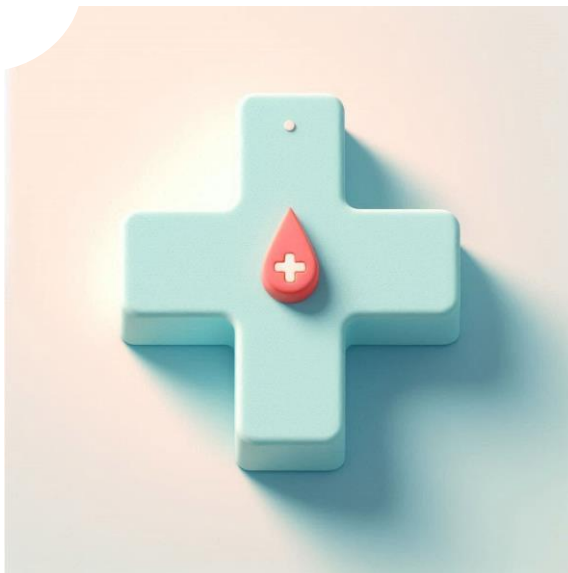
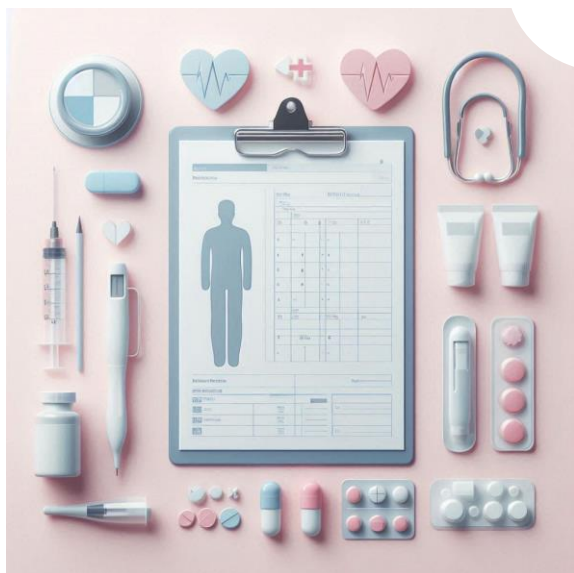




Division of
HEMATOLOGY
Department of Medicine
Phramongkutklao Hospital

Managements of Anticoagulant-associated Bleeding

Rattapan Lamool B Pharm MD

Division of Hematology Department of Medicine

Phramongkutklao Army Hospital and College of Medicine

Introduction

- Bleeding is the dominant adverse event of any anticoagulant.
- Clinical effects of bleeds
 - Deter patients and physician from initiating anticoagulants (despite very high-risk of stroke)
 - Reduced quality of life
 - Time-consuming and cost increments
- Bleeding in patients with AF differ from VTE regarding risk factors.
- Annual rate of VKA-related major hemorrhage is around 1.7% - 3.4%.

Introduction

- Increased risk for bleeding with decreasing renal function reported for dabigatran and VKAs.
- Most common major bleeding is gastrointestinal tract (in AF, more frequent in rivaroxaban and dabigatran than VKAs).
- 50% reduction of ICH and fatal bleeds with DOACs compared with VKAs in AF patients (2 cranial bleeds and 1 fatal bleed per 1000 patients per year).

Indication	No. of trials	Type of major bleed	VKA	DOAC
Atrial fibrillation	4	All major bleeds	1769	2091
		Gastrointestinal	583 (33%)	1005 (48%)
		Intracranial	425 (24%)	272 (13%)
VTE treatment	7	All major bleeds	263	161
		Gastrointestinal	83 (32%)	50 (31%)
		Intracranial	45 (17%)	17 (11%)

Initial Assessment

- Crucial for treatment decisions to achieve hemostasis and preserve organ function.
- Assessing bleed severity: major or non-major bleeds
- Additional information
 - Time of ingestion of last dose
 - Comorbidities and concomitant treatments that contribute to bleeding (e.g. concurrent anti-thrombotic agents, thrombocytopenia, renal and hepatic functions)

Criteria of Major Bleeding

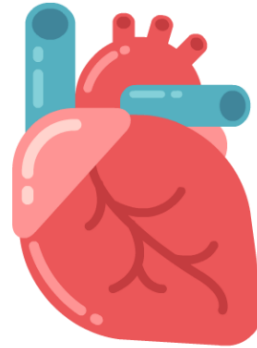
Classification	ISTH	TIMI (non-CABG)	GUSTO	BARC
Major bleed	- Fatal bleed or - Symptomatic plus critical organ or - Hb drop ≥ 2 g/dL or transfusion of ≥ 2 units of RBCs	- Fatal bleed or - Overt or intracranial bleed with Hb drop ≥ 5 g/dL or Hct drop $\geq 15\%$	Intracranial or bleed with bleed with hemodynamic compromise and requires intervention	- Type 5: fatal bleed - Type 4: CABG-related - Type 3: overt bleed plus Hb drop ≥ 3 g/dL or any transfusion or requiring interventions or intracranial/intraocular bleed - Type 2: overt, actionable sign of hemorrhage
Clinically relevant non-major bleeding (CRNMB)	Bleed requiring medical intervention	- Minor: clinically overt bleed plus Hb drop 3 - <5 or Hct drop 10 – $<12\%$ - No observed blood loss: Hb drop ≥ 4 g/dL or Hct drop $\geq 12\%$ - Overt bleed requiring intervention	Moderate: requires blood transfusion (no hemodynamic compromise)	Type 2: any overt, actionable sign of hemorrhage plus requiring intervention or hospitalization
Minimal	Not defined	Overt bleed plus Hb drop < 3 g/dL or Hct drop $< 10\%$	Mild: bleeding that does not meet criteria above	Type 1: bleeding that is not actionable

Criteria of Major Bleeding in Clinical Practice



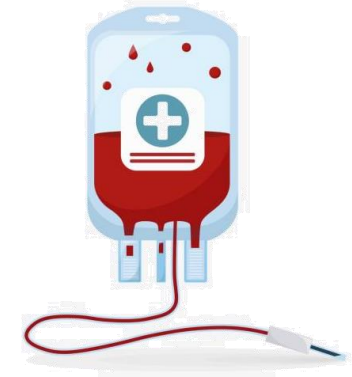
Hemodynamic instability

- Non-invasive: SBP < 90 mmHg or decrease > 40 mmHg, orthostatic BP changes, or signs of poor organ perfusion
- Invasive: MAP < 65 mmHg



Bleeding in critical site

- Compromised the organ's function, cause severe disability, or necessitate surgical procedures
- CNS bleeds (include spinal and ocular), thoracic (include posterior epistaxis), pericardial, intra- or retroperitoneal bleeds, intraarticular bleeds, and intramuscular bleeds
- **Intraluminal GI bleeding is not considered a critical site.**



Overt bleeding with

- Hemoglobin drop ≥ 2 g/dL or
- Administration of ≥ 2 units of packed RBCs

Managements of Anticoagulant-Associated Bleeding

- **Supportive measures in all patients**

- Discontinuation of anticoagulant and other medications affected hemostasis
- Compression or procedural management
- Volume resuscitation and transfusion support
- Correction of metabolic disturbances⁽²⁾ e.g. hypothermia, acidosis, hypocalcemia etc.
- Others: antifibrinolytic agents for traumatic patients (early administration within the first 3 hours) or mucosal bleeding or activated charcoal (for recent ingestion (2 – 4 hours) of DOACs)⁽²⁾

- **Reversal agents in selected patients**

- Specific agents: protamine sulfate, idarucizumab, andexanet alfa, and cirapartag
- Non-specific prohemostatic agents: prothrombin complex concentrate (PCC) and activated PCC (APCC)

Fluid Resuscitation and Transfusion Support



Fluid resuscitation

- Resuscitation with isotonic crystalloids (NSS or RLS).
- Aggressive fluid resuscitation may be given potential complications esp. patients with variceal bleeding.

Transfusion support

- Restrictive strategy to maintain Hb ≥ 7 g/dL (or ≥ 8 g/dL in patients with underlying CVDs).
- Maintain platelets $\geq 50 \times 10^9$ /L and fibrinogen > 100 mg/dL
- Activation of massive transfusion protocol for patients requiring > 3 units of RBCs within 1 hour.



Reversal Management

- Reasonable to consider specific reversal agent than non-specific hemostatic agents.⁽¹⁾
- Many patients with DOAC-associated bleeding do not require reversal agents and may be managed with supportive measure alone.⁽²⁾
- Both criteria are required for administration of reversal agent (except supratherapeutic INR in VKAs).
 - **Major bleeding:** life-threatening, critical organ, or is not controlled with maximal supportive measures
 - Demonstration or reasonable expectation of **clinically relevant drug levels**

Measurement of Coagulation Activity: Laboratory

- Laboratories: qualitative assays (for emergency conditions) and quantitative assays (for drug monitoring)
- Basic coagulation tests (PT and PTT) should be requested in all patients.
- Specialized coagulation tests are usually not widely available and non-practical in emergency conditions.
- Measurement of the anticoagulation activity of DOACs is more complex.
 - Usually not available.
 - Basic coagulation tests have insufficient sensitivity.
 - The minimum level that may contribute to bleeding or surgical bleeding risk is unknown.

Measurement of Coagulation Activity: Laboratory

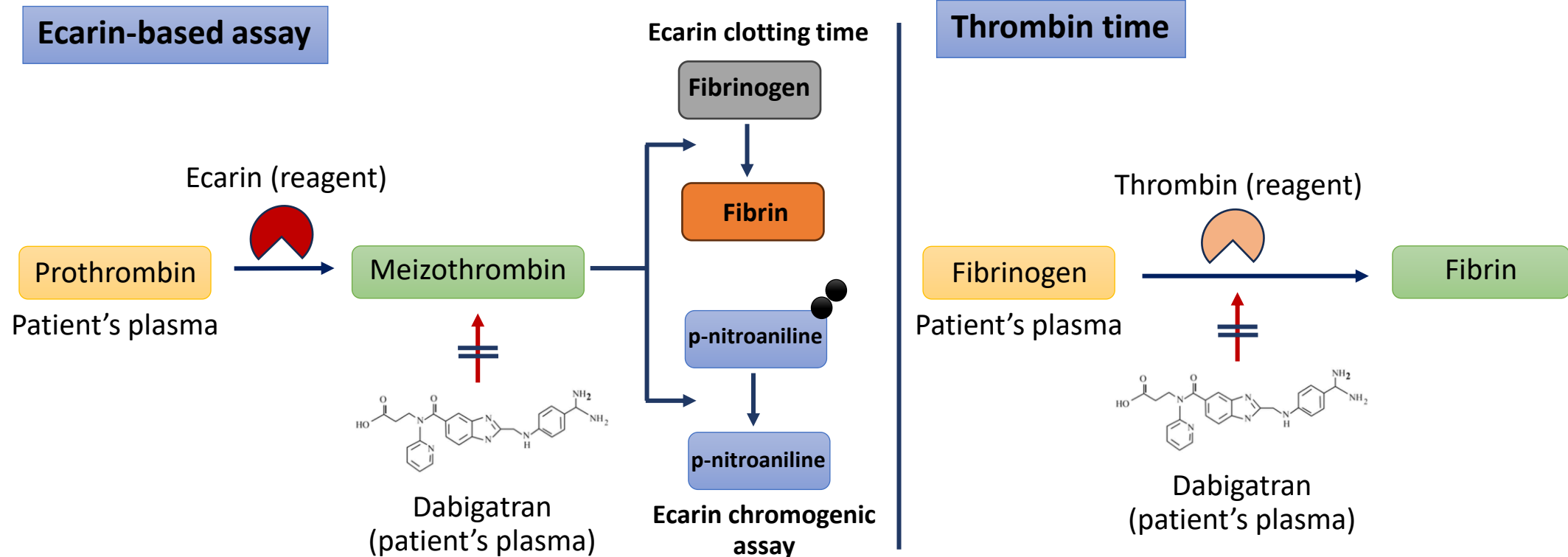
Direct thrombin inhibitor and conventional test (in normal renal function)

	On therapy	Above on therapy	Comment
PT	Usually unaffected	Will be prolonged	Depending on reagent's sensitivity
aPTT	Often prolonged	Always prolonged	- Often prolonged at the peak - At trough, likely to prolong if reagent is sensitive to dabigatran - Normal aPTT does NOT RULE OUT clinically relevant drug level
Thrombin time (TT)	Always prolonged	Always prolonged	Extremely sensitive, normal TT can confidently RULE OUT the presence of significant amount

- Normal thrombin time is safe for surgery.
- Major bleeding with prolonged TT and aPTT, idarucizumab may be considered; in the setting of prolonged TT and normal aPTT (esp. normal renal function), supportive care can be provided.

