Reversal Agents for Anticoagulation Therapy

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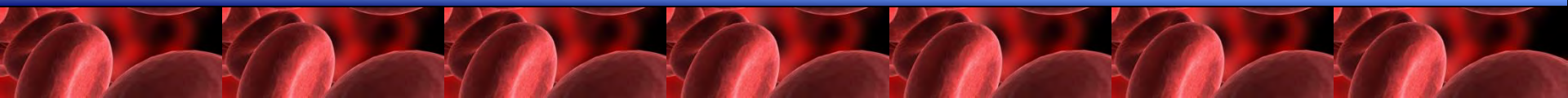
Joseph E. Kiss, MD
Professor of Medicine
Division of Hematology-Oncology
Department of Medicine
University of Pittsburgh School of Medicine
Medical Director
Clinical Apheresis and Blood Services
Vitalant Northeast Division
Pittsburgh, PA



DISCLOSURES

MEDICAL ADVISORY:

SANOFI-GENZYME
HAEMONETICS
ARGENYX
CME OUTFITTERS
GRIFOLS

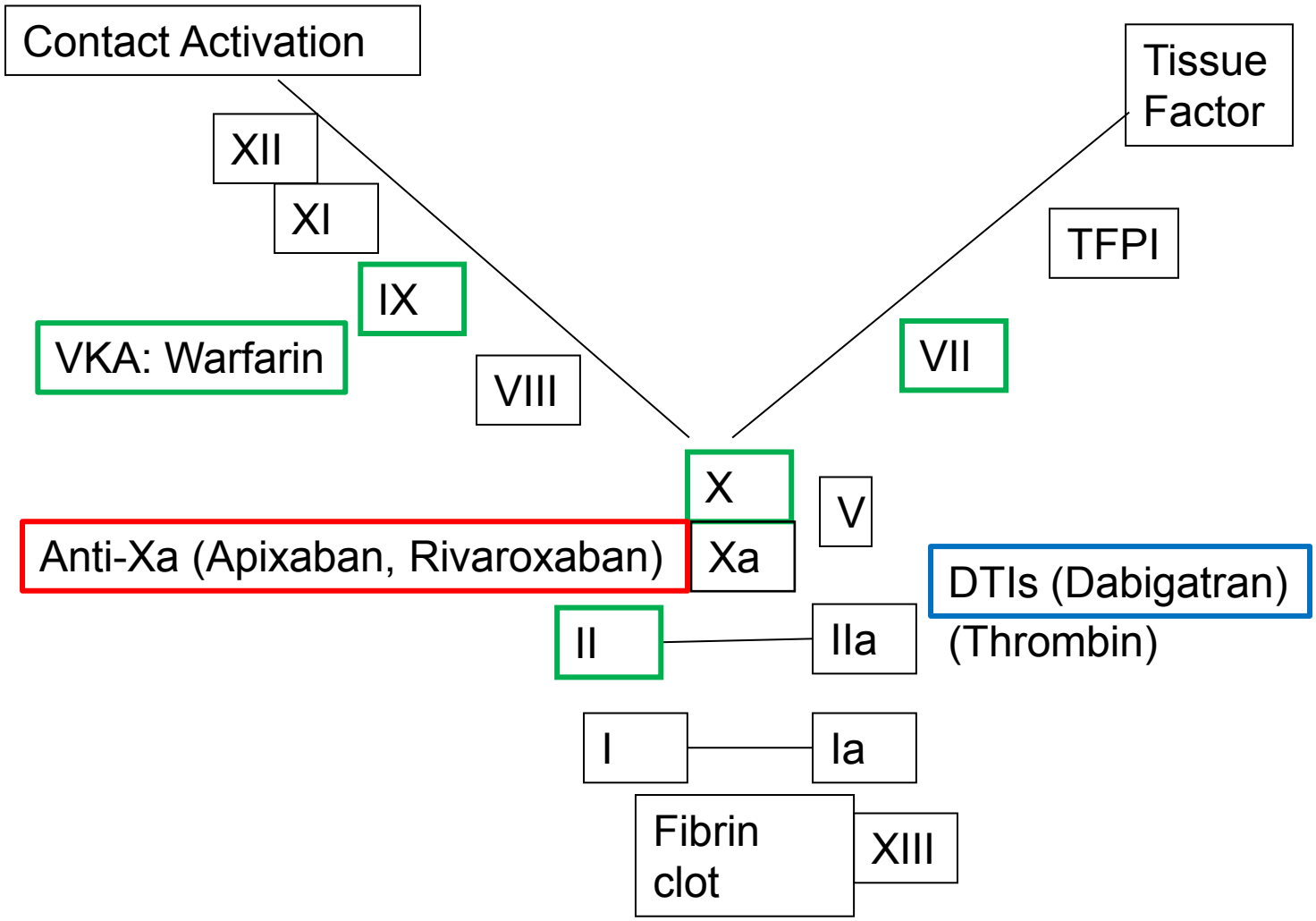
Discussion Topics

- Clinical assessment of major hemorrhage
- Clinical evaluation of residual anticoagulant effects
- Use(fulness) of laboratory assays
- When to initiate reversal?
- Review current products used in management of anticoagulant-associated hemorrhage/anticoagulant reversal

Introduction

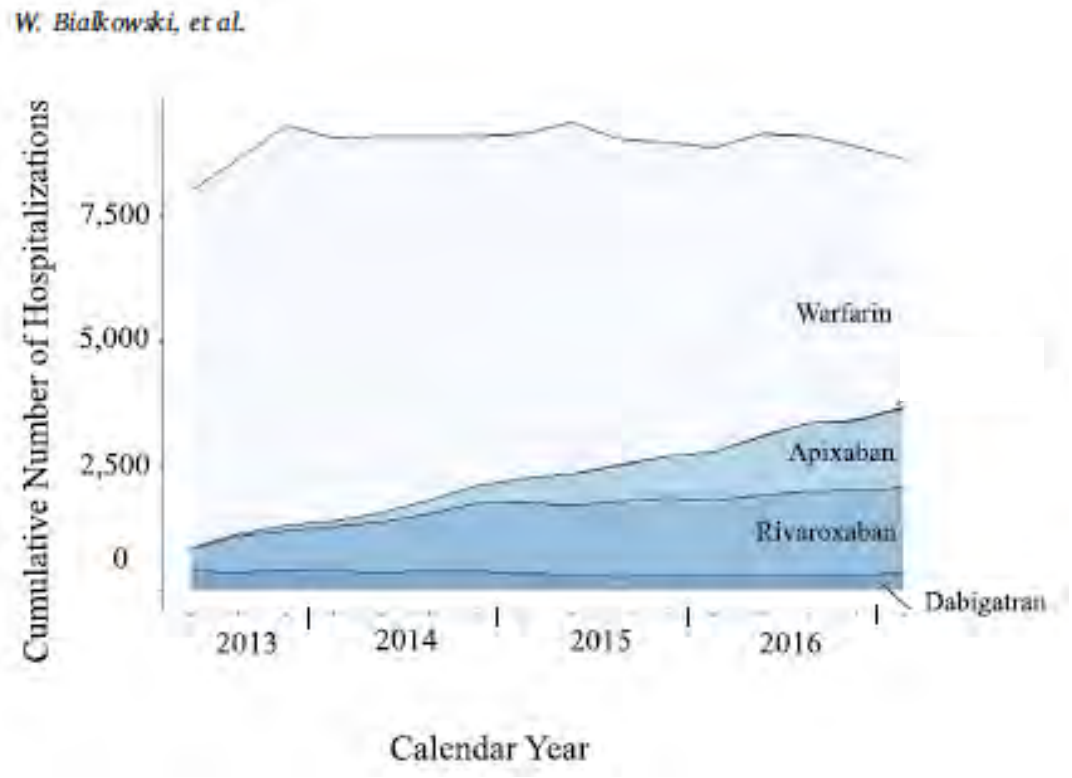
- Oral Anticoagulants (OACs)
  - Vitamin K Antagonists (VKAs): Warfarin
  - Direct OACs (DOACs): Dabigatran, Riveroxaban, Apixaban, Edoxaban, Betrixaban
- Increasing use, well over 6 million patients in 2018
- RCTs and Meta-analysis: Rates of major bleeding/mortality lower in DOACs than VKAs but still a significant clinical issue
  - 7.57% with DOACs
  - 11.05% warfarin

J Thromb Haemost. 2015;13:2012-20.



