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Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation

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Disclosures

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

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Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation: Warfarin

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Objective

- Discuss the literature related to the pharmacologic reversal of warfarin during life-threatening bleeding

Vitamin K Antagonists (Warfarin)

- Inhibits epoxide reductase → inhibits vitamin K dependent synthesis of active forms of clotting factors II, VII, IX, X, Protein C, and Protein S

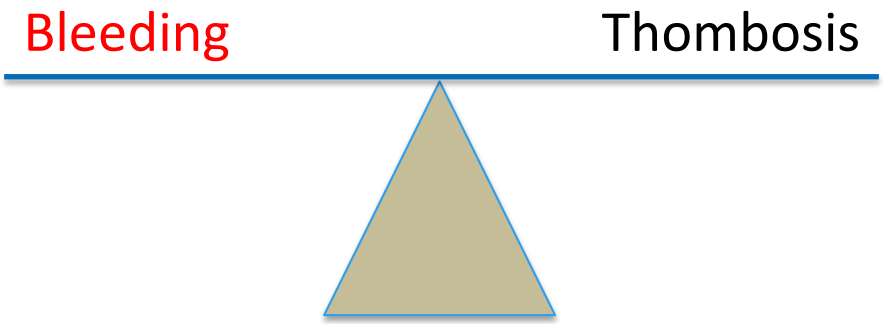
- 30-50% reduction in factor activities leads to therapeutic effect

$$INR = \left(\frac{PT_{pt}}{PT_{ref}} \right)^{ISI}$$

ISI = International Sensitivity Index

Considerations for Reversal

- Symptomatic vs. asymptomatic
- Life-threatening vs. non life-threatening
- INR target (full or partial reversal)
- Last dose of warfarin
- Other anticoagulants (ex: LMWH)



Reversal of Vitamin K Antagonist Anticoagulation

Vitamin K Administration

- 5 – 10 mg IV or PO

Factor Replacement

- Plasma (FFP)
- Prothrombin complex concentrates
  - 3-F
  - 4-F
- rFVIIa

- 80 yo male with an LVAD
- Receiving warfarin, INR 4.3
- Presents with unresponsiveness (sudden onset)
- Diagnosed with an intracranial hemorrhage

Which reversal strategy should be implemented for this patient?

- A Don’t administer any reversal agents, too much risk for thrombosis
- B Vitamin K alone
- C Vitamin K and FFP
- D Vitamin K and 4-F PCC

Plasma vs. PCC

	FFP	PCC
Blood typing required	YES	NO
Thawing time	30-45 min	0
Infection risk	YES	YES*
Thrombosis risk	YES	YES
TRALI risk	YES	NO
Clotting factor concentration	LOW	HIGH
Infusion volume	10-20 mL/kg	< 200 mL
Speed of INR correction	Slow	Quick
Duration of INR correction	6 hours	≥ 24 hours
Expense	Moderate	High

*Risk is greatly attenuated by heat treatment and nanofiltration (Kcentra)

Phase IIIb multi-center, open label (Part 1)