Measurement of Coagulation Activity: Laboratory

- **Specific measurements:** LCMS, ecarin venom-based assay, and dilute thrombin time (dTT) which measure accurate dabigatran concentrations (ng/mL)



Measurement of Coagulation Activity: Laboratory

Direct FXa inhibitor and conventional test (in normal renal function)

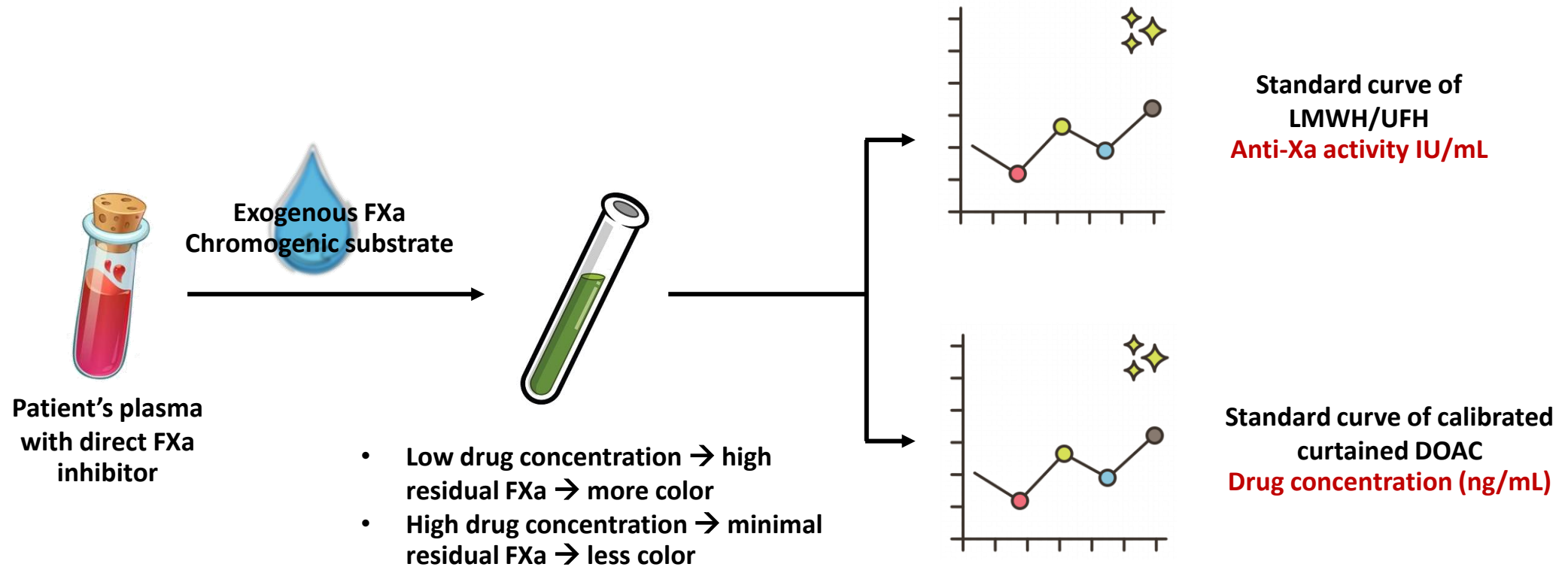
	On therapy	Above on therapy	Comment
PT	Variably prolonged depending on the sensitivity of reagent	Often prolonged	Normal PT DOES NOT rule out clinically drug level
aPTT	Usually unaffected	May be prolonged	None

Direct FXa inhibitor and specific test

Test	Methods	Interpretation
Conventional	Anti-Xa for LMWH/UFH: Chromogenic assay	- Normal test rules out clinically relevant drug level (Xai concentration not affecting coagulation): < 0.5 IU/mL for bleeding and < 0.3 IU/mL for surgery - Elevated: Xai present and affecting anticoagulation
Specific	LC-MS/MS: Molecular detection DOAC-specific anti-Xa: Chromogenic assay	- Monitoring in treatment-failure cases - Cut-off level < 75 ng/mL for bleeding < 50 – 30 ng/mL for surgery

Measurement of Coagulation Activity: Laboratory

Direct FXa inhibitor and specific test



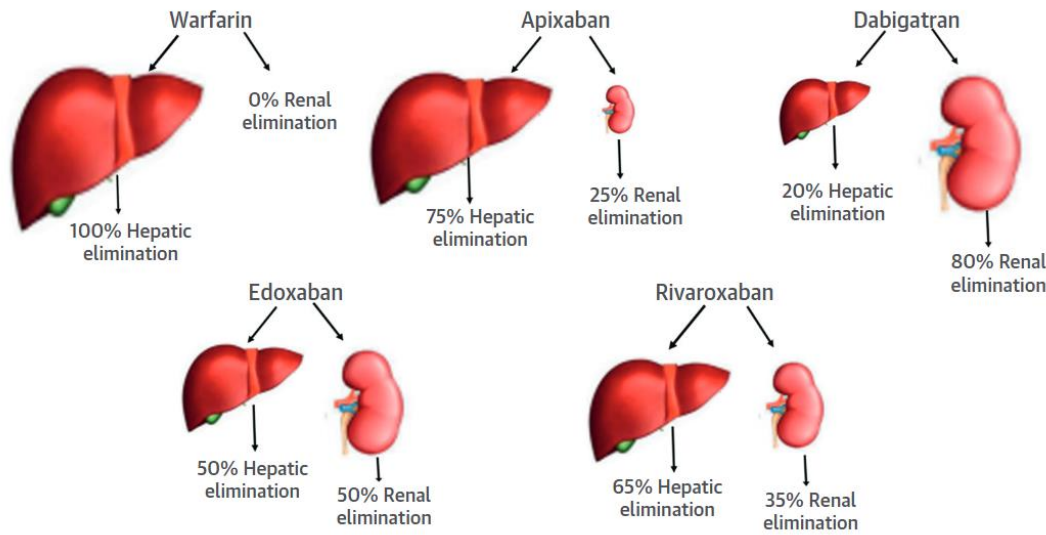
Measurement of Coagulation Activity: Laboratory

Drug	Clinical Objectives			
	Exclude Clinically Relevant Drug Levels		Determine Whether On-Therapy or Above On-Therapy Levels Are Present	
	Suggested Test	Interpretation	Suggested Test	Interpretation
Dabigatran	TT, aPTT	• Normal TT excludes clinically relevant levels, but prolonged TT does not discriminate between significant and insignificant levels. • Normal aPTT usually excludes clinically relevant levels if a sensitive reagent is used.	aPTT	• Prolonged aPTT suggests that on-therapy or above on-therapy levels are present, but normal aPTT may not exclude on-therapy level
Direct FXa inhibitors	UFH or LMWH anti-FXa	• Normal PT and aPTT dose not exclude clinically relevant levels (especially apixaban) • Anti-FXa below the lower limit of quantitation probably excludes clinically relevant levels	PT	• Prolonged PT suggests that on-therapy or above on-therapy levels are present, but normal PT may not exclude on-therapy level (especially apixaban)

Measurement of Coagulation Activity: Clinical

- Additional information: time of ingestion of last dose and pharmacokinetics factors (drug interaction, and hepatic and renal functions)

Essential data of pharmacokinetics of anticoagulants⁽²⁾



	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Half-life (hr.)	20 – 60	12	12 – 17	10 – 14	7 - 13
Protein binding	99%	87%	35%	55%	95%
Renal clearance	None	25%	80%	50%	35%
Hepatic clearance	100%	75%	20%	50%	65%
Requires CYP450	Yes	Yes	No	Minimal	Yes

Measurement of Coagulation Activity: Clinical

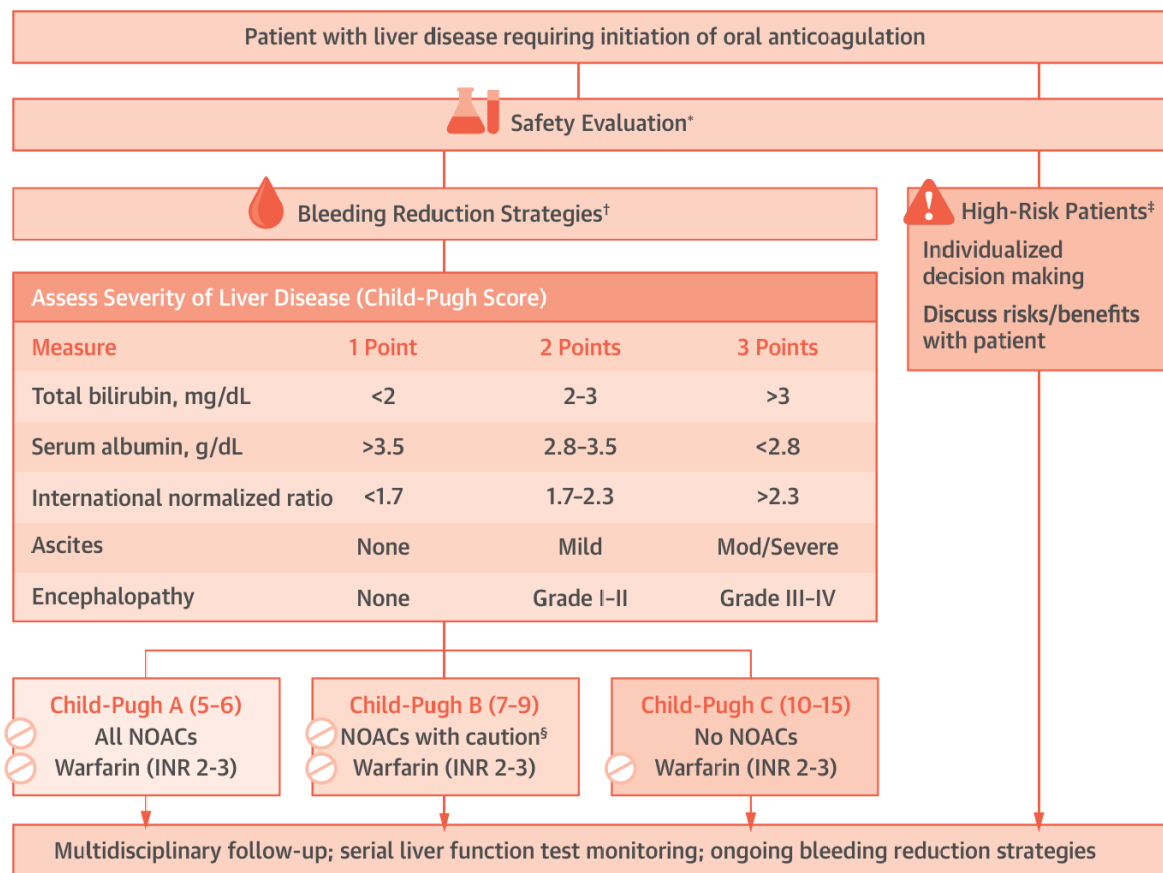
- Association of half-life and renal insufficiency should be interpreted in CKD.