Sites of Action of OACs

NHLBI REDS-III Database OAC Usage Trends



Methods: More than 1.5 million hospitalizations were screened and 3731 patients with major hemorrhage were identified in the REDS-III Recipient Database. Propensity score matching and stratification were used to account for potentially confounding factors.

Thrombosis Research 185 (2020) 109–118

Assessment of Bleeding: Definitions

- Serious/Major: Interruption of AC
  - Significant blood loss resulting in hemodynamic instability, ≥ 2 g/dl drop in Hgb, or requiring ≥ 2 unit RBC transfusion
  - Critical site/Closed space bleeding
  - Intervention, eg., surgery, IR, endoscopy
- Minor clinically significant
  - Healthcare assessment, eg, ED visit
  - Often requires holding AC or dose adjustment but not AC reversal

Critical Sites, eg:
ICH, other CNS
Pericardium
Airway, posterior epistaxis
Neck
Hemothorax, Abd, Retroperitoneum
Extremity: Compartment, Joint

Clinical Assessment

- Risk stratification for bleeding severity
  - Bleeding site: Active?||Rate of bleeding?
  - Anticoagulant, last dose? Other medications (eg., antiplatelet) that affect hemostasis?
  - Co-morbidities, esp. renal disease, hepatic disease? Thrombocytopenia?
- Determine anticoagulation state: Interval since last dose and $t_{1/2}$ for drug
- What is indication for anticoagulant and impact of discontinuation?

OACs: Selected Pharmacokinetic Features

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Inhibition of VKOR	Direct thrombin inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible	Factor Xa inhibitor (free or bound), reversible
Onset of action	Slow, indirect inhibition of clotting factor synthesis	Fast	Fast	Fast
Offset of action	Long	Short	Short	Short
Absorption	Rapid	Rapid, acid-dependent	Rapid	Rapid
Bioavailability (%)	100	6.5	80*	50
t_{max} (h)	2.0-4.0	1.0-3.0	2.5-4.0	1.0-3.0
V_d (L)	10	60-70	50-55	21
Protein binding (%)	99	35	95	87
$t_{1/2\beta}$ (h)	40	12-17	9-13	8-15
Renal excretion	None	80	33	25
Fecal excretion	None	20	28	50-70

Canadian Journal of Cardiology 29 (2013) S24–S33

Residual Activity of DOACs (since last dose)

	Half-life, hrs (CrCl ≥ 50 ml/min, Normal Hepatic Fxn)	Times 5 Half-lives for Complete Reversal
Dabigatran	12-17	3 days
Riveroxaban	5-9	1-2 days
Apixaban	8-15	1.5-3 days
Edoxaban	6-11	1-2 days
Warfarin	N/A - Loss of effect depends on VKA clearance and Factor synthetic rates	5 days

OAC Non-urgent Reversal (no significant bleeding)

WARFARIN (DC drug)		
INR<4.5	INR ≥ 4.5 to < 10	INR ≥ 10
Omit dose; Adjust dose	Omit 1-2 doses; Adjust dose. If high bleeding risk, consider Low dose vit. K, 1-2.5 mg	Oral vitamin K 2.5-5.0 mg; If NPO, consider IV vitamin K 2.5-5.0 mg

Periprocedural Management: Assess Bleeding Risk*
Warfarin Minor surgery: Hold 2-3 days Major surgery: Hold 5 days
Dabigatran CrCl ≥ 50 mL/min: Hold 1-2 days CrCl ≤ 50 mL/min: Hold 3-5 days
Apixaban, Riveroxaban, Edoxaban Low bleeding risk: Hold at least 24 hrs Moderate/High bleeding risk: Hold at least 48 hours

Modified from:
ACCP Chest 2012;41:Suppl; e152s-e184s.

*Low risk procedures may not require holding AC: e. g., dental extraction, BMBx, cataract surgery, skin bx, etc.

Recommended Duration of Effect of AC Based on Bleeding Severity/Risk

	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	**≥80**	**50-79**	**30-49**	**15-29**	**<15**	**≥30**	**15-29**	**<15**
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥48 h.
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	48 h		No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥72 h.

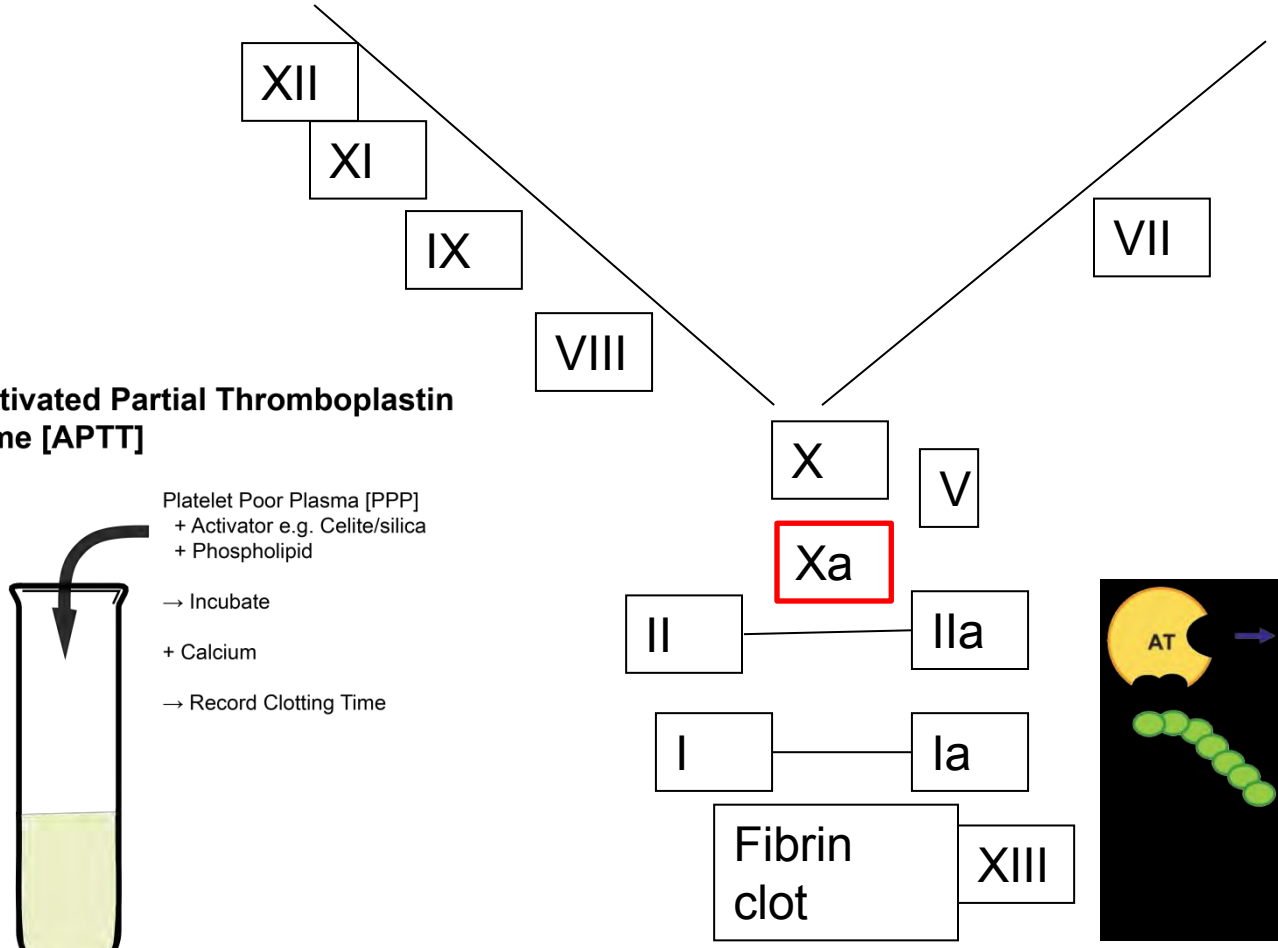
With adequate renal function, hemostatic risk is reduced within 1 or 2 days after discontinuation of drug