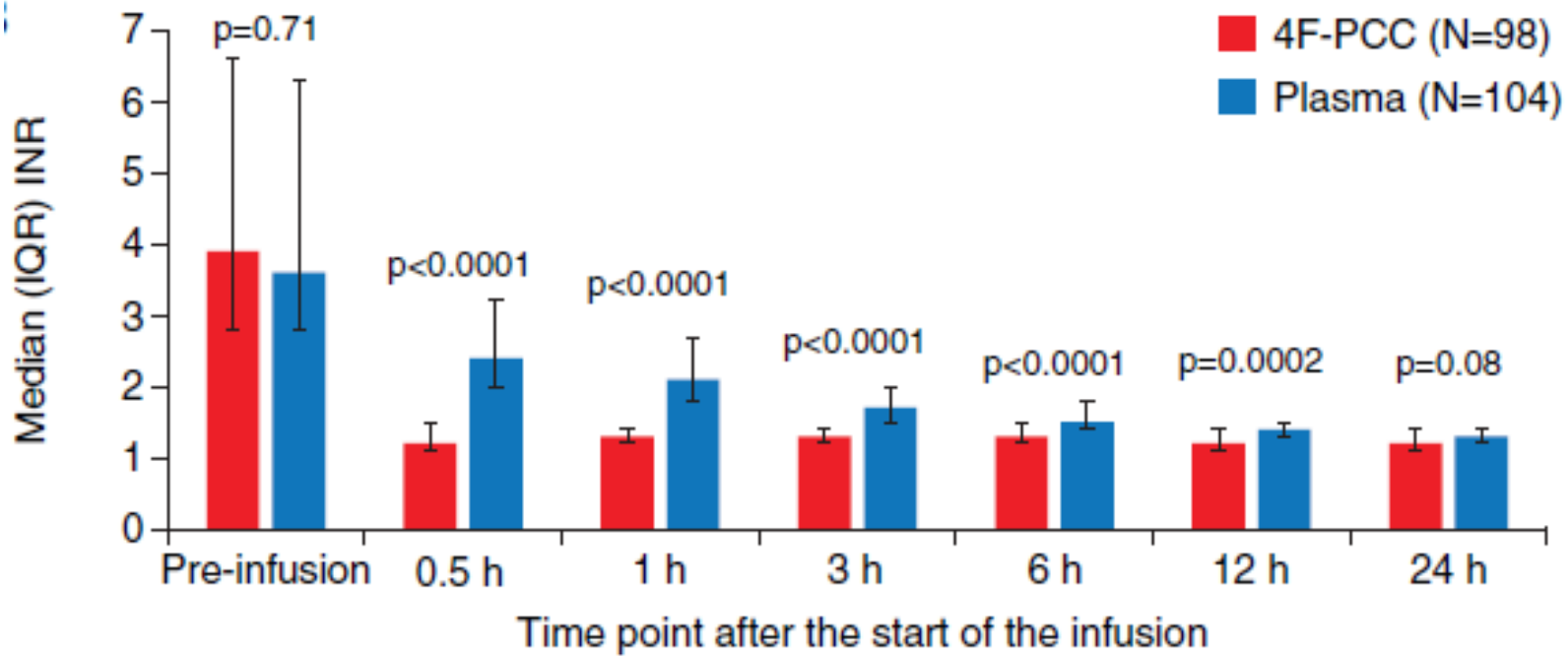
- Acute life-threatening bleeding, warfarin, INR ≥ 2 (n = 202)
- Dose of study treatments (+ Vitamin K)

Baseline INR	4F-PCC (units/kg)	Plasma (mL/kg)
2 to < 4	25	10
4-6	35	12
> 6	50	15

Max: 100 kg
Plasma rate: 1 unit/30-minute interval

Sarode R, et al. *Circulation* 2013; 128:1234-43

Co-Primary Endpoints



- "Effective" hemostasis: 72.4% PCC vs. 65.4% FFP
- Rapid INR reduction: 62.2% PCC vs. 9.6% FFP
- Thromboembolic events: 7.8% PCC vs. 5.5% FFP

Sarode R, et al. *Circulation* 2013; 128:1234-43

Phase IIIb multi-center, open label (Part 2)

- Urgent surgical or invasive procedure within 24 hours, warfarin, INR ≥ 2 (n = 168)