CrCl, mL/min	Dabigatran					Apixaban, Betrixaban, Edoxaban, or Rivaroxaban		
	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	- Apixaban, edoxaban, rivaroxaban: 6-15 - Betrixaban: 19-27	- Apixaban: 17 - Edoxaban: 17 - Rivaroxaban: 9	- Apixaban: 17 (off dialysis) - Edoxaban: 10-17 (off dialysis) - Rivaroxaban: 13 (off dialysis)

Suggestion duration for withholding DOAC in high bleeding risk

≥ 80	≥ 48 hr.	Consider measuring agent-specific anti-Xa level and/or withholding ≥ 72 hr
79 - 50	≥ 72 hr.	
49 - 30	≥ 96 hr.	
29 - 15	≥ 120 hr.	
< 15 (off dialysis)	Consider measuring dTT	

Measurement of Coagulation Activity: Clinical

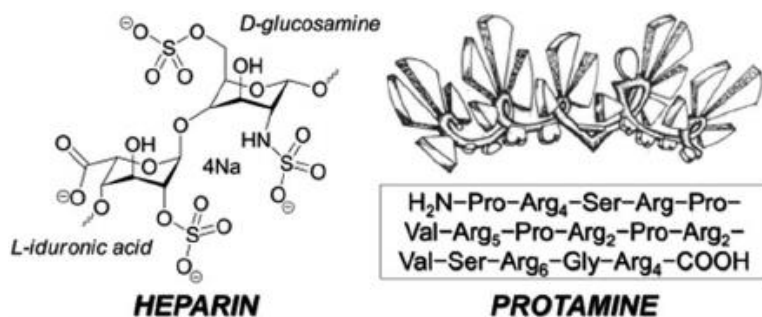


- Liver disease could influence several aspects of pharmacokinetics.
- Increased the fraction of free drug in plasma due to hypoalbuminemia (esp. rivaroxaban and apixaban)
- Decreased hepatic elimination (apixaban and rivaroxaban via CYP450 mechanism and edoxaban via conjugation mechanism)
- Half-life may being prolong in liver impairment (very limited data)
- Laboratory assessment may useful

Heparin Reversal: Protamine Sulfate



- Protamine is a polycationic compound derived from fish sperm.
- Designed to **neutralized** the anticoagulant effect of **UFH**, it binds the heparin and forming stable salts.
- Effectiveness is dependent on molecular weight of heparin and its sulfate charge density.



- Its **efficacy** is **lower** for **LMWH** due to decreased binding (and limited data about effectiveness).
 - Fully reverse anti-FII activity but partly antagonized of anti-FXa activity (60% for enoxaparin)
 - Mainly for reversal of enoxaparin and dalteparin

Heparin Reversal: Protamine Sulfate

- **Clinical uses**

- Reverse the effects of high-dose UFH in cardiovascular surgery (reversal of UFH in other scenarios is seldom needed due to short half-life of UFH).
- Reverse anticoagulation effect of LMWH (due to its long half-life).

- Administration: infused slowly (> 10 minutes) to avoid immunoallergic reactions with maximum dose 50 mg at a time.

- **Adverse reactions**

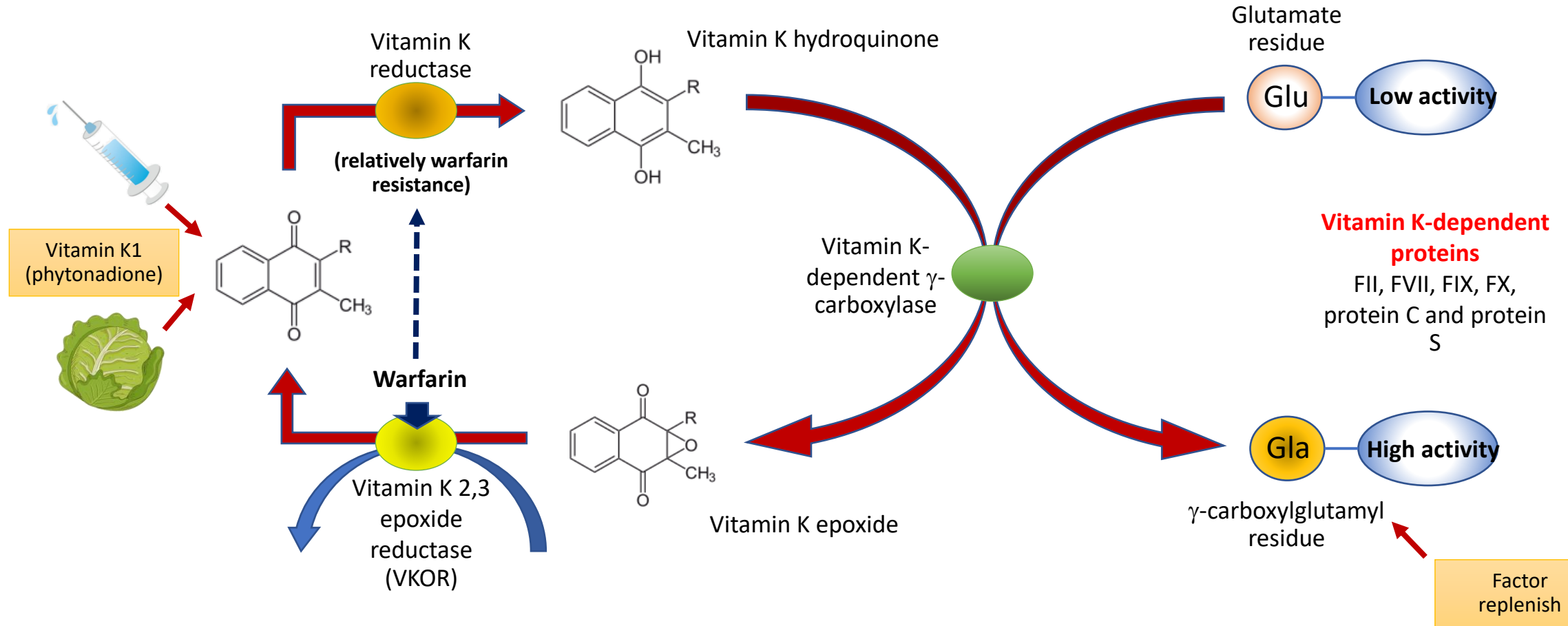
- Allergic reactions (include anaphylaxis)
- Complement-mediated hypersensitivity with pulmonary vasoconstriction and right sided heart failure
- Paradoxical anticoagulant effects (inhibition of factor V in high-dose and facilitation of fibrinolysis)⁽¹⁾ especially reversal of non or partial reversal anti-Xa activity⁽²⁾

Heparin Reversal

Agent	Dose of protamine
UFH	Immediate: 1 – 1.5 mg of protamine/100 units UFH 30 – 60 mins: 0.5 – 0.75 mg of protamine/100 units UFH > 60 mins: 0.375 mg of protamine/100 units UFH (usually not required after 3 hours) Typical adult dose in emergency is 25 mg⁽²⁾
LMWH	Dalteparin: 1 mg of protamine neutralized 100 units dalteparin, if bleeding continues or PTT remains prolonged 2 – 4 hours after protamine, may give a second dose of 0.5 mg of protamine per 100 units dalteparin Enoxaparin < 8 hours after last dose: 1 mg of protamine per 1 mg of enoxaparin 8 – 12 hours after last dose: 0.5 mg of protamine per 1 mg of enoxaparin > 12 hours after last dose (administered every 12 hours): not required if bleeding continues or PTT remains prolonged 2 – 4 hours after protamine, may give a second dose of 0.5 mg of protamine per 1 mg of enoxaparin

- Protamine have no significant effect to fondaparinux, limited effective data from recombinant FVIIa and aPCC but may be considered for reversal.

Warfarin Reversal: Mechanism of Action



Warfarin Reversal

- Specific reversal agent of VKAs: vitamin K (IV or oral)
 - Restores intrinsic hepatic carboxylation of vitamin K – dependent clotting factors in a dose dependent manner
 - Administration for IV: 5 – 10 mg in 25 to 50 mL of NSS and infusion time should be > 15 – 30 minutes (prevention of anaphylactoid reaction)
 - IV administration has a rapid reduction an INR (4 – 6 hours) compared with oral (18 – 24 hours)
- Repletion therapy
 - Reversal effect of vitamin K takes time
 - In patients with acute bleeding, co-administration of vitamin K and repletion therapy with vitamin K-dependent coagulation factors (VKDF) is recommended.⁽²⁾

Warfarin Reversal

- VKDF replacement can be achieved by administering plasma or prothrombin complex concentrate (PCC).
- Limitations and disadvantages of plasma
 - Time delays for ABO blood typing and thawing of frozen plasma
 - Large volumes and long infusion times
 - Risk of complications: pathogen transmission and transfusion-related complications
- Prothrombin complex concentrates
 - Non-activated PCCs: 3F-PCC (FII, FIX, and FX) and 4F-PCC (FII, FVII, FIX, and FX)
 - Activated PCC

Warfarin Reversal: Efficacy of 4F-PCC in Bleeding

Patient's characteristics

	4F-PCC (n = 98)	Plasma (n = 104)
Mean age	69.8	69.8
Age $\geq$ 65 years	66.3%	70.2%
Median baseline INR	3.90 (1.8 – 20.0)	3.6 (1.9 – 38.9)
GI bleeding	64.3%	61.5%
ICH	12.2%	11.5%
Indications		
Arrhythmia	57.1%	51.0%
Thromboembolism	18.4%	20.2%

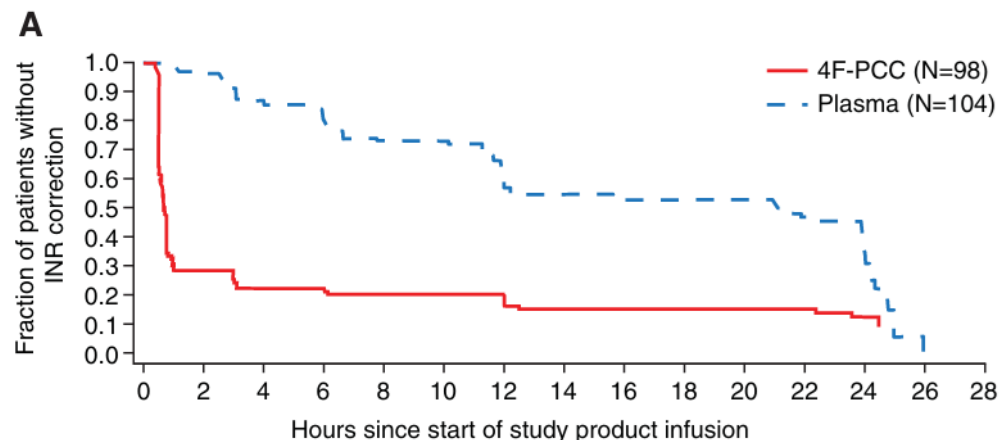
- Randomized controlled trial in 202 patients
- Adult patients receiving VKA therapy with an INR $\geq$ 2.0 and acute major bleeding (not include criteria of critical organ bleeding)

Baseline INR	4F-PCC Dose, IU of Factor IX per kg Body Weight*	Plasma Dose, mL per kg Body Weight*
2 to <4	25	10
4–6	35	12
>6	50	15

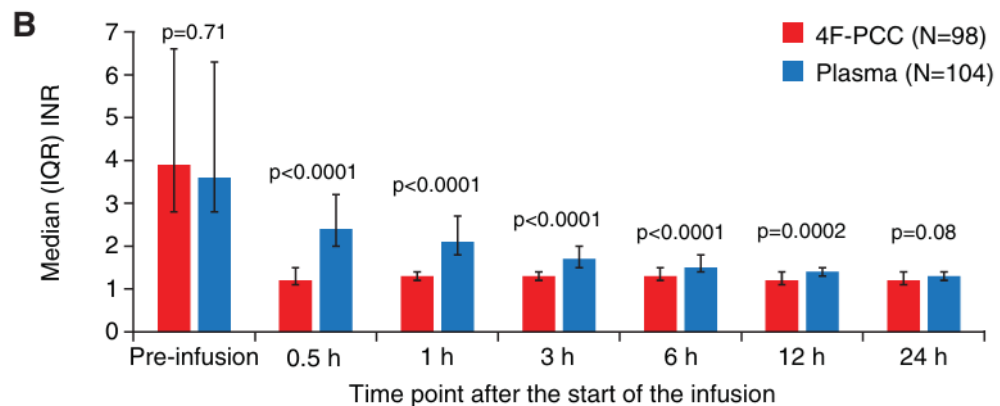
4F-PCC indicates 4-factor prothrombin complex concentrate; and INR, international normalized ratio.

*Dose calculation based on 100 kg body weight for patients weighing >100 kg. Maximum dose $\leq$ 5000 IU of factor IX (4F-PCC) or $\leq$ 1500 mL (plasma).