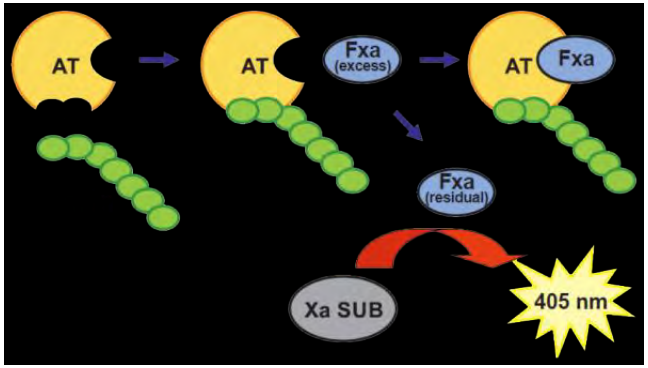
JACC VOL. 76, NO. 5, 2020
AUGUST 4, 2020:594-622

Primer on Laboratory Assays

- VKA: PT/INR
- DOACS: specialized testing is not routinely indicated
  - Check PT/INR/APTT, determine time since last dose, consider renal (and hepatic) function
- When to obtain specialized test: Does laboratory have validated or calibrated assays? If yes, consider-
  - Major Bleeding
  - Emergent invasive procedure/surgery
  - Absorption/GI issues
  - AKI/drug clearance uncertain

PT/aPTT vs Anti-Xa





Anti-Xa Assay (UFH or LMWH)

Max Lee, MD

Anti-Xa Assay for UFH or LMWH

https://blog.ucdmc.ucdavis.edu/labbestpractice/index.php/2017/10/16/anti-factor-xa-for-monitoring-of-unfractionated-heparin-therapy/

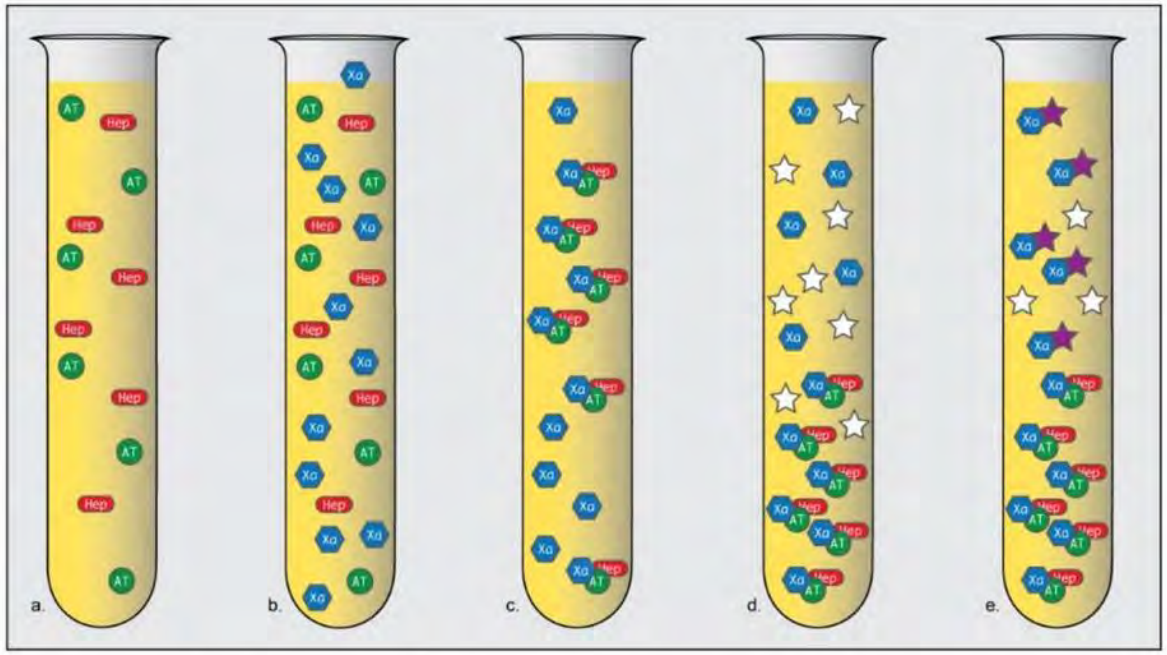


Figure 1: Overview of antifactor Xa test. A sample of heparinized patient platelet-poor plasma is obtained (a). A known amount of factor Xa is added to this sample (b) which enhances the binding of heparin and anti-thrombin (c). A chromogenic substrate is added (d) that binds to excess Xa (e), producing a color change that can be measured in a spectrophotometer. The color change is directly proportional to the amount of unbound Xa; from the degree of color change, the functional activity of heparin (inversely proportional to the color change) can be calculated. (Adapted from Mayo Medical Labs "Anti-Xa Assay for Heparin Monitoring [Hot Topic]"[4].)

And can be modified for other anti-Xa inhibitors, riveroxaban and apixaban

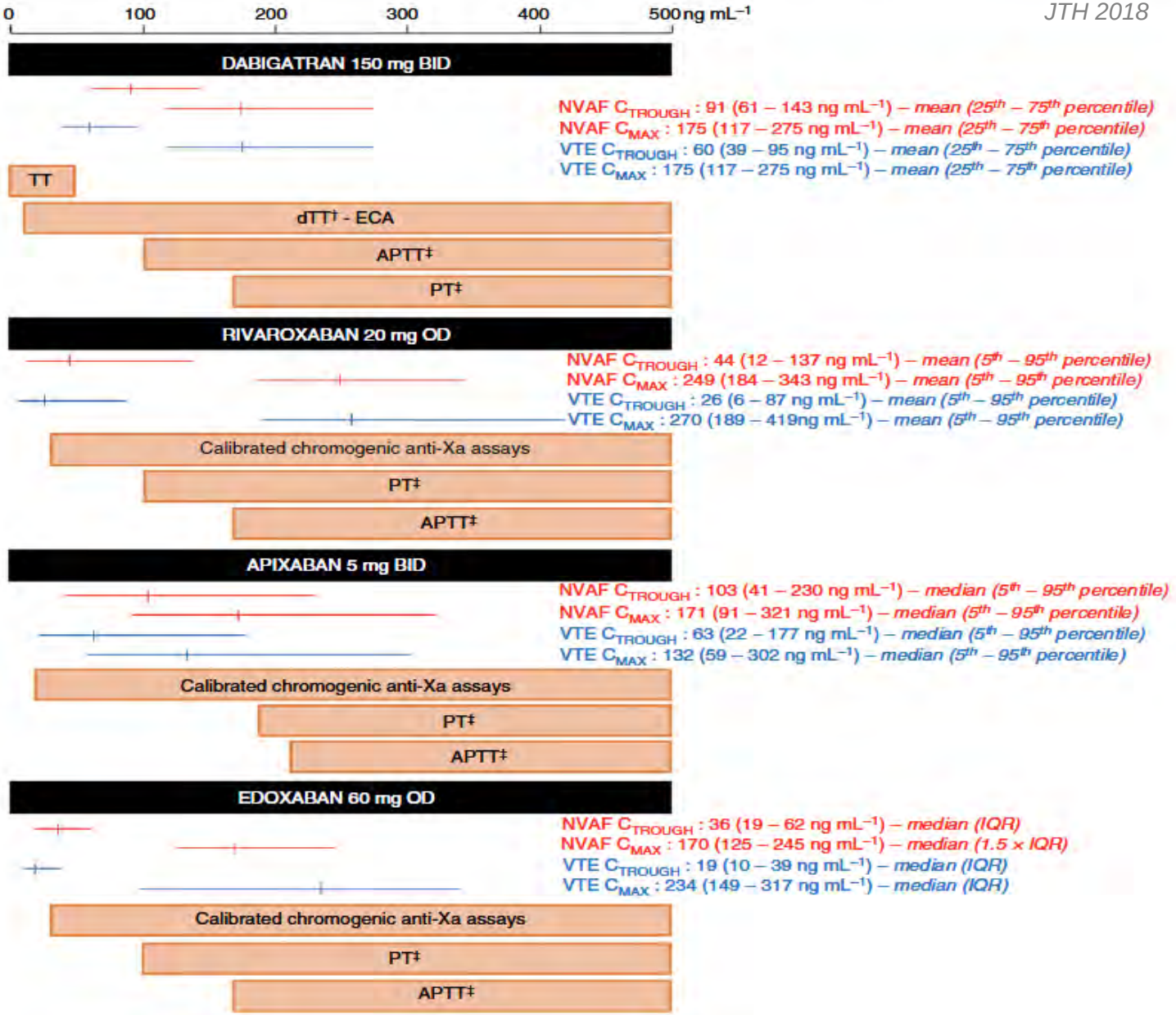
Max Lee, MD

Expected Effects of DOACS on Clinical Coagulation Test Results| Samuelson BT, et al.