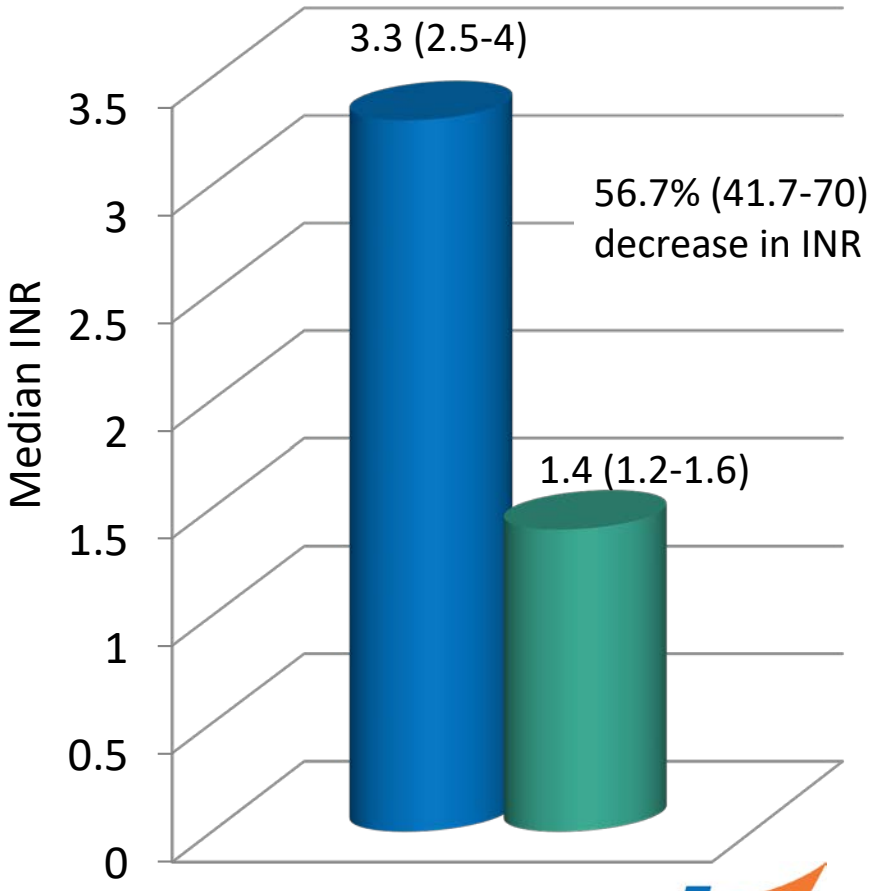
	4F-PCC (n = 87)	Plasma (n = 81)	
Effective hemostasis	89.7%	75.3%	Difference 14.3%, 95% CI 2.8-25.8
Rapid INR reduction	55.2%	9.9%	Difference 45.3%, 95% CI 31.9-56.4
Thromboembolic events	8%	7%	

- PCC 89% less volume than FFP
- Infusion time: 21 vs. 141 min

Goldstein J, et al. *Lancet* 2015; 385:2077-87

Fixed Dose PCC (1500 units)

- Retrospective, n = 39
- Median age = 70 years
- Mean weight = 79.5 kg (IQR 72.1-95.3)
- ICH = 71.8%
- Dose of 4F-PCC 1659 units (range, 1569-1710)
  - 20.4 (17.3-22.6) units/kg
- No thromboembolic events



Klein L, et al. *Am J Emerg Med* 2015; 33:1213-18

CHEST Guideline Recommendations

9.3 Treatment of Anticoagulant-Related Bleeding

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C).

We suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C).

Guyatt GH, et al. *CHEST* 2012; 141 (suppl 2):7S-47S
Ageno W, et al. *CHEST* 2012; 141 (suppl 2): 44s-88S

Stroke Guideline Recommendations

VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K *(Class I; Level of Evidence C)*. PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP *(Class IIb; Level of Evidence*