Warfarin Reversal: Efficacy of 4F-PCC in Bleeding



- Effective hemostasis (excellent and good) was achieved in 72.4% in PCC arm and 65.4% in plasma arm.
- Non-inferiority in efficacy of 4F-PCC compared with plasma.
- Rapid INR reduction was achieved in 62.2% of 4F-PCC versus 9.6% receiving plasma.

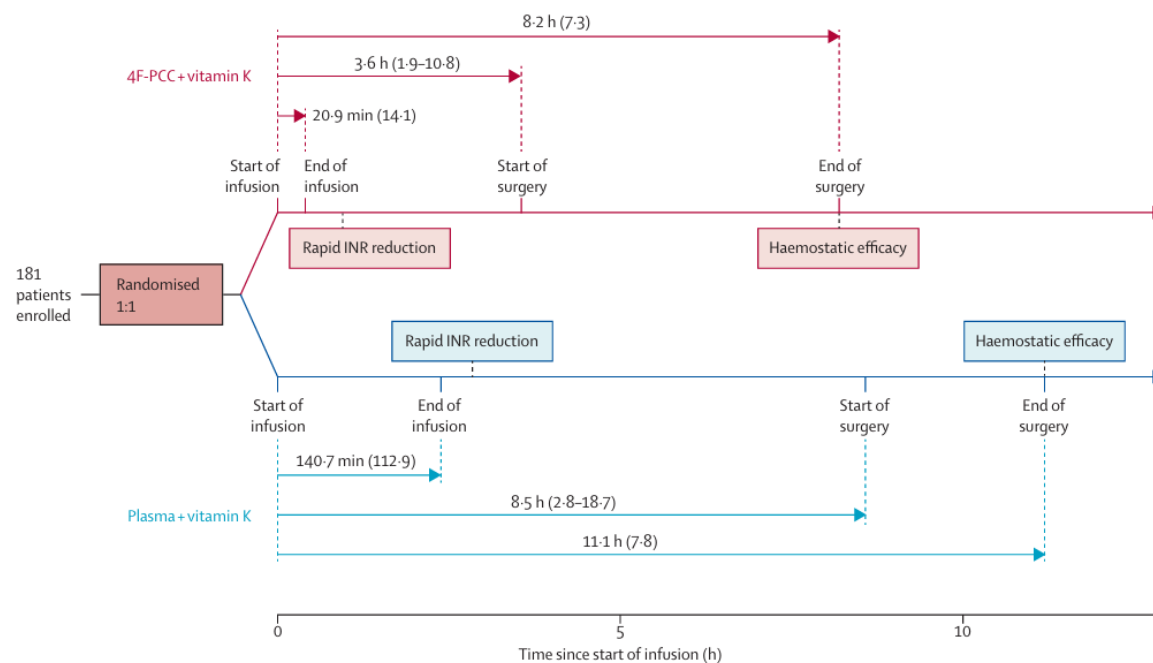


Warfarin Reversal: Efficacy of 4F-PCC in Bleeding

AE	No. (%) of Patients	
	4F-PCC (n=103)	Plasma (n=109)
Any nonserious AE*	66 (64.1)	71 (65.1)
Related AE†	10 (9.7)	23 (21.1)
AE leading to treatment discontinuation	0	3 (2.8)
Serious AE*	32 (31.1)	26 (23.9)
Related serious AE†	2 (1.9)	4 (3.7)
AEs of interest		
Deaths to day 30	6 (5.8)	5 (4.6)
Deaths to day 45	10 (9.7)	5 (4.6)
Related deaths (to day 45)‡	1 (1.0)	0
Thromboembolic AE	8 (7.8)	7 (6.4)
Related thromboembolic AE†	4 (3.9)	3 (2.8)
Fluid overload or similar cardiac event	5 (4.9)	14 (12.8)
Related fluid overload or similar cardiac event†	0	7 (6.4)

- The study was not powered to demonstrate significant differences between groups of safety outcomes.
- From reviews (based on single-arm studies) there is a low risk of TE events in patients treated with PCCs for VKA reversal.
- Underlying disease and dosing may be important factors in increasing TE risk.
- Thromboembolic events were reported with the extended used in hemophilic patients.⁽²⁾

Warfarin Reversal: Efficacy of 4F-PCC in Surgery

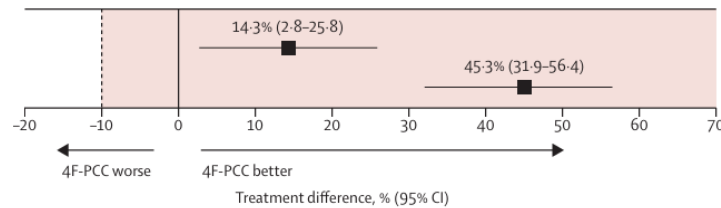


- Multicenter, open-label, phase 3b RCT in adult patients needing rapid VKA reversal before an urgent surgical or procedure.
- Intervention: vitamin K concomitant with a single dose of either 4F-PCC or plasma.
- Intravenous infusion of study treatment based on baseline INR and body weight
- Type of surgery: 19% – 23% major orthopedic surgery, 15% - 19% invasive procedures, 1% cranial neurosurgery, 27% - 58% other surgeries

INR	4F-PCC (IU of FIX)	Plasma
2 – < 4	25 IU/kg	10 mL/kg
4 - 6	35 IU/kg	12 mL/kg
> 6	50 IU/kg	15 mL/kg

Warfarin Reversal: Efficacy of 4F-PCC in Surgery

Primary endpoint and co-primary endpoint



	4F-PCC (n=87)	Plasma (n=81)	p value
Effective haemostasis (primary endpoint)	78 (90%)	61 (75%)	0.0142
Rapid INR reduction (co-primary endpoint)	48 (55%)	8 (10%)	<0.0001

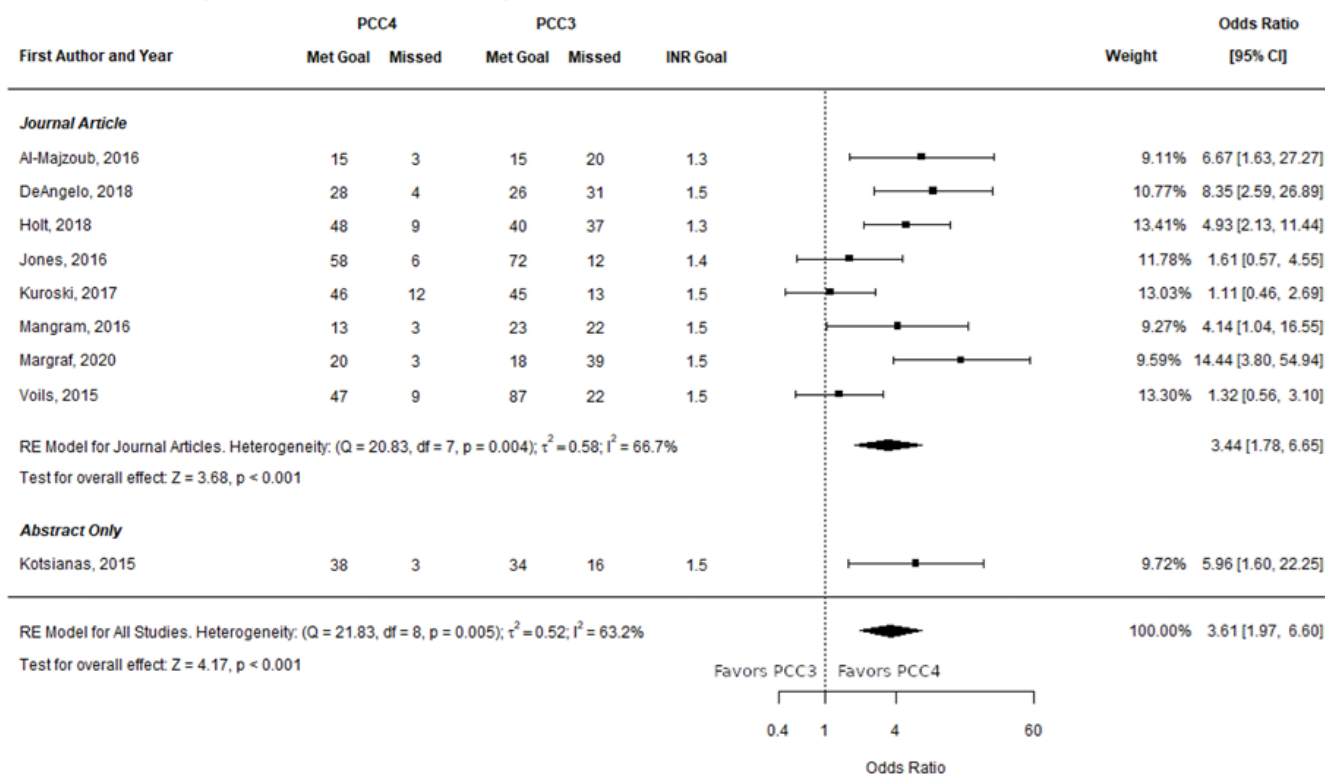
- Effective hemostasis was achieved in 90% of patients in the 4F-PCC group versus 75% in the plasma group (difference 14.3%, 95%CI 2.8 – 25.8).
- Rapid INR reduction was achieved in 55% of patients in the 4F-PCC group versus 10% in the plasma group (difference 45.3%, 95%CI 23.1 – 56.4).

Safety

	4F-PCC (n=88)	Plasma (n=88)
Any adverse event	49 (56%)	53 (60%)
Related adverse event*	8 (9%)	15 (17%)
Adverse event leading to treatment discontinuation	0	0
Serious adverse event	22 (25%)	23 (26%)
Related serious adverse event*	3 (3%)	3 (3%)
Adverse events of interest		
Deaths to day 45†	3 (3%)	8 (9%)
Thromboembolic adverse event‡	6 (7%)	7 (8%)
Fluid overload or similar cardiac event	3 (3%)	11 (13%)
Bleeding after primary outcome assessment	3 (3%)	4 (5%)

