2 hr
4 hr
8 hr
12 hr

Thrombosis

- 18% at start of trial and 10% final
- ~ 50% arterial
- Higher than PCC or Idarucizumab trials (4/6%)
  - Prothrombotic effect?
  - Blocks TFPI


Xa
Xa
TFPI
Xa
TFPI
VIIa
TF


Xa
And
TFPI
X
Xa
TFPI
Xa
TFPI
VIIa
TF

Eligibility Criteria

- 2-3/9 OHSU ICH would have been in trial
- Sicker patients selected out?
  - MGH 40% death rate

PCC

- Prothrombin Complex Concentrates (4 factor)
- Increasing data on effectiveness
  - Low rates of thrombosis
- Can use before procedures
- Does - 50 units/kg

PCC

- Recent meta-analysis
- Effectiveness 69-77%
- Mortality 14%
- Thrombosis 4%

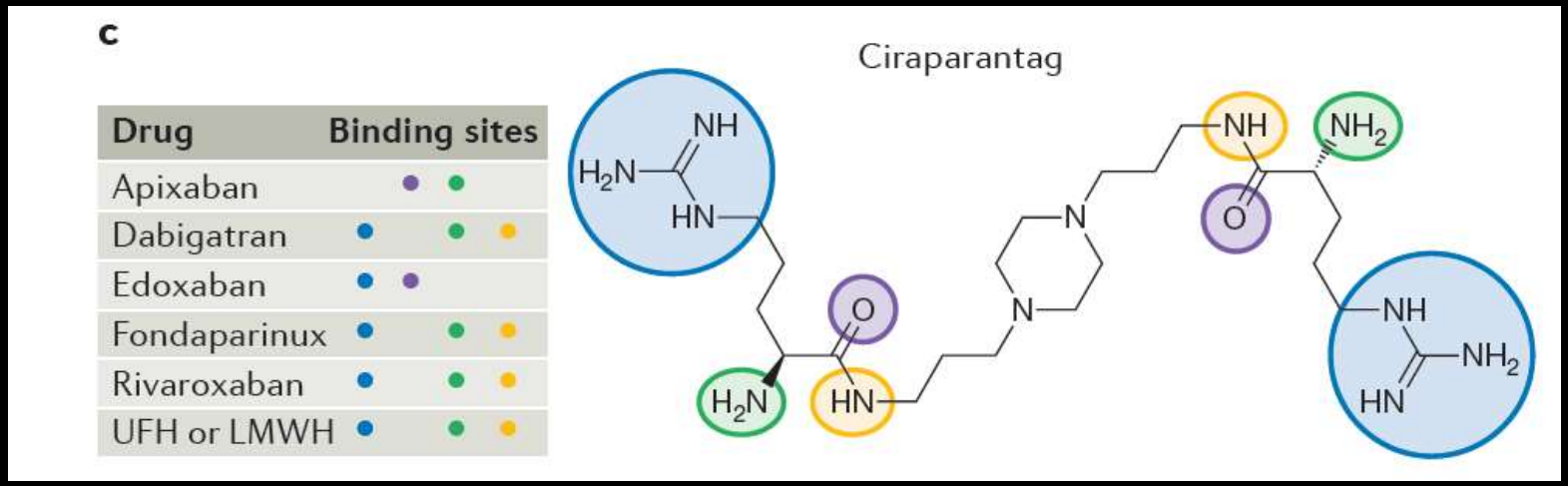
- Blood Adv. 2019 Jan 22;3(2):158-167.

Bleeding!

- Warfarin and anti-Xa
  - 50 units/kg of 4 factor PCC
  - For warfarin add vitamin K
- Dabigatran
  - Idarucizumab 5grams

The Future!

- Ciraparantag
  - "broad spectrum" reversal agent
  - Prolonged clinic effect
  - In clinical trials



Anticoagulation: When to Restart after a Bleed

- Very common problem
- Increasing data on subject
- Risk of rebleed varies with site of bleed and presence of anatomic lesions

Risk of Rebleeding

- ICH/SDH: long term risk of recurrence ~2%
  - Higher if cerebral amyloid angiopathy present (deep lobar bleeds)
- Gastrointestinal
  - Higher (10-20%?) especially if lesion present