Hemphill JC, et al. *Stroke* 2015;46:DOI: 10.1161/STR.0000000000000069

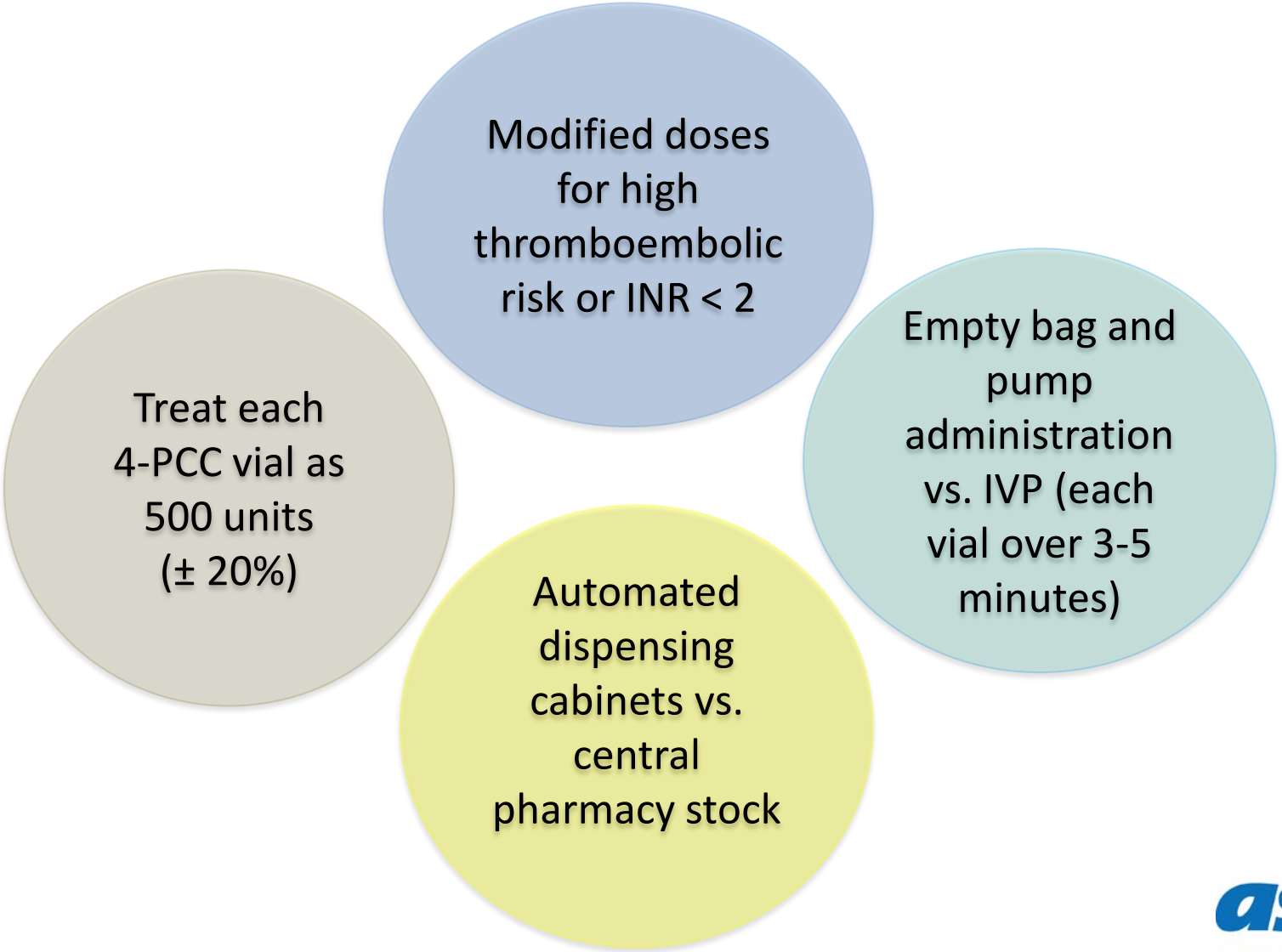
Thromboembolic Events

- Retrospective, 18 months (n = 113), evaluated up to 60 days

Categories	Thromboembolic event (%)	Deaths (%)
Total	7 (6.1)	17 (15)
Indication for VKA reversal		
ICH (n = 16)	2 (7.4)	2 (12.5)
GI bleed (n = 27)	2 (9.5)	3 (11.1)
Other bleeds (n = 21)	3 (6.7)	1 (4.8)
Emergent procedure (n = 45)	0	10 (22.2)
Elevated INR (n = 4)		1 (25)
Pre-PCC INR		
≤ 2 (n = 19)	1 (5.3)	1 (5.3)
2-4 (n = 45)	2 (4.4)	9 (20)
4-6 (n = 16)	0	2 (12.5)
>6 (n = 33)	4 (12.1)	5 (15.2)