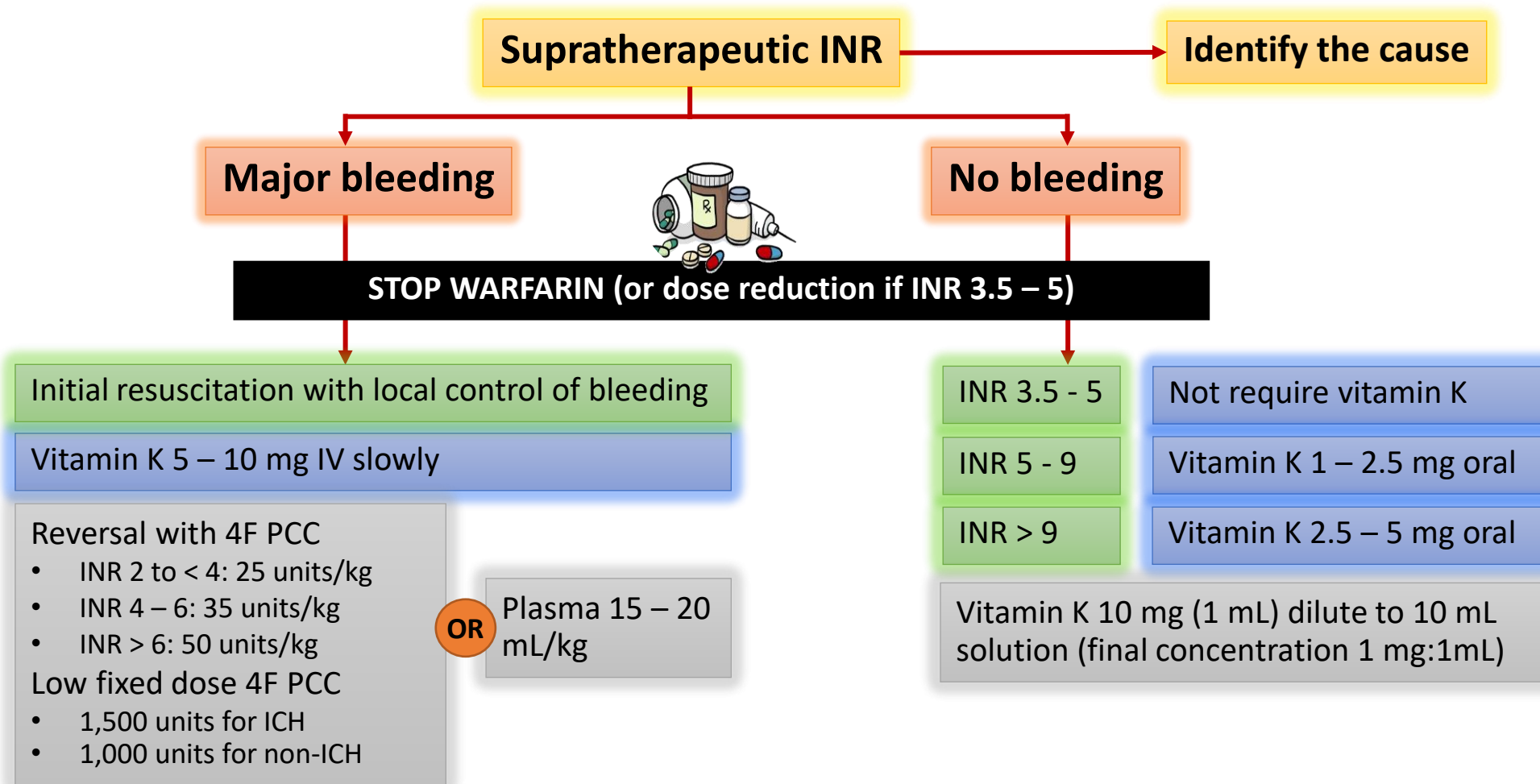
Warfarin Reversal: 3F-PCC and 4F-PCC

Impact of Prothrombin Complex Concentrate on International Normalized Ratio Goal



- Systematic review and meta-analysis of retrospective studies
- Indications of reversal: surgery, ICH, GIB, or other bleeding types
- Dose of PCC: 25 – 40.99 units/kg
- More than 3 times the odds of reversal to goal INR when they were given 4F-PCC compared to 3F-PCC (OR = 3.61, 95%CI: 1.97-6.60).
- No meaningful clinical association or statistically in thromboembolism or survival.

Warfarin Reversal: Algorithm

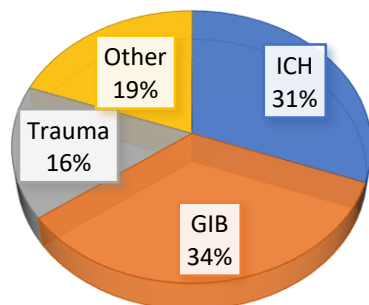


Dabigatran Reversal: REVERSE-AD Trial

- The maximum percentage reversal was 100% in bleeding patients since after the first infusion.

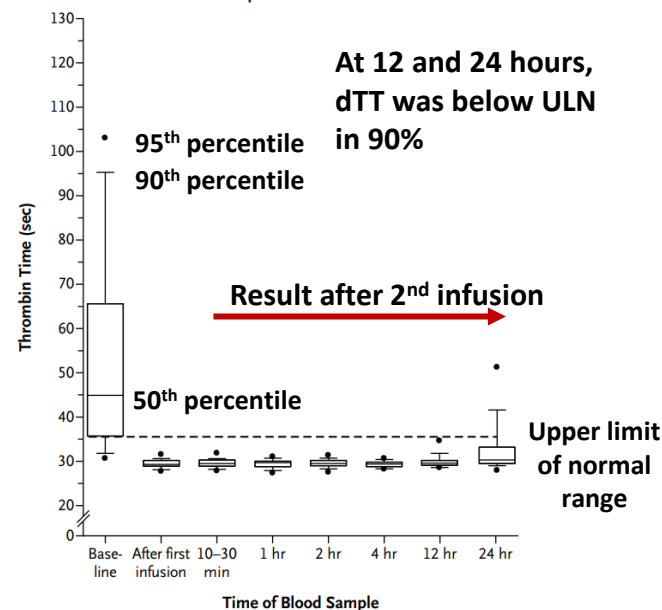
Characteristics

- Median age 77 years
- Median time since last dose: 15.2 hours.
- Elevated dTT at baseline 78%, and ECT 92%.



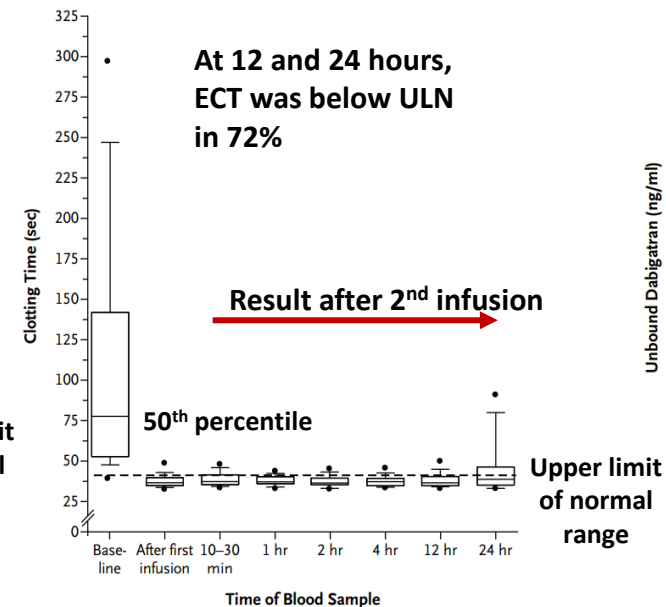
Laboratory outcome

A Dilute Thrombin Time in Group A



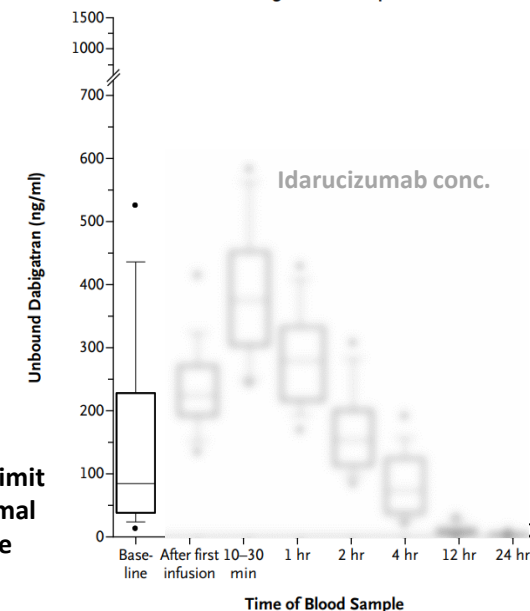
Diluted thrombin time

C Ecarin Clotting Time in Group A



Ecarin clotting time

A Concentration of Unbound Dabigatran in Group A



Unbound dabigatran concentration

Dabigatran Reversal: REVERSE-AD Trial

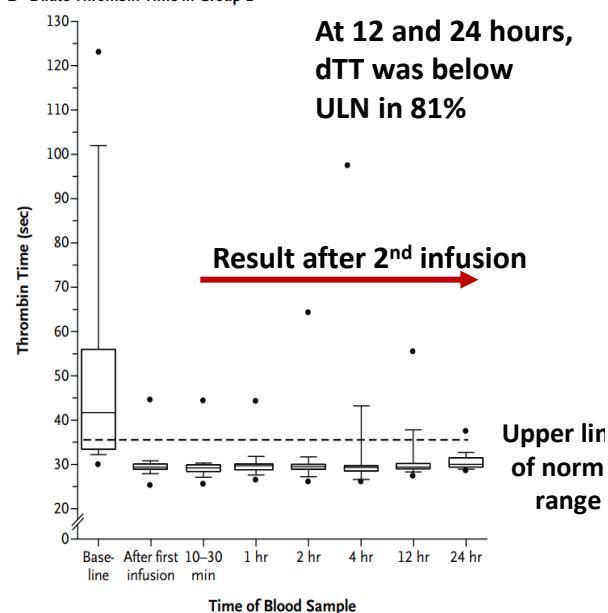
- The maximum percentage reversal was also 100% in surgical patients since after the first infusion.

Characteristics

- Median age 76 years
- Median time since last dose: 16.6 hours.
- Elevated dTT at baseline 72%, and ECT 87%.

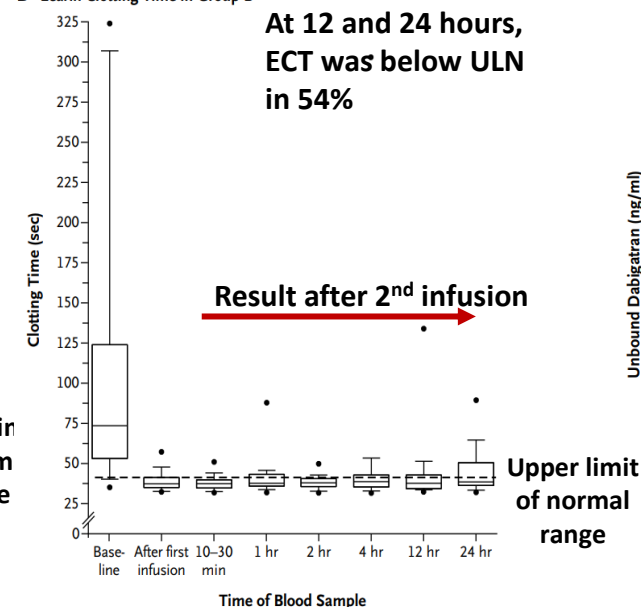
Laboratory outcome

B Dilute Thrombin Time in Group B



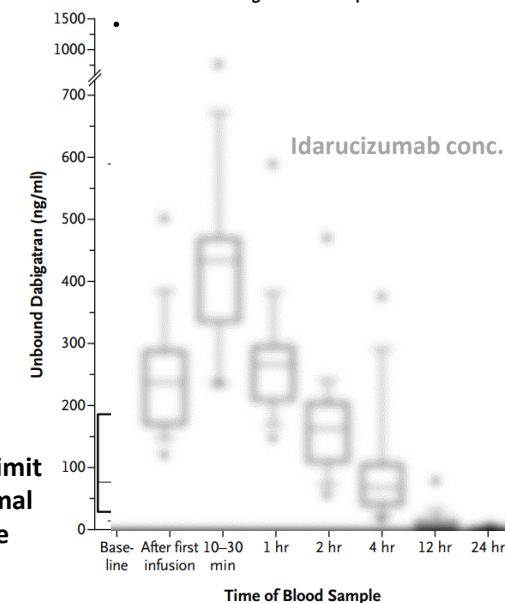
Diluted thrombin time

D Ecarin Clotting Time in Group B



Ecarin clotting time

B Concentration of Unbound Dabigatran in Group B



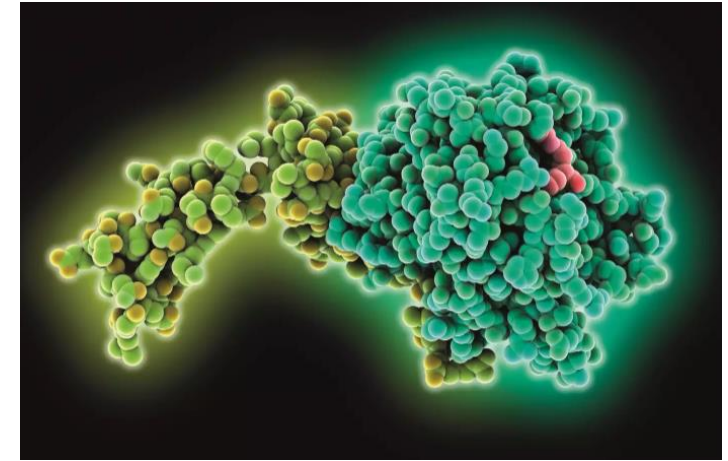
Unbound dabigatran concentration

Dabigatran Reversal: REVERSE-AD Trial

- **Bleeding outcomes:** Median investigator-reported time to cessation of bleeding was 11.4 hours.
- **Surgical outcomes:** 92% normal intraoperative hemostasis, 5.4% mild and 2.6% moderate abnormal intraoperative hemostasis.
- 18 deaths overall, 10 deaths due to vascular causes (including 5 fatal bleeding).
- Thrombotic events occurred in 5/90 patients or 5.55% (9.09% in patients with normal clotting tests and 4.41% in abnormal clotting tests): DVT, pulmonary embolism, cardiac thrombus, NSTEMI, and stroke.