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
PT/INR	↑	↑	↑↑	↑↑
APTT	↑↑	↑	↑	↑
TT	↑↑↑	–	–	–
dTT	↑↑↑	–	–	–
antiXa	–	↑↑↑	↑↑↑	↑↑↑

(d)TT– (dilute) Thrombin Time: Method of choice to quantify dabigatran
Anti-Xa: Method of choice to quantify anti-Xa inhibitors

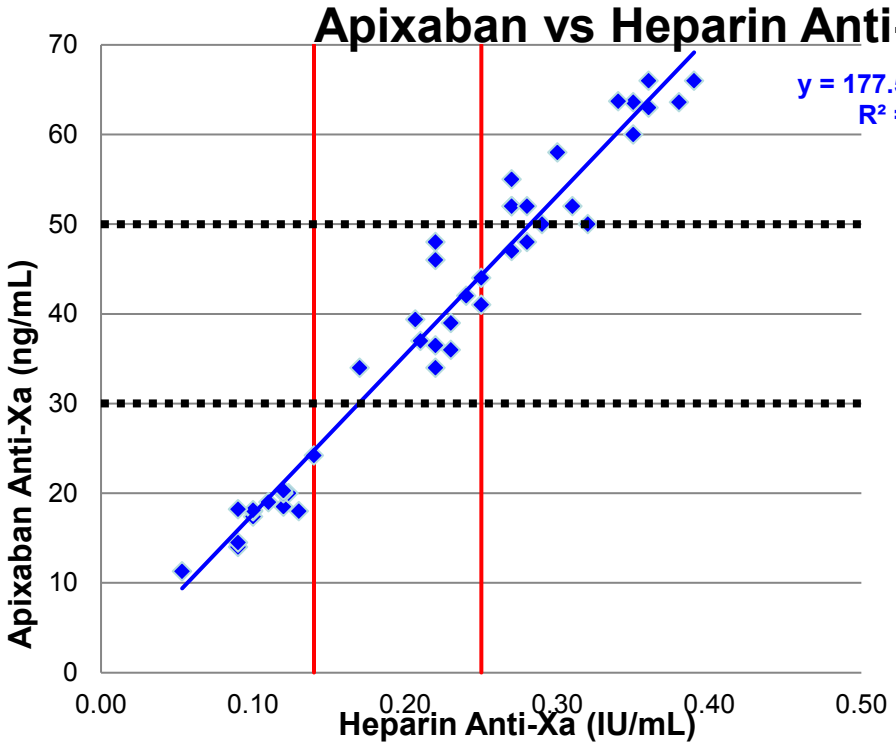
JTH 2018

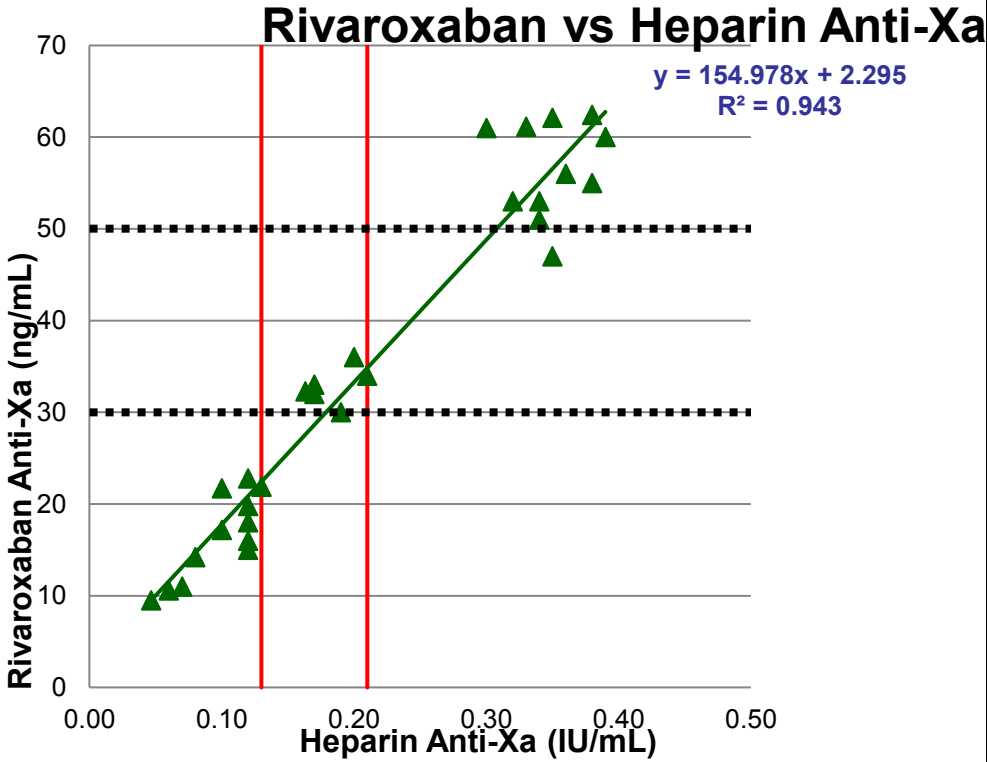

0
100
200
300
400
500 ng mL⁻¹
DABIGATRAN 150 mg BID
NVAF C_{TROUGH} : 91 (61 – 143 ng mL⁻¹) – *mean (25th – 75th percentile)*
NVAF C_{MAX} : 175 (117 – 275 ng mL⁻¹) – *mean (25th – 75th percentile)*
VTE C_{TROUGH} : 60 (39 – 95 ng mL⁻¹) – *mean (25th – 75th percentile)*
VTE C_{MAX} : 175 (117 – 275 ng mL⁻¹) – *mean (25th – 75th percentile)*
TT
dTT† - ECA
APTT‡
PT‡
RIVAROXABAN 20 mg OD
NVAF C_{TROUGH} : 44 (12 – 137 ng mL⁻¹) – *mean (5th – 95th percentile)*
NVAF C_{MAX} : 249 (184 – 343 ng mL⁻¹) – *mean (5th – 95th percentile)*
VTE C_{TROUGH} : 26 (6 – 87 ng mL⁻¹) – *mean (5th – 95th percentile)*
VTE C_{MAX} : 270 (189 – 419ng mL⁻¹) – *mean (5th – 95th percentile)*
Calibrated chromogenic anti-Xa assays
PT‡
APTT‡
APIXABAN 5 mg BID
NVAF C_{TROUGH} : 103 (41 – 230 ng mL⁻¹) – *median (5th – 95th percentile)*
NVAF C_{MAX} : 171 (91 – 321 ng mL⁻¹) – *median (5th – 95th percentile)*
VTE C_{TROUGH} : 63 (22 – 177 ng mL⁻¹) – *median (5th – 95th percentile)*
VTE C_{MAX} : 132 (59 – 302 ng mL⁻¹) – *median (5th – 95th percentile)*
Calibrated chromogenic anti-Xa assays
PT‡
APTT‡
EDOXABAN 60 mg OD
NVAF C_{TROUGH} : 36 (19 – 62 ng mL⁻¹) – *median (IQR)*
NVAF C_{MAX} : 170 (125 – 245 ng mL⁻¹) – *median (1.5 x IQR)*
VTE C_{TROUGH} : 19 (10 – 39 ng mL⁻¹) – *median (IQR)*
VTE C_{MAX} : 234 (149 – 317 ng mL⁻¹) – *median (IQR)*
Calibrated chromogenic anti-Xa assays
PT‡
APTT‡

Primer on Laboratory Assays, cont.