Joseph R, et al. *Transfusion* 2016;56:799-807

4F-PCC in Practice



- 80 yo male with an LVAD
- Receiving warfarin
- Presents with unresponsiveness (sudden onset)
- Diagnosed with an intracranial hemorrhage

Which reversal strategy should be implemented for this patient?

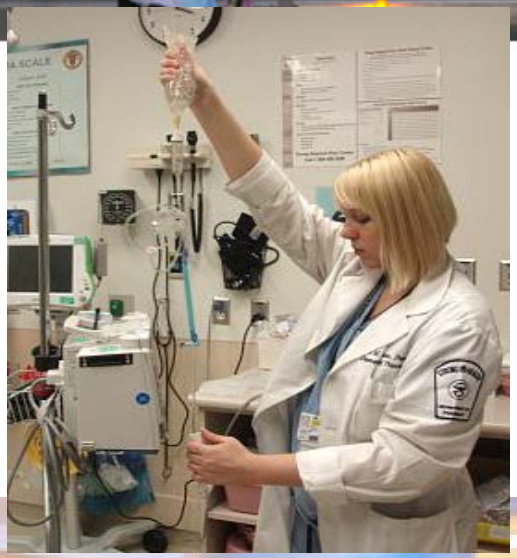
- A Don’t administer any reversal agents, too much risk for thrombosis
- B Vitamin K alone
- C Vitamin K and FFP
- D Vitamin K and 4-F PCC

Key Takeaways

- Key Takeaway #1
  - Several options for warfarin reversal
    - Vitamin K, FFP, 4F-PCC (modified dose)
- Key Takeaway #2
  - Not just about “fixing” the INR, need to thing about overall anticoagulation and risk vs. benefit
- Key Takeaway #3
  - 4F-PCC are not without ADE, need to consider thromboembolic risk (reserve for life-threatening bleeding) or need for emergent life-saving intervention

Thank You!

UNIVERSITY of ROCHESTER MEDICAL CENTER



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Assistant Professor of EM, Harvard Medical School

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65 y/o m

74/52 mm Hg

122 bpm

“No regular blood tests means no disruption to your routine.”

(True or False) Commonly available lab tests are not helpful for estimating dabigatran activity.

A TRUE

B FALSE

(True or False) Commonly available lab tests are not helpful for estimating dabigatran activity.