Reversal of Direct FXa Inhibitors

- Andexanet alfa (andexanet) is a recombinant modified human (catalytically inactive) FXa decoy protein.
- Bind FXa inhibitors with high affinity.
- Specific reversal agents for both direct and indirect FXa inhibitors (enoxaparin).
- Rapidly reduced both plasma unbound FXa inhibitors and anti-FXa activity.⁽²⁾
- Because of short half-life (1 hour), administered as a bolus plus a 1-to-2 hour infusion is recommended.
- Approved in 2018 for apixaban and rivaroxaban.⁽²⁾

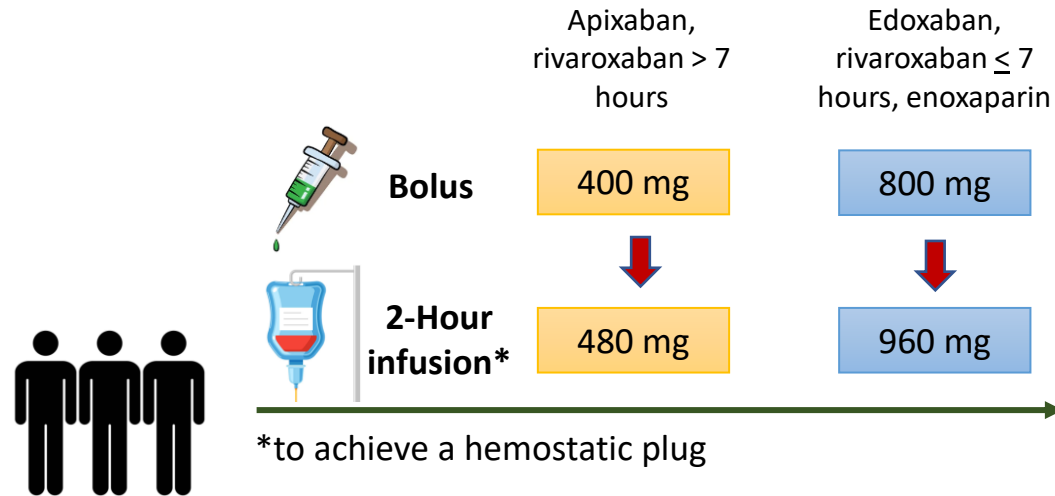


Dosage Administration⁽²⁾

- For apixaban or who received rivaroxaban > 7 hours: bolus 400 mg (> 15 min period) and 2-hour infusion of 480 mg.
- For edoxaban, enoxaparin, or who received rivaroxaban ≤ 7 hours : bolus 800 mg (> 30 min period) and 2-hour infusion of 960 mg.

Reversal of Direct FXa Inhibitors

- ANNEXA-4: prospective, open-label, single group study in acute major bleeding.

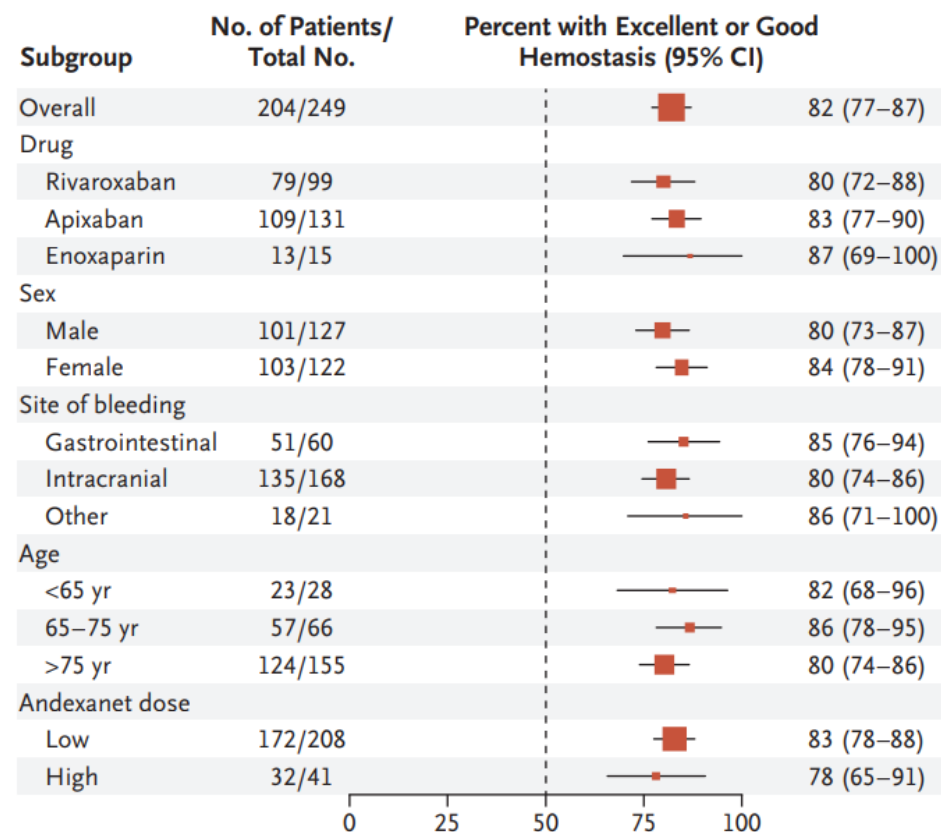


- Age ≥ 18 YOs
- Received FXa inhibitors (both direct and indirect) within the past 18 hours
- Acute major bleeding
- **Exclusion:** urgent surgery, severe ICH (GCS 3 – 7, ICH volume > 60 mL), or expected survival < 1 month

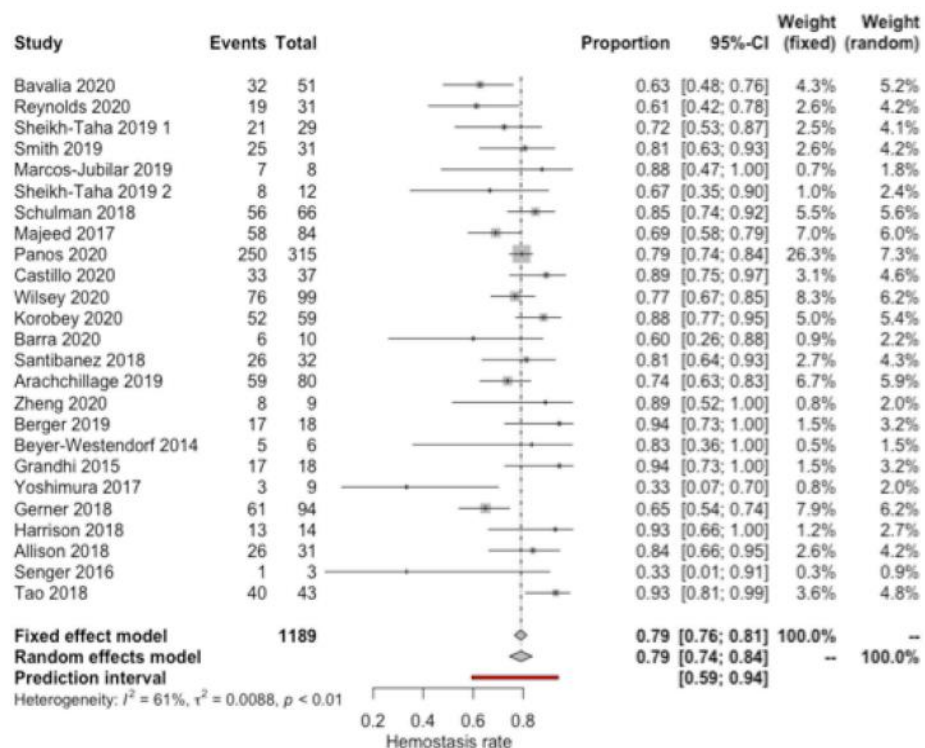
Efficacy outcome	Frequency
Anti-FXa activity and unbound fraction of level of FXa inhibitor	3 hours and 15 minutes before, at the end of bolus and infusion, 4 hours, 8 hours, 12 hours after administration
Endogenous thrombin potential	Baseline, 8 hours, 12 hours, and 3 days after administration
CT or MRI brain	Before (within 3 hours), 1 hours, 12 hours and 30 days after administration
Hemostatic efficacy	• Hemostasis for ICH: if increase in volume $\leq 20\%$ at both 1 and 12 hours OR good if increase in volume $\leq 35\%$ at 12 hr. • Hemostasis for nonvisible bleeding: excellent if decrease in both corrected Hb and Hct $\leq 10\%$ at 12 hr. and good if decrease $\leq 20\%$ with ≤ 2 units of transfusion • Hemostasis for visible bleeding: excellent if cessation within 1 hour OR good if < 4 hr. without intervention
Adverse events	Throughout 30-day period

Reversal of Direct FXa Inhibitors

- In patients who received apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours and presented with acute major bleeding.
- Mean age of 77 years, AF was the primary indication (80%).
- Site of bleeding: ICH 64% and GI 26%.
- 92% reduction of anti-Xa activity after bolus administration in apixaban and rivaroxaban, and 38% and 62% after 12 hours, respectively.
- Excellent or good hemostatic efficacy at 12 hours was 82% (95%CI, 77 – 81): 85% for GI bleeding and 80% of ICH.
- 10% had thrombotic event during the 30-day follow-up period (44% CVA, 38% DVT, 20% myocardial infarction, and 14% pulmonary embolism).

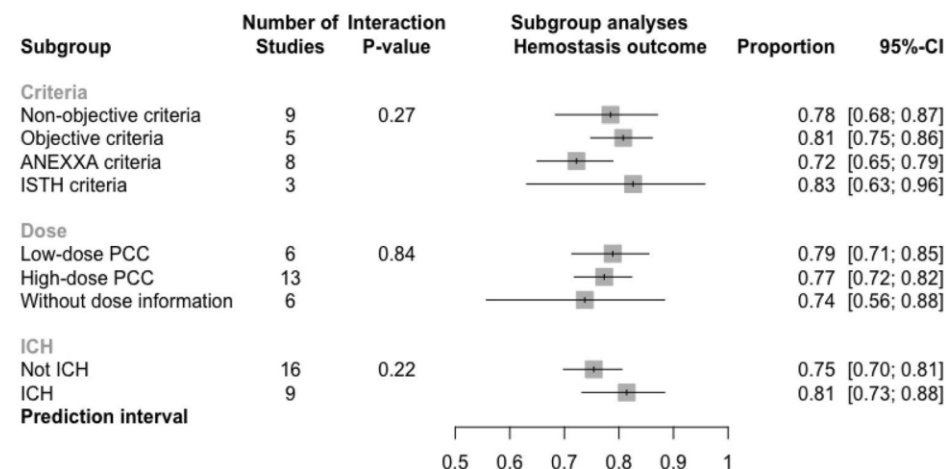


4F-PCC and FXaI Bleeding (Off-label Use)