- What to monitor: DTI || Dabigatran
  - Normal aPTT likely excludes excess level
  - Normal TT excludes clinically relevant level
  - Only dTT correlates with plasma concentration
- What to monitor: Anti-Xa || Rivaroxaban, Apixaban, Edoxaban
  - Prolonged PT indicates drug presence
  - Normal (subtherapeutic) anti-Xa level for UFH (validated in laboratory) excludes clinically relevant level
  - Only calibrated anti-Xa correlates with plasma concentration

++Normal PT/aPTT does not exclude clinically significant drug level++

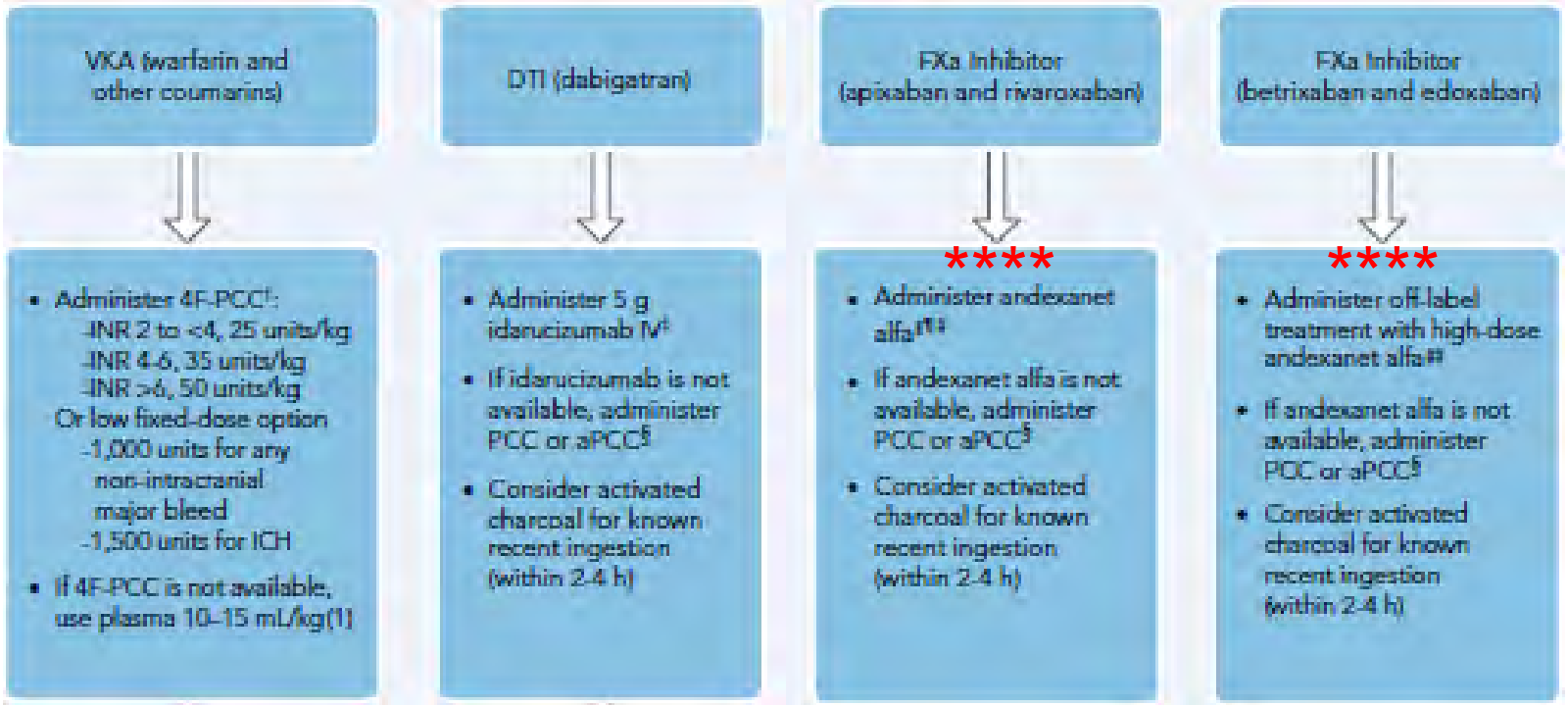




Data from J. Seheult, MD

Hemostatic Reversal Agents:

4F-Prothrombin Complex Concentrate (4F-PCC) – Contains FII, VII, IX, X
Idarucizumab – Moab binds dabigatran
Andexanet – FXa decoy – neutralizes antiXa



**** Andexanet requires Neurosurgery or Neurology approval per UPMC P & T Committee Policy

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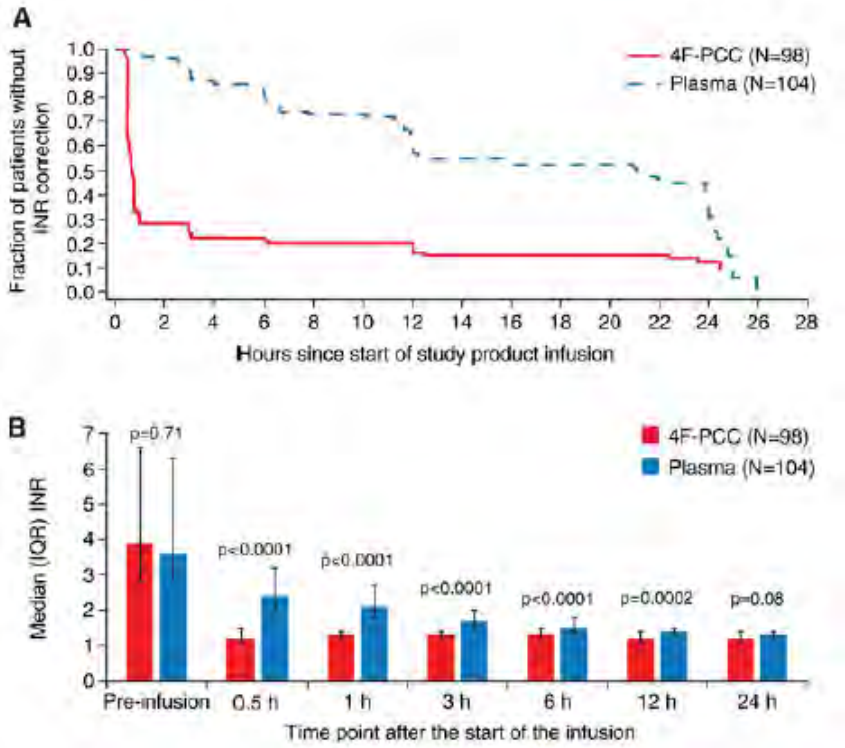
AUGUST 4, 2020:594–622

INR



4-Factor PCC vs. Plasma in Major Bleeding – Sarode, et al.

Circulation. 2013 September 10; 128(11): 1234–1243.

Hemostatic Efficacy by Time of Rating (Post Hoc Analysis; Intention-to-Treat Efficacy Population)

	Treatment Group		Difference 4F-PCC Minus Plasma, % (95% CI)*
	4F-PCC (n=98)	Plasma (n=104)	
No. of bleeds assessed for hemostatic efficacy at 4 h (visible, musculoskeletal)	23	28	
No. (%) of patients with effective hemostasis	19 (82.6)	14 (50.0)	32.6 (4.5 to 60.7; P=0.0200)
No. of bleeds assessed for hemostatic efficacy at 24 h (gastrointestinal, intracranial, other nonvisible)	75	76	
No. (%) of patients with effective hemostasis	52 (69.3)	54 (71.1)	−1.7 (−17.6 to 14.2; P=0.95)

4F-PCC indicates 4-factor prothrombin complex concentrate; and CI, confidence interval.

Idarucizumab: A Specific Monoclonal Antibody Reversal Agent for Dabigatran: Reverse AD

Table 2. Indications for Dabigatran Reversal.

Indication	Group A (N=301)*
	no. of patients (%)
Bleeding	
Intracranial	98 (32.6)
Subdural	39 (13.0)
Subarachnoid	26 (8.6)
Intracerebral	53 (17.6)
Gastrointestinal	137 (45.5)
Lower	47 (15.6)
Upper	52 (17.3)
Unknown	42 (14.0)
Intramuscular	9 (3.0)
Retroperitoneal	10 (3.3)
Intrapericardial	7 (2.3)
Intraarticular	5 (1.7)
Intraocular	1 (0.3)
Other	52 (17.3)
Not identified	4 (1.3)
Trauma-related	78 (25.9)
	Group B (N=202)†
Reason for procedure‡	
Abdominal condition or infection: hernia, peritoneal infection	49 (24.3)
Fracture or septic arthritis: involvement of the hip or femur	41 (20.3)
Cardiovascular condition: pacemaker implantation, aneurysm repair	37 (18.3)
Central nervous system condition: craniotomy	17 (8.4)
Pancreatic or hepatobiliary disease: cholecystitis, cholangitis	14 (6.9)
Respiratory condition: chest trauma	14 (6.9)
Kidney and urinary tract condition: acute renal failure	11 (5.4)
Septicemia or sepsis	8 (4.0)
Skin condition: abscess, hematoma	6 (3.0)
Postoperative complications	3 (1.5)
Uterine condition	1 (0.5)
Poisoning: deliberate overdose	1 (0.5)

* Patients may have had more than one type of bleeding.
† Procedure was canceled for five patients.
‡ For some categories, frequent events are listed as examples.