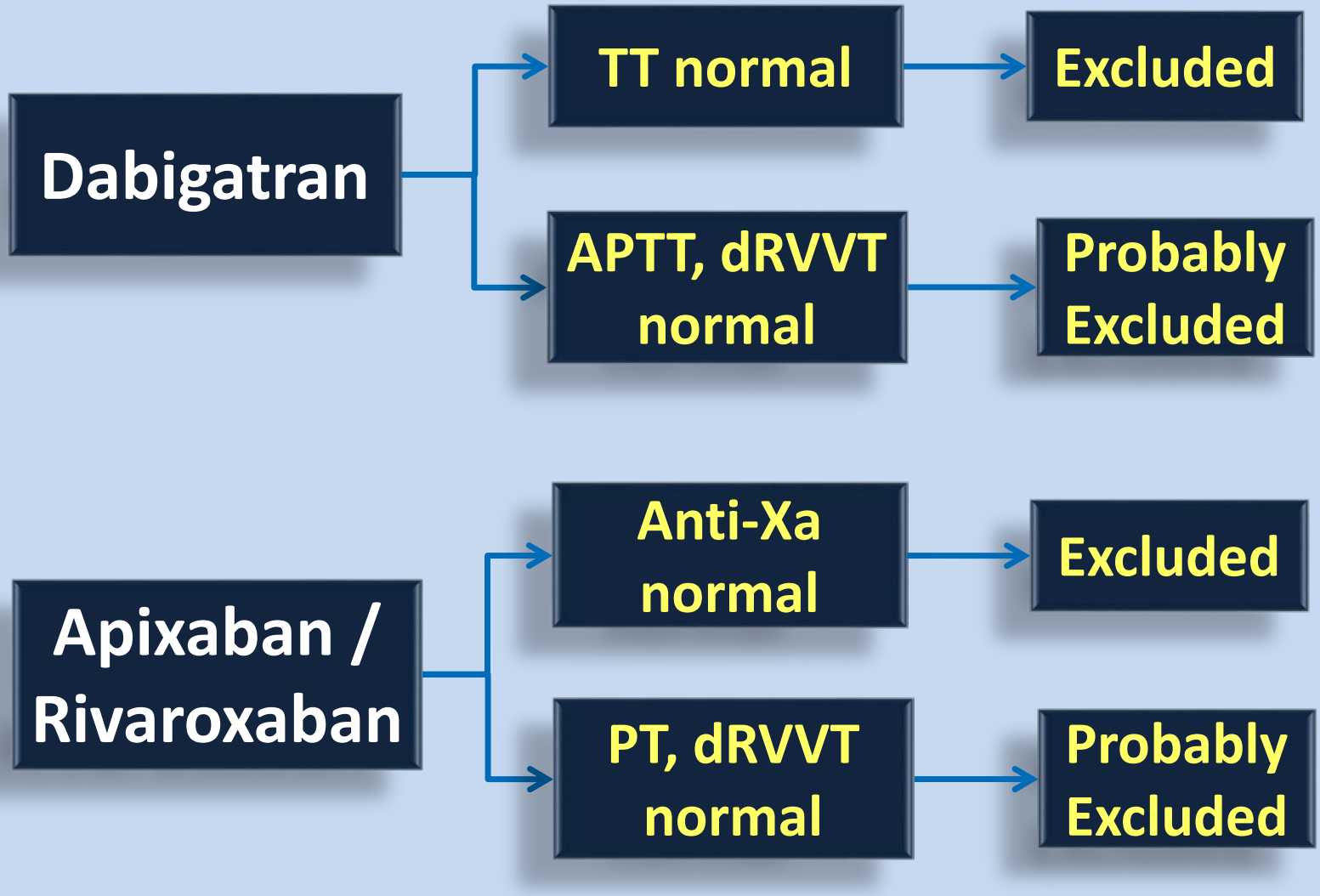
A TRUE

B **FALSE**

	Sub-therapeutic	Low Therapeutic (trough)	High therapeutic (peak)	Supra-therapeutic
PT	✗	✗	✓	✓
APTT	✗	✗/✓	✓	✓
TT	✓	✓	±	±
ECT/ECA	✗	✓	✓	✓
dTT/DTI	✗	✓	✓	✓
Anti-Xa assay	This assay unaffected by dabigatran			
ACT	✗	✗	✓	✓
dRVVT	✗	✓	✓	✓

✗ Unaffected or normal result
✓ Measureable result
± Non-linear or unmeasureable result

Favaloro EJ, et al. *Semin Thromb Hemost* 2015;41:208-27.
Hawes DM, et al. *J Thromb Haemost* 2013;11:1493-1502.



Favaloro EJ, et al. *Semin Thromb Hemost* 2015;41:208-27.
Lippi G, et al. *Clin Chem Lab* 2015;53:185-97.