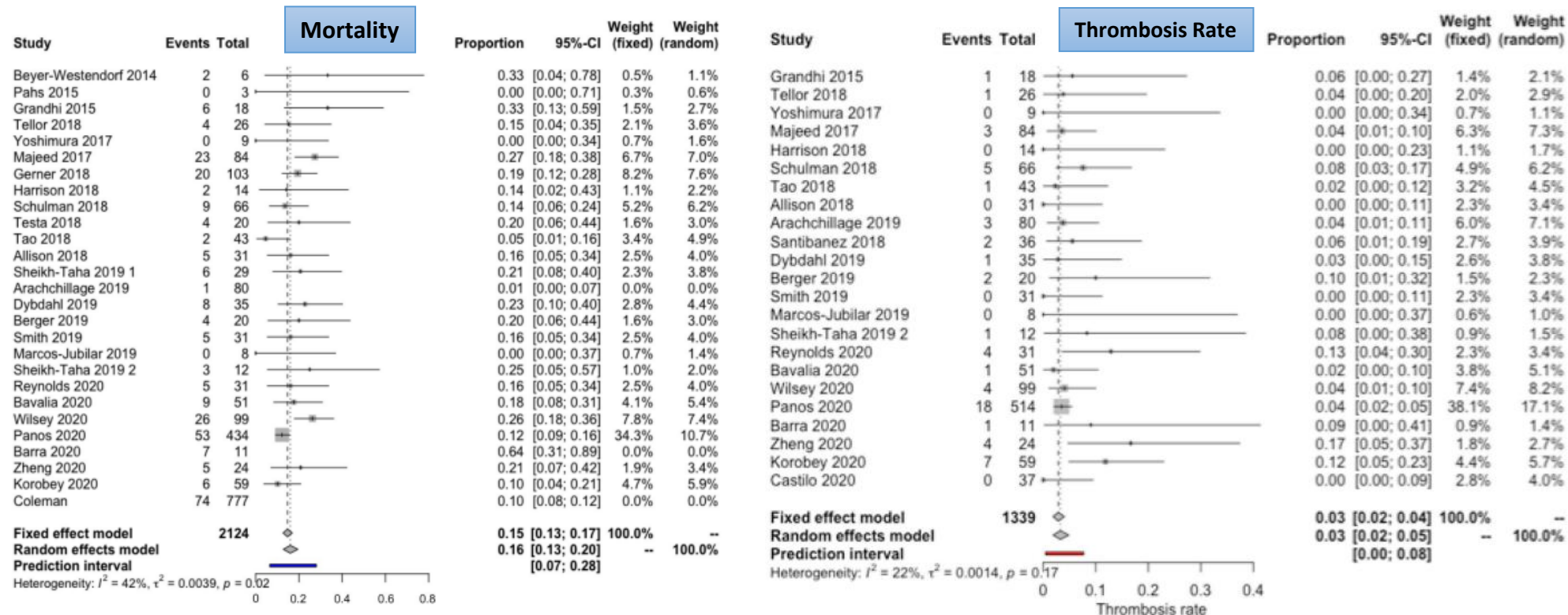


Hemostatic rate

- Incidence of effective hemostasis was 79% (CI 0.74-0.84), but there was significant statistical heterogeneity ($I^2 = 61\%$, $p < 0.01$).
- No statistically significant changes between hemostasis criteria or dose of PCC.

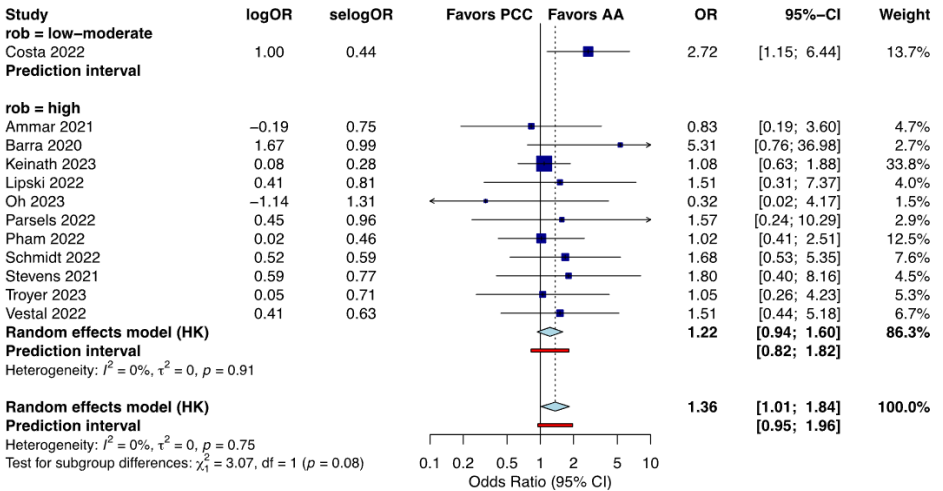


4F-PCC and FXaI Bleeding (Off-label Use)



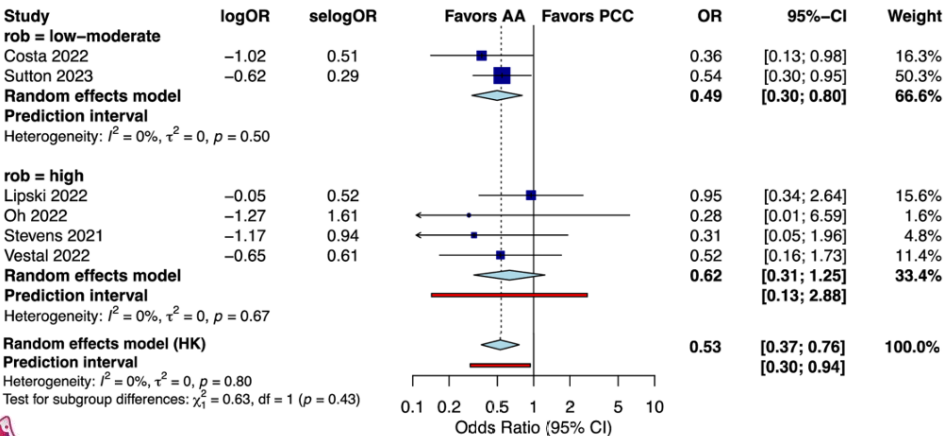
- Complications up to 30-day after PCC administration
- ICH had higher mortality 22%.
- Thromboembolic adverse events was 3% (CI 0.02-0.05).

Reversal of Direct FXals: Andexanet and PCC



Hemostatic efficacy

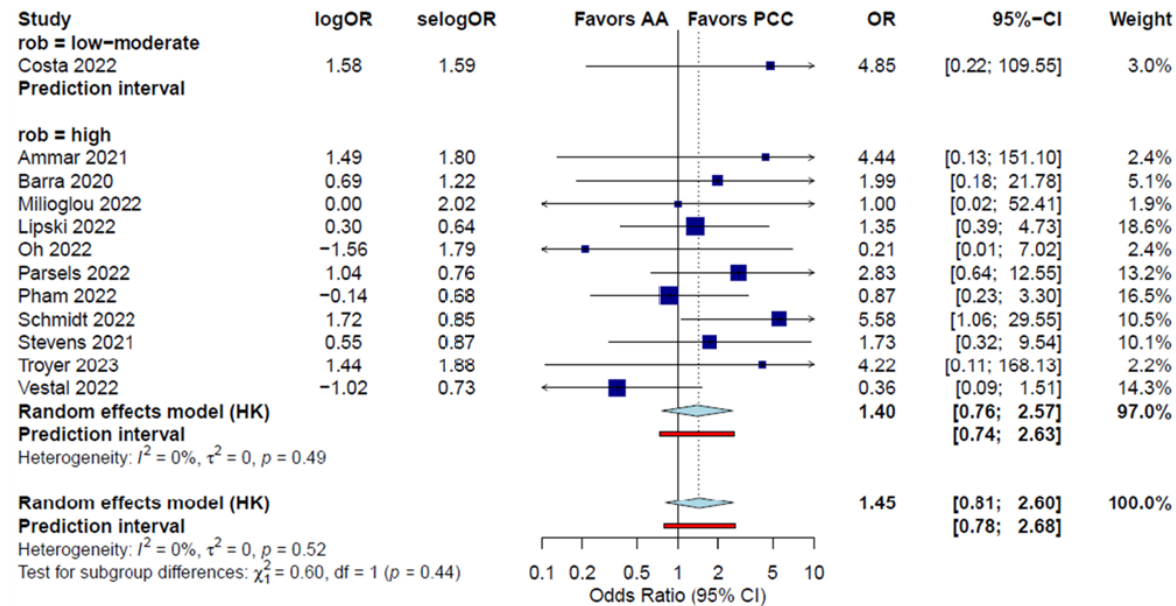
- Recent systemetic review and meta-analysis of efficacy and safety of Andexanet and PCC in the reversal of direct-FXa inhibitors.
- 72% of included studies had a high-risk of bias.
- Pooled effects showed improvement in hemostatic efficacy of Andexanet (OR 1.36, 95%CI 1.01 – 1.84) and reductions in 30-day mortality (OR 0.53, 95%CI 0.37 – 0.76)



30-day mortality rate

Reversal of Direct FXaIs: Andexanet and PCC

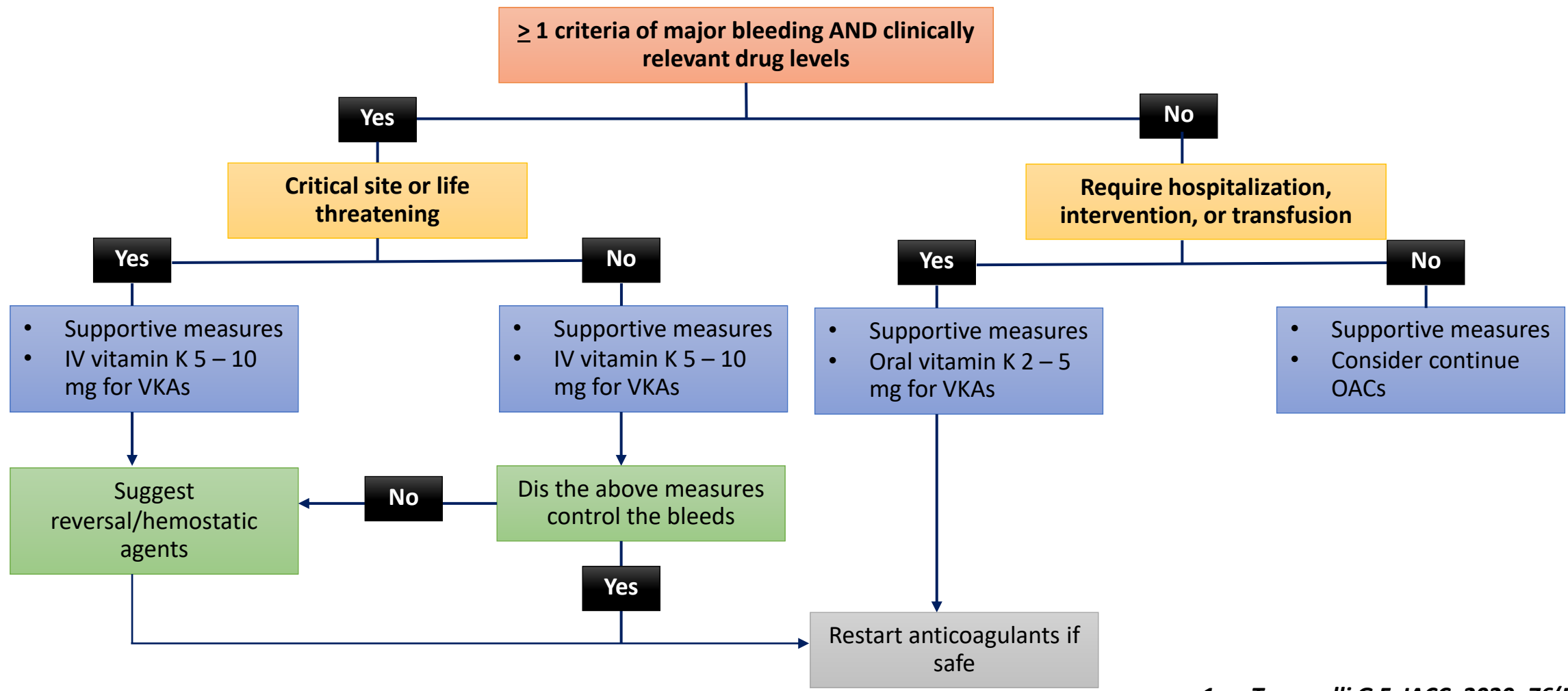
- The difference in thrombotic events with Andexanet versus PCC was not statistically significant.