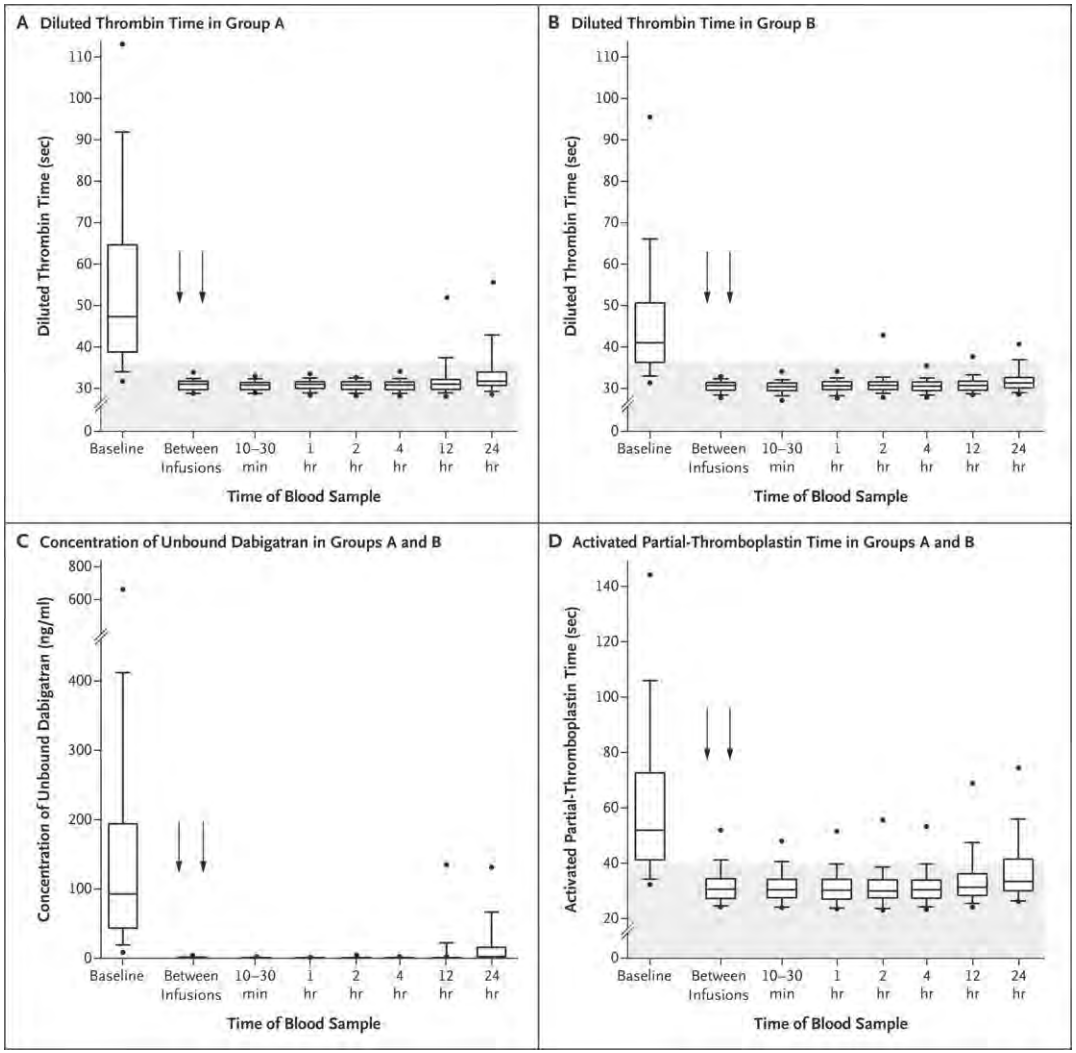
Pollack CV Jr et al. N Engl J Med 2017;377:431-441

OUTCOMES:
GROUP A. Median time to the cessation of bleeding in ICH & GIB was 2.5 hours

GROUP B. Median time to the initiation of the intended procedure was 1.6 hours; Periprocedural hemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%

The NEW ENGLAND JOURNAL of MEDICINE

Idarucizumab: Key Measurements Before and After Administration



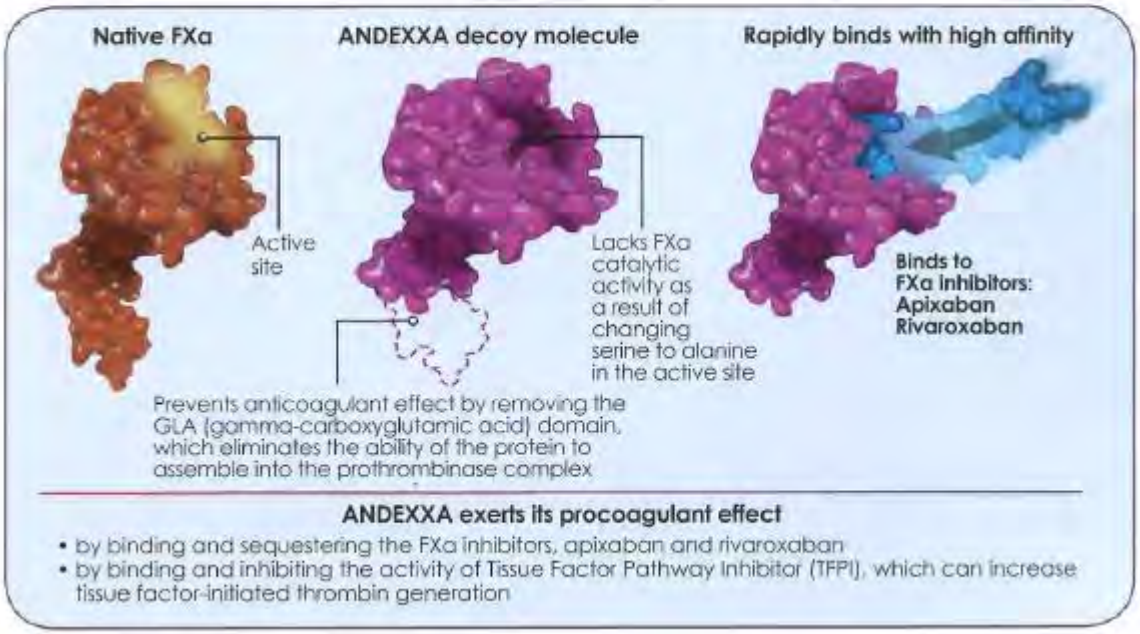
Pollack CV Jr et al. N Engl J Med 2017;377:431-441