GI Bleeding

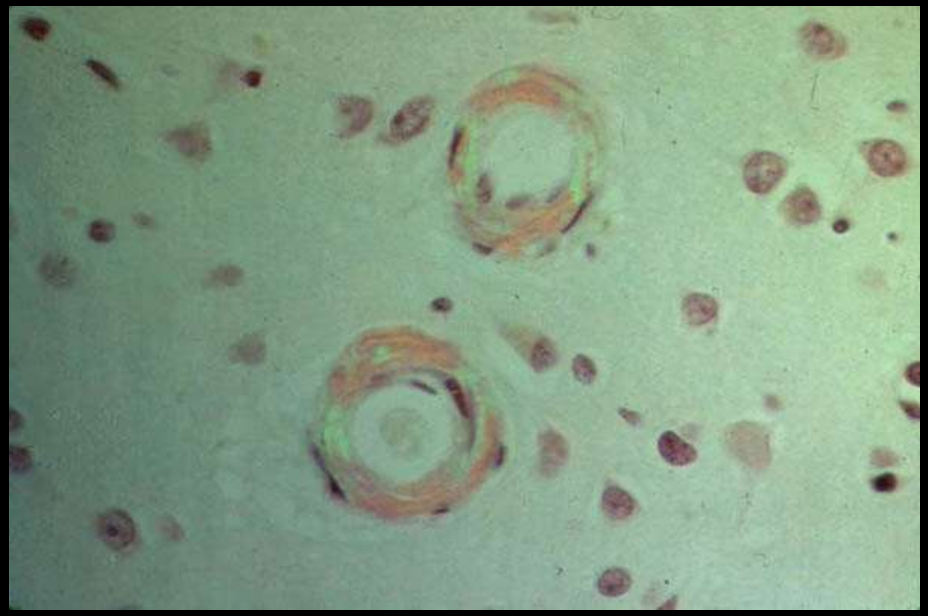
- 9 studies show restarting anticoagulation
  - Associated with less thrombosis
  - Associated with less mortality
  - Minimal increase in the risk of bleeding
  - Apixaban less bleeding
- Restart 7 days

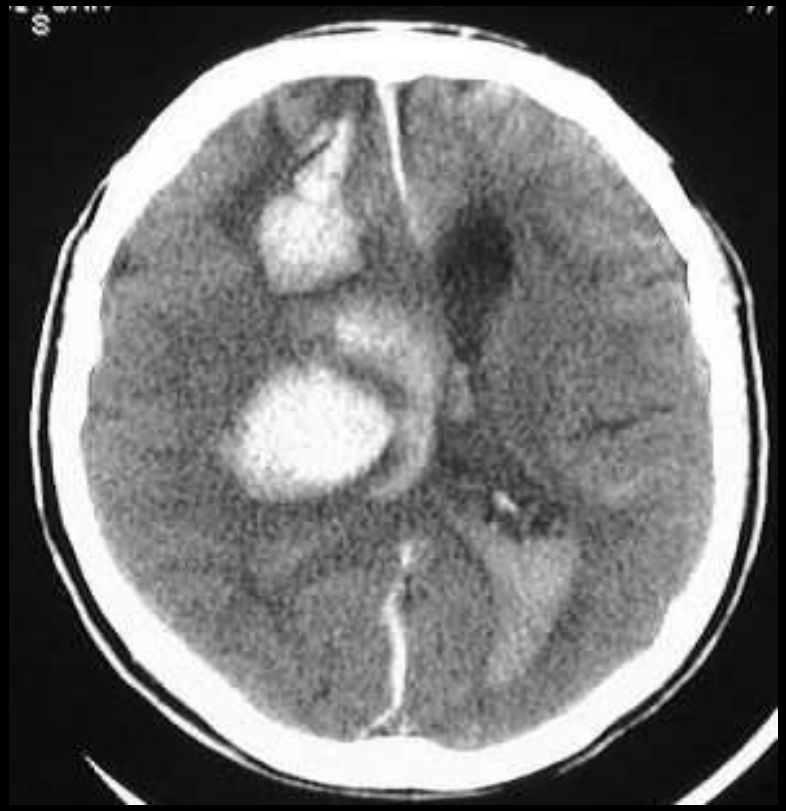
All GI bleeding patients needs work-up

Ann Pharmacother. 2017 Nov;51(11):1000-1007

CNS Bleeding

- Risk of rebleeding 1-2%
- Higher if lobar bleed
  - Cerebral amyloid angiopathy
- Increasing data that is better to restart anticoagulation





CNS Bleeding

Meta-analysis 10 studies

	Restart	Stop	HR
Death	18.7%	32.3%	0.51
Stroke	3.5%	7.0%	0.56
New ICH	6.7%	7.7%	NS

Thromb Res. 2017 Dec;160:97-104

Aspirin after ICH

- Not a substitute for anticoagulation
  - No affect on stroke rates
  - Increased risk of bleeding
- Nothing or anticoagulation

CNS Bleeding

- Unless evidence of CAA restart anticoagulation
- Apixaban may be safer
- No concurrent antiplatelet therapy
- Restart 7-14 days

DOAC Do's!

- Use in
  - High risk patients
  - Atrial fibrillation
  - Patients unstable INR
  - First line venous thrombosis/embolism
  - Cancer patients
  - Orthopedic prophylaxis

DOAC Don’ts!

- Don’t use wrong dose
- Don’t use with mechanical valves
- Don’t use in very obese patients