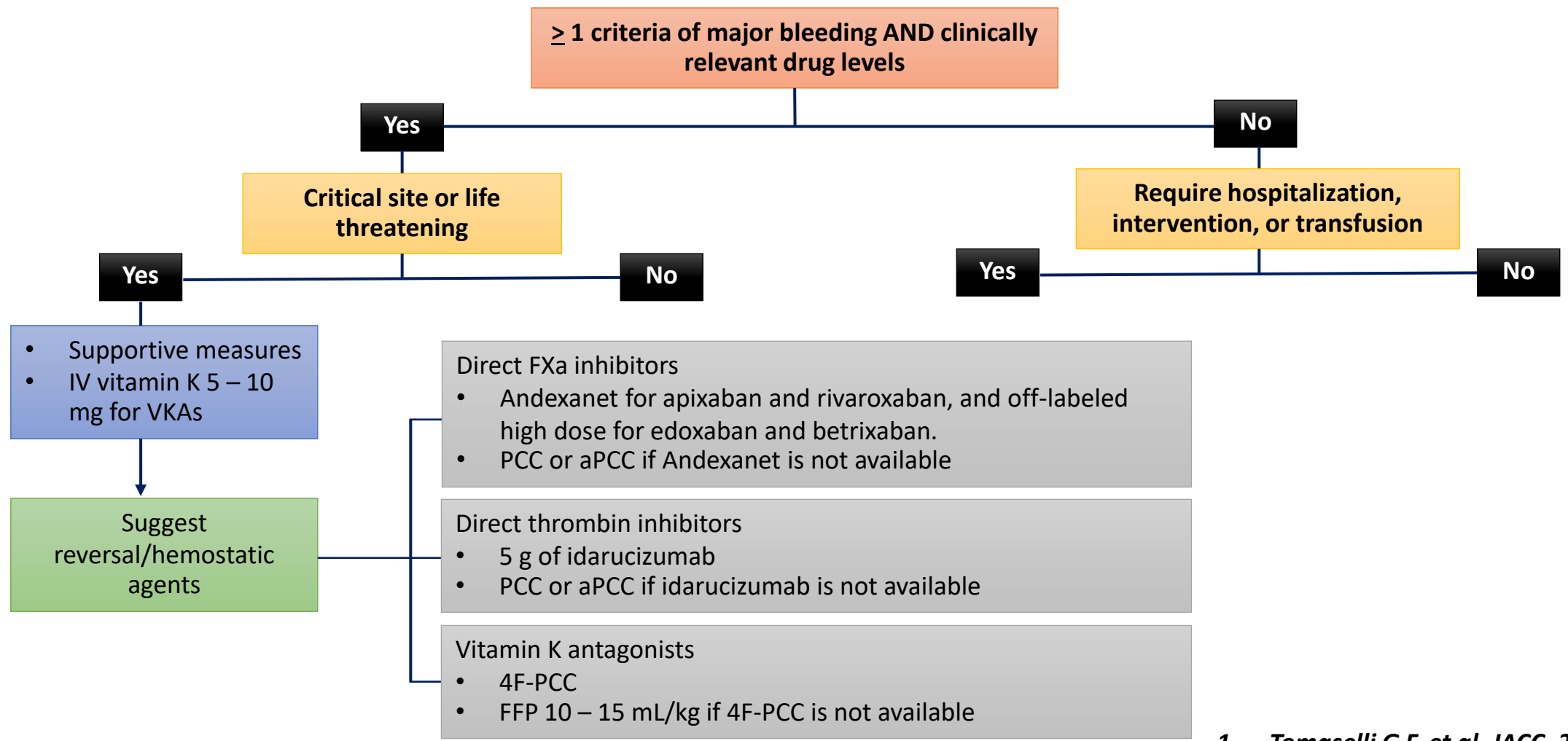
Reversal of Direct FXIa Inhibitors

- Asundexian (half-life 14 – 17 hours) and milvexian (half-life 9 – 12 hours) are the oral FXIa inhibitors in the most advanced stages of development.
- Rate of major bleeding
 - 0 in milvexian versus < 1% in enoxaparin for the prevention of VTE in total knee arthroplasty (AXIOMATIC-TKR, 2021)
 - 0.2% in asundexian versus 0.7% in apixaban in patients with atrial fibrillation (OCEANIC-AF)
- Intravenous tranexamic acid may reduce the risk of peri-operative bleeding.
- Serious bleeding: tranexamic acid and low-dose rFVIIa (or aPCC, if rFVIIa is unavailable)

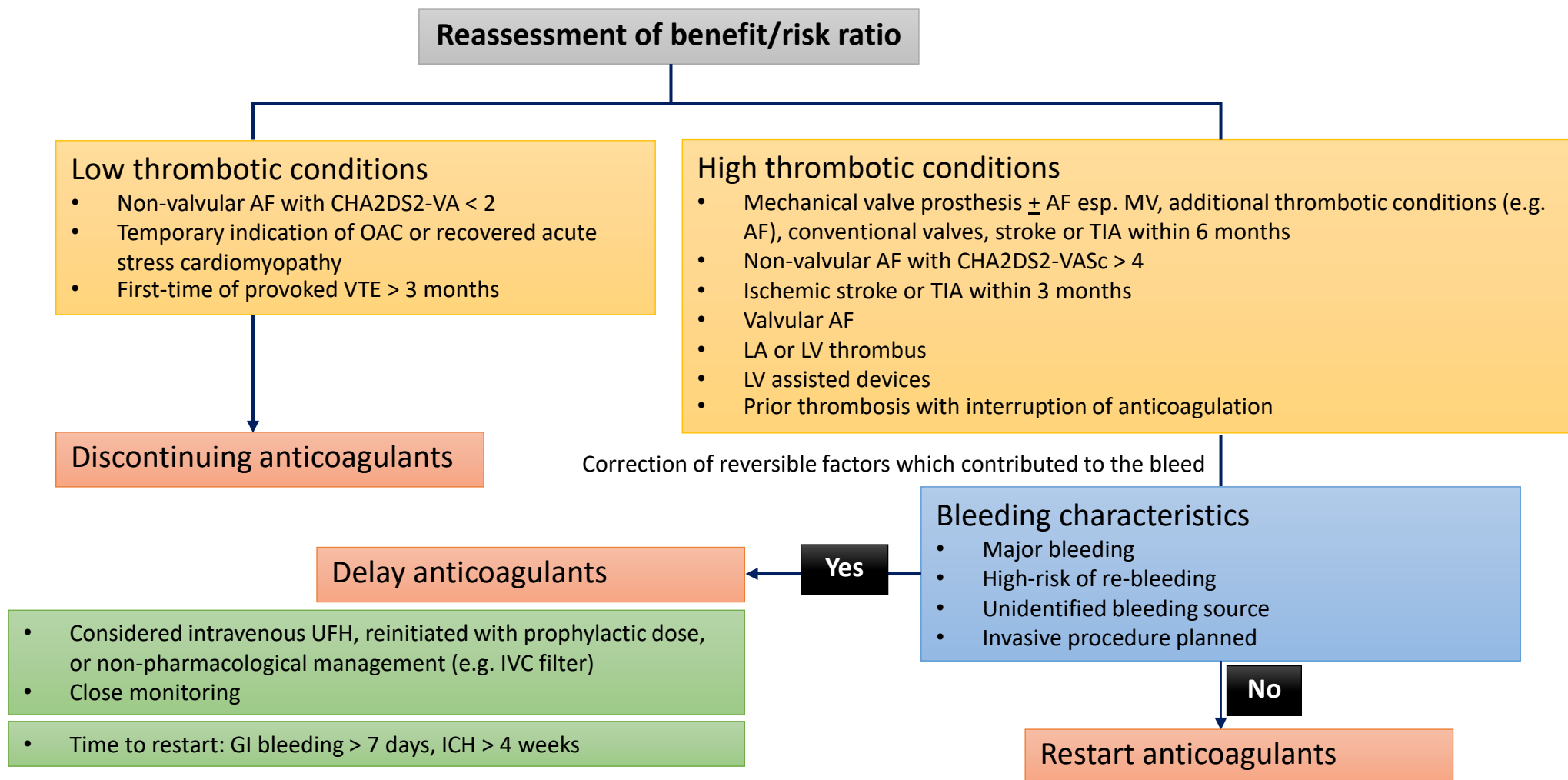
Conclusion



Conclusion



Resumption of Anticoagulants



References

- Siavash Piran and Sam Sculman. **Treatment of bleeding complications in patients on anticoagulation therapy.** Blood. 2019; 133(5): 425 – 433.
- Adam Cuker, Allison Burnett, Darren Triller, et al. **Reversal of direct anticoagulants: Guidance from the Anticoagulation Forum.** The American Journal of Hematology. 2019; 94: 697 – 709.
- Tomaselli G F, Mahaffey K W, Cuker A, et al. **2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.** Journal of the American College of Cardiology. 2020; 76(5): 594 – 622.
- Arman Qamar, Muthiah Vaduganathan, Norton J. Greenberger, et al. **Oral Anticoagulation in Patients With Liver Disease.** Journal of the American College of Cardiology. 2018; 71(19): 2162 – 2173.
- Ravi Sarode. **Direct oral anticoagulant monitoring: what laboratory tests are available to guide us?** Hematology Am Soc Hematol Educ program. 2019; 2019(1): 194 – 97. doi: 10.1182/hematology.2019000027.

References

- Jean M. Connors. **Testing and monitoring direct oral anticoagulants.** Blood. 2018; 132(19): 2009 – 13.
- Jennifer Yee and Colin G. Kaide. **Emergency Reversal of Anticoagulation.** Western Journal of Emergency Medicine. 2019; 20(5): 770 – 781.
- Elias Bekka and Evangelia Liakoni. **Anticoagulation reversal (vitamin K, prothrombin complex concentrates, idarucizumab, Andexanet- α , protamine.** British Pharmacological Society. 2024; 1 – 11.
- Charles V. Pollack, Paul A. Reilly, Joanne van Ryn, John W. Eikelboom. **Idarucizumab for Dabigatran Reversal – Full Cohort Analysis.** The New England Journal of Medicine. 2017; 377(5): 431 – 441.
- Deborah M. Siegal, John T. Curnutte, Stuart J. Connolly, et al. **Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity.** The New England Journal of Medicine. 2018; 373(25): 2413 – 2424.

References

- Stuart J. Connolly, Mark Crowther, John W. Eikelboom, Michael Gibson, et al. **Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors.** The New England Journal of Medicine. 2019; 380(14): 1326 – 35.
- Liu S, Shen G, and Li W. **Structural and cellular basis of vitamin K antagonisms.** Journal of Thrombosis and Haemostasis. 2022; 20: 1971 – 1983.
- Hirsh J, Fuster V, Ansell J, et al. **American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy.** Circulation. 2013; 107: 1692 – 1711.
- Ravi Sarode, Truman J. Milling, Majed A. Refaai, et al. **Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding.** Circulation. 2013; 128: 1234 – 1243.
- Joshua N Goldstein, Majed A Refaai, Truman J Milling Jr, et al. **Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial.** Lancet. 2015; 385: 2077 – 2086.

References

- David J. Margraf, Sarah J. Brown, Heather L. Blue, et al. **Comparison of 3-factor versus 4-factor prothrombin complex concentrate for emergent warfarin reversal: a systematic review and meta-analysis.** BMC Emergency Medicine. 2022; 22:14. <https://doi.org/10.1186/s12873-022-00568-x>.
- Ioannis Milioglou , Ioannis Farmakis, Mandy Neudeker, et al. **Prothrombin complex concentrate in major bleeding associated with DOACs; an updated systematic review and meta-analysis.** Journal of Thrombosis and Thrombolysis. 2021; 52(4): 1137 – 1150.
- C. Michael White, Kimberly Snow Caroti, Youssef Bessada, et al. **Andexanet alfa versus PCC products for factor Xa inhibitor bleeding: A systemic review with meta-analysis.** Pharmacotherapy. 2024; 44: 394 – 408.
- Jerrold H. Levy, Joseph R. Shaw, Lana A. Castellucci, et al. **Reversal of direct oral anticoagulants: guidance from the SSC of the ISTH.** Journal of Thrombosis and Haemostasis. 2024; 22: 2889 – 2899.
- Jeffery I. Weitz, John Strony, Walter Ageno, et al. **Milvexian for the Prevention of Venous Thromboembolism.** The New England Journal of Medicine. 2021; 385(23): 2161 – 2171.

References

- J. P. Piccini, M. R. Patel, J. Steffel, et al. **Asundexian versus Apixaban in Patients with Atrial Fibrillation**. The New England Journal of Medicine. 2024; DOI: 10.1056/NEJMoa2407105.
- Stephanie Carlin and John Eikelboom. **Restarting Anticoagulation After Major Bleeding in Patients With Atrial Fibrillation**. Canadian Journal of Cardiology. 2024; 40: 1291 – 1293.