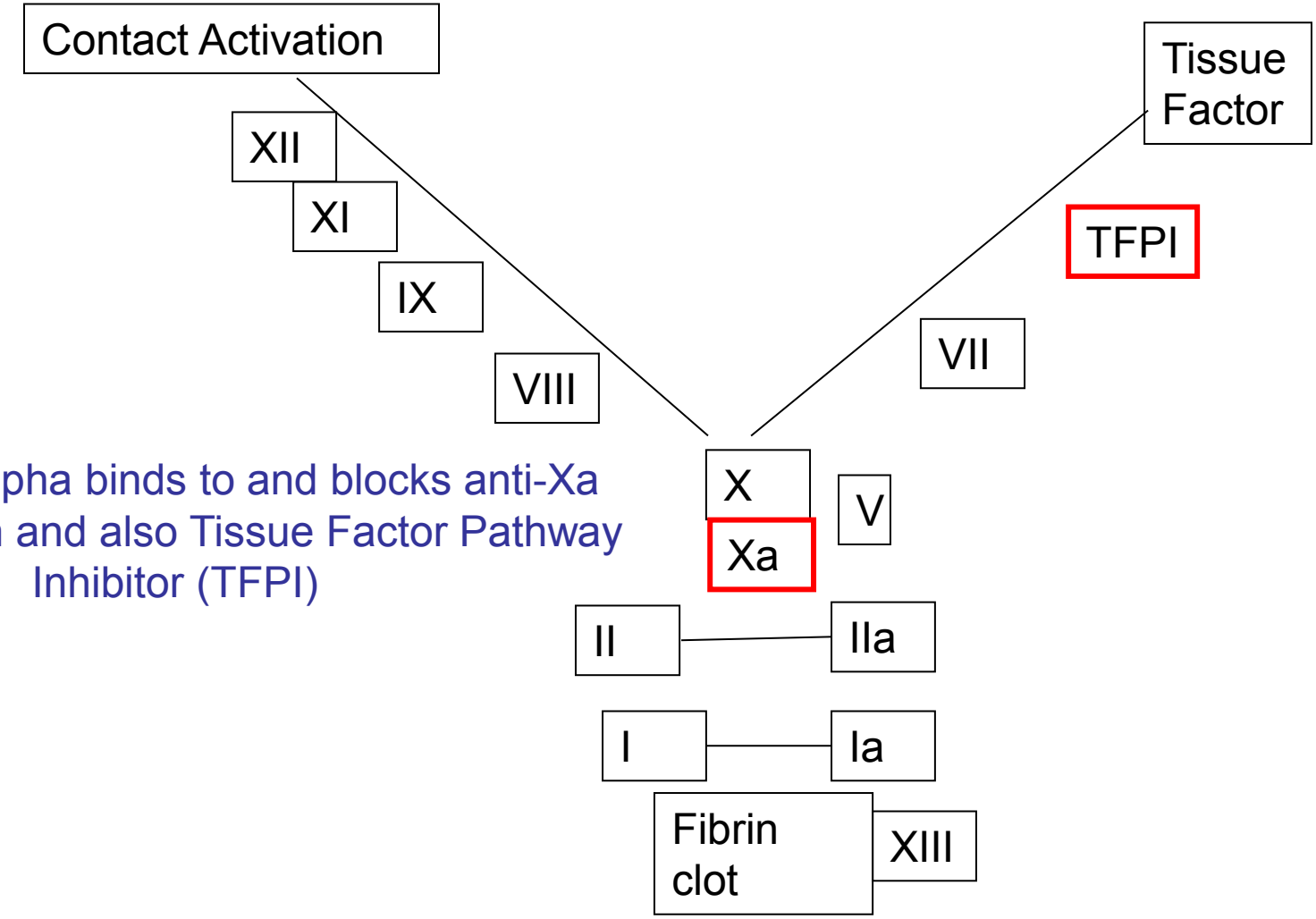
The NEW ENGLAND JOURNAL of MEDICINE

Andexanet alpha: Specific Anti-Xa Reversal Agent

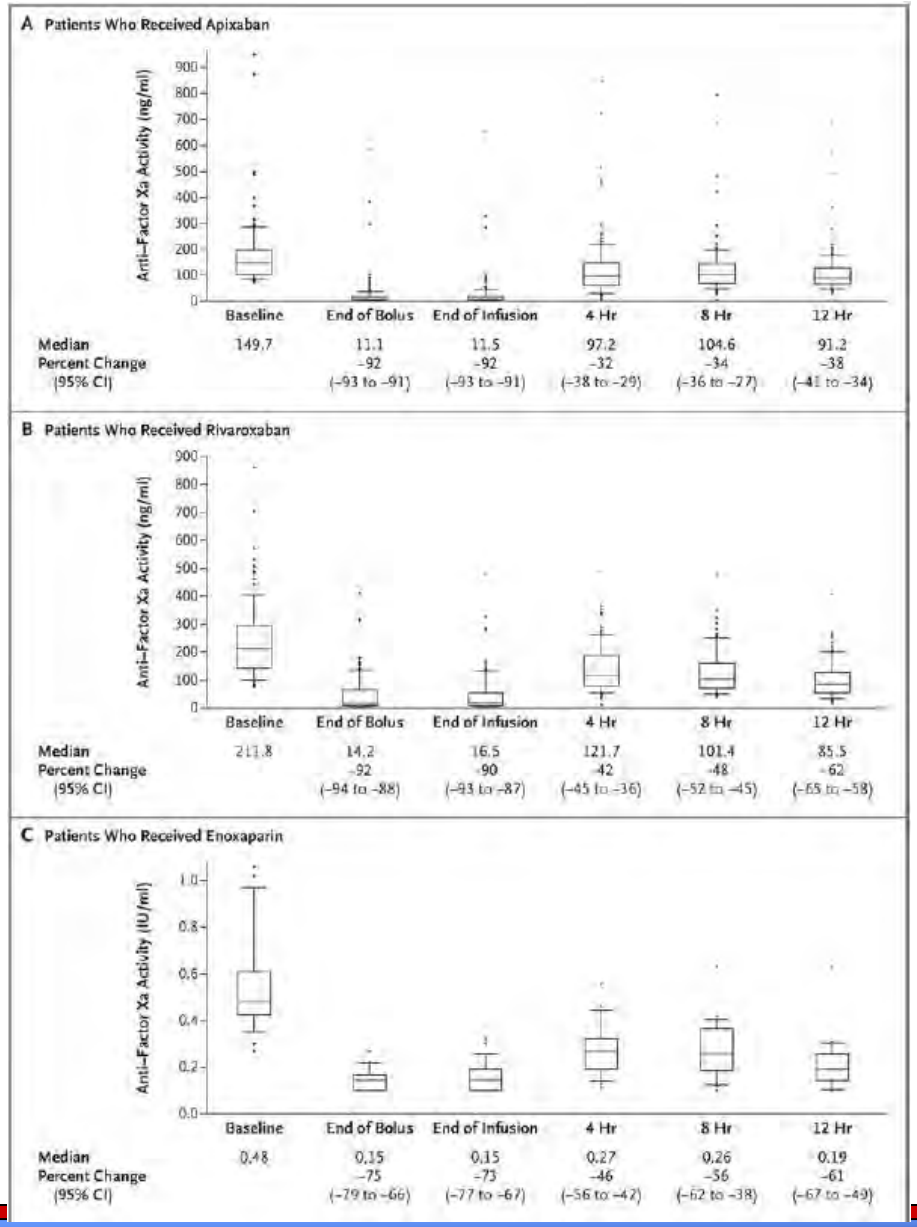
ANDEXXA® is a modified recombinant FXa protein that binds to circulating FXa inhibitors[1]

ANDEXXA acts as a FXa decoy[1,2]





Andexanet alpha binds to and blocks anti-Xa inhibitor action and also Tissue Factor Pathway Inhibitor (TFPI)

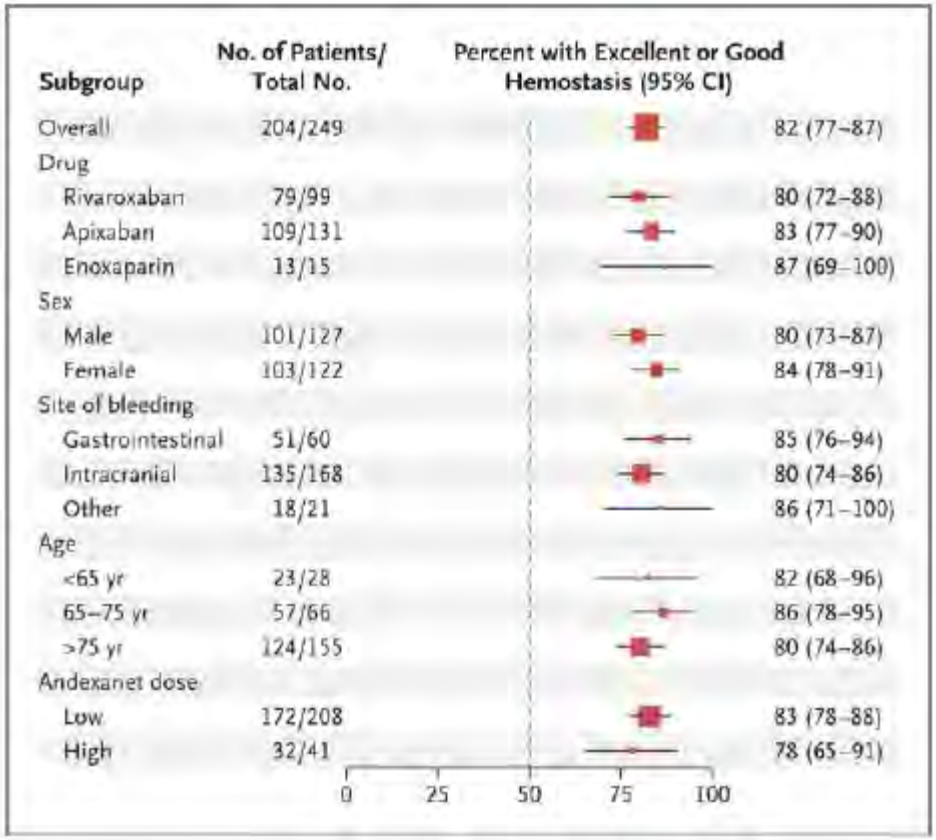


Andexanet alpha for Bleeding and anti-Xa Inhibitors: ANNEXA-4 Connolly SJ, et al.

- **Administration of the bolus dose resulted in reversal of anti-factor Xa activity for 2-4 hours**
- **Inhibition of TFPI activity sustains for ~22 hours after bolus administration**

N Engl J Med. 2019 April 04; 380(14): 1326–1335. doi:10.1056/NEJMoa1814051.

Andexanet alpha for Bleeding and anti-Xa Inhibitors: ANNEXA-4 Connolly SJ, et al.



N Engl J Med. 2019 April 04; 380(14): 1326–1335. doi:10.1056/NEJMoa1814051.

OAC Reversal: Summary of Options

Reversal Agent	Warfarin	Dabigatran	Direct anti-Xa inhibitors
4F-PCC (F II, VII, IX, X)	**1st line**	2nd line	2nd line
Idarucizumab	Not indicated	**1st line**	Not indicated
Andexanet	Not indicated	Not indicated	**1st line***
aPCC (F II, VIIa, IX, X)	Not indicated	3rd line	3rd line
Plasma	If 3F or 4F-PCC not available	Not indicated	Not indicated

4F, four factor; 3F, 3 factor; PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate

*Note only approved for rivaroxaban and apixaban

Modified from Tomaselli et al, J Am Coll Cardiol. 2017;70:3042-67.

DOAC Reversal using PCCs

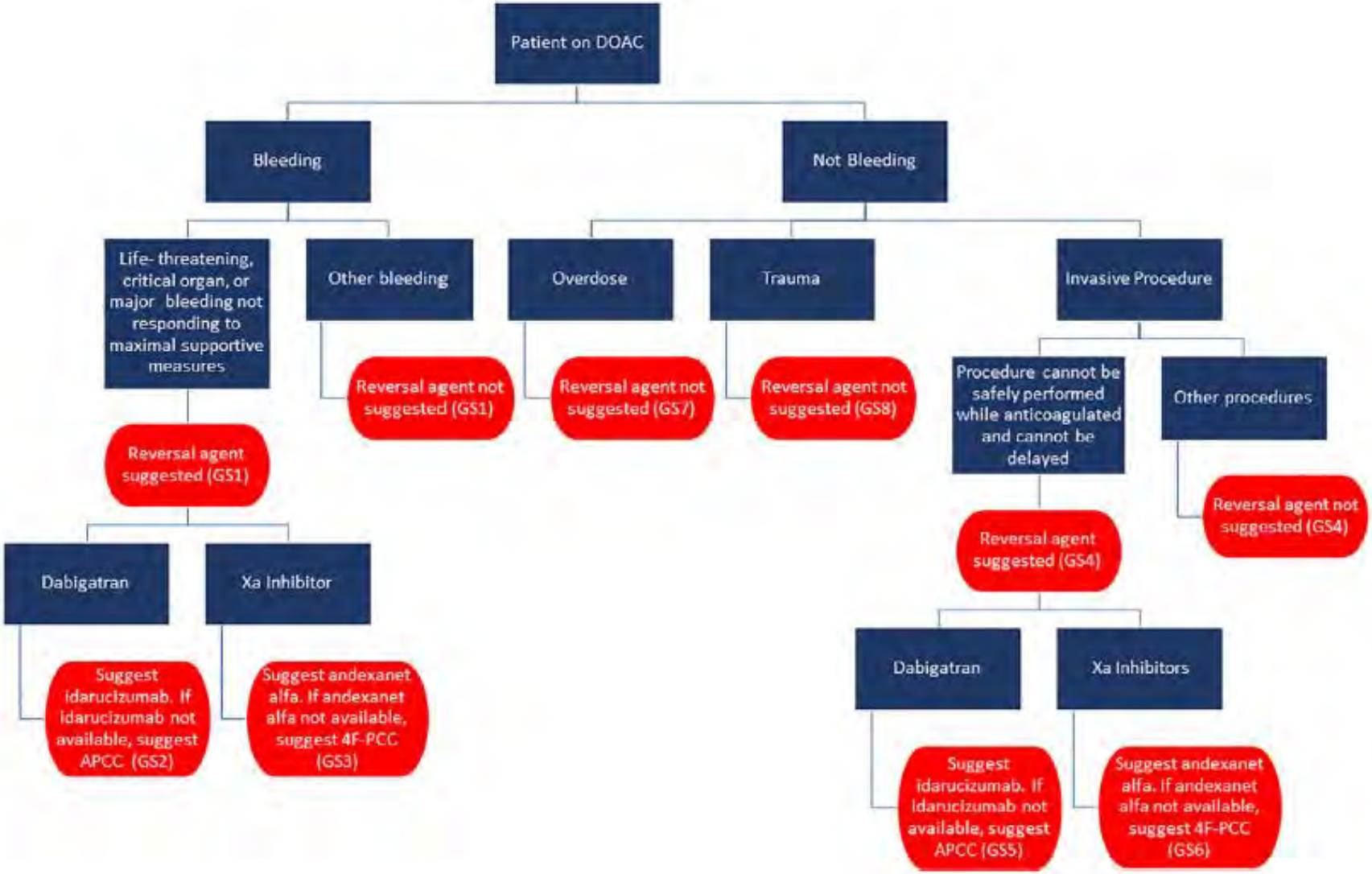
- Meta-analysis PCCs for direct FXa reversal
  - 10 studies, 340 patients
  - Effective management outcome of major bleeding in 69% compared to 83% ANNEXA-4 trial using andexanet
  - Conclusion: Quality of studies…makes it difficult to determine whether 4F-PCC in addition to cessation of direct oral FXa inhibitor is more effective than cessation of direct oral FXa inhibitor alone in patients with direct Fxa inhibitor–related major bleeding.

blood advances 22 JANUARY 2019 · VOLUME 3, NUMBER 2

Activated Prothrombin Complex Concentrate (aPCC) ("FEIBA")

- **Warnings/Precautions:** Increased risk of thromboembolic events esp. after high-doses (>200units/kg/day) and/or in patients with thrombotic risk factors (eg, DIC, atherosclerosis, crush injury, septicemia, concomitant recombinant factor VIIa).
- Monitor patients receiving doses >100units/kg for DIC development, acute coronary ischemia, and signs/symptoms of other thromboembolic events; discontinue if occurs and treat.

DOAC Management Guidance from the "Anticoagulation Forum"



Am J Hematol. 2019;94:697–709.

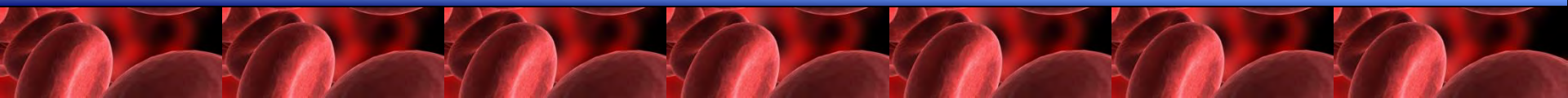
Summary: Reversal of OACs

- For major hemorrhage
  - Stop AC and initiate measures to control bleeding source
  - Assess anticoagulant effect (interval since last dose), clinical risk, and coagulation tests

    2020 ACC: “For dabigatran, nl TT **or aPTT** usually excludes clinically relevant levels if sensitive reagents are used. Ant-Xa levels (general or drug specific) can be used to exclude clinically relevant levels for Factor Xa inhibitors”
- Specific anticoagulant reversal should be administered for life-threatening hemorrhage and considered for major bleeding that does not resolve with initial management
- Once bleeding is controlled, timely assess when/whether to restart anticoagulation

Thank you!

jkiss@itxm.org




vitalant
GIVE BLOOD
Save the Humans