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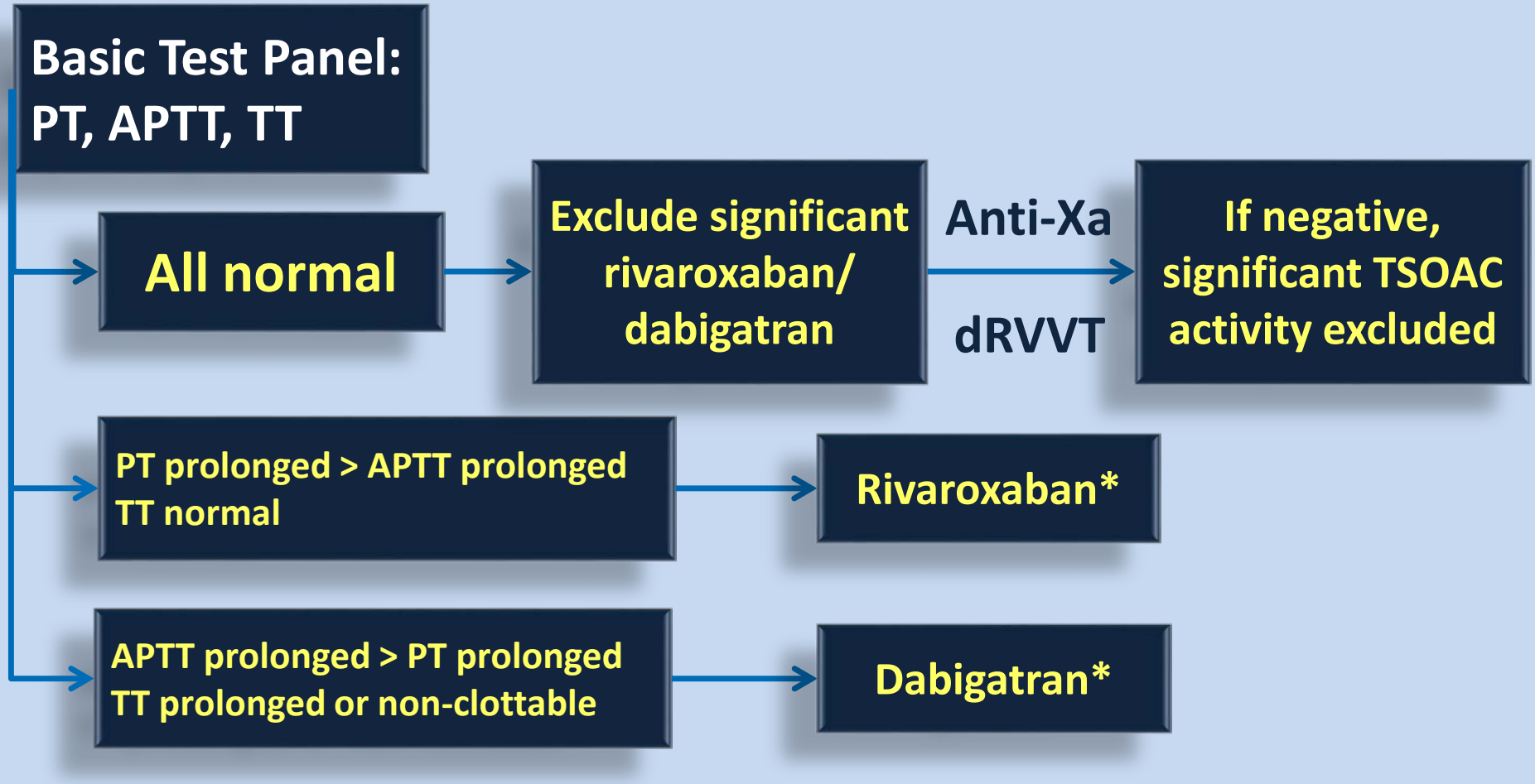
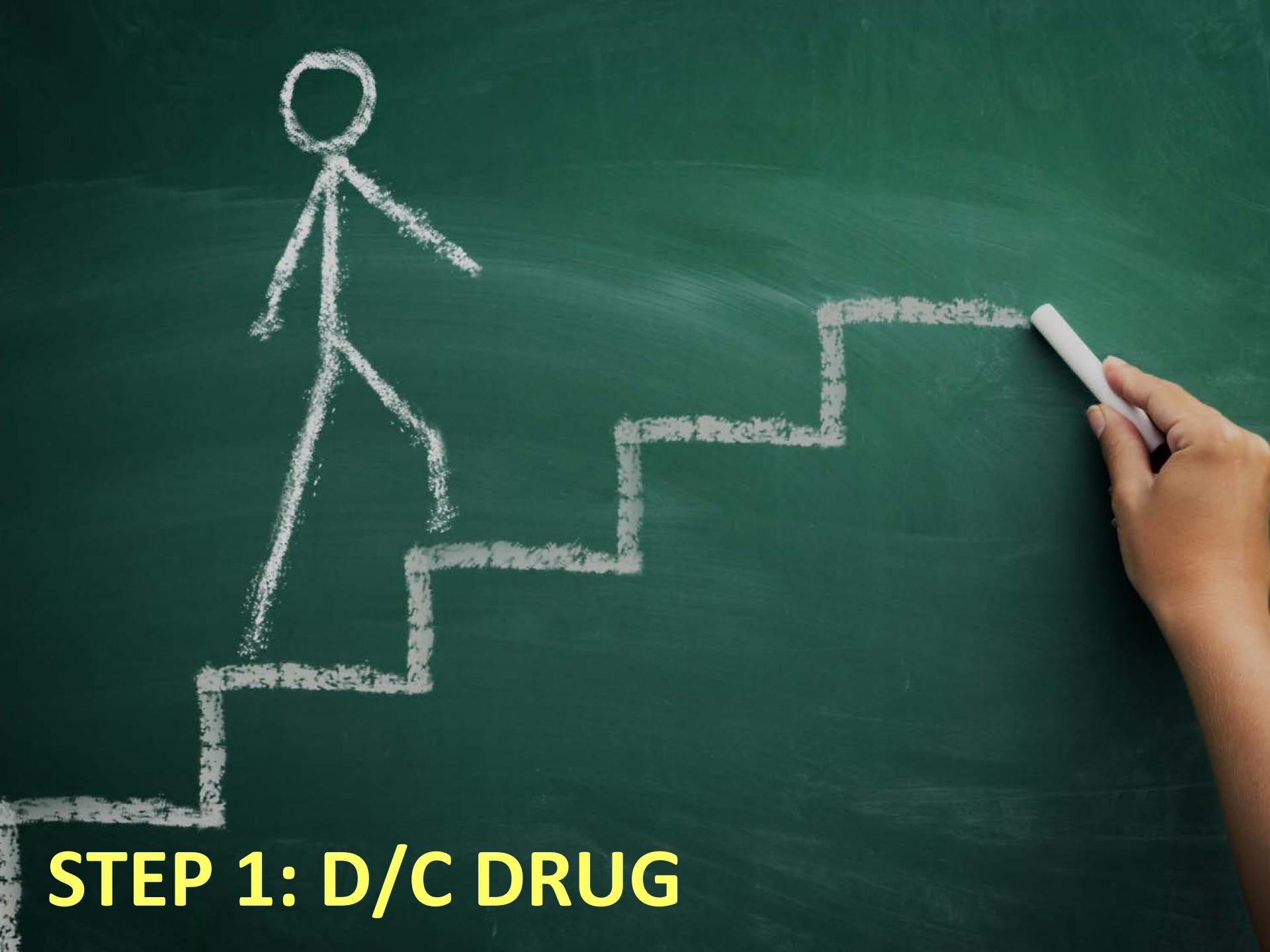


* Suggestive; requires confirmation

Favaloro EJ, et al. *Semin Thromb Hemost* 2015;41:208-27.
Lippi G, et al. *Clin Chem Lab* 2015;53:185-97.

UNKNOWN


STEP 1: D/C DRUG


STEP 2: ANTIDOTE
STEP 1: D/C DRUG

ANTIDOTE

Tier 1: Systematic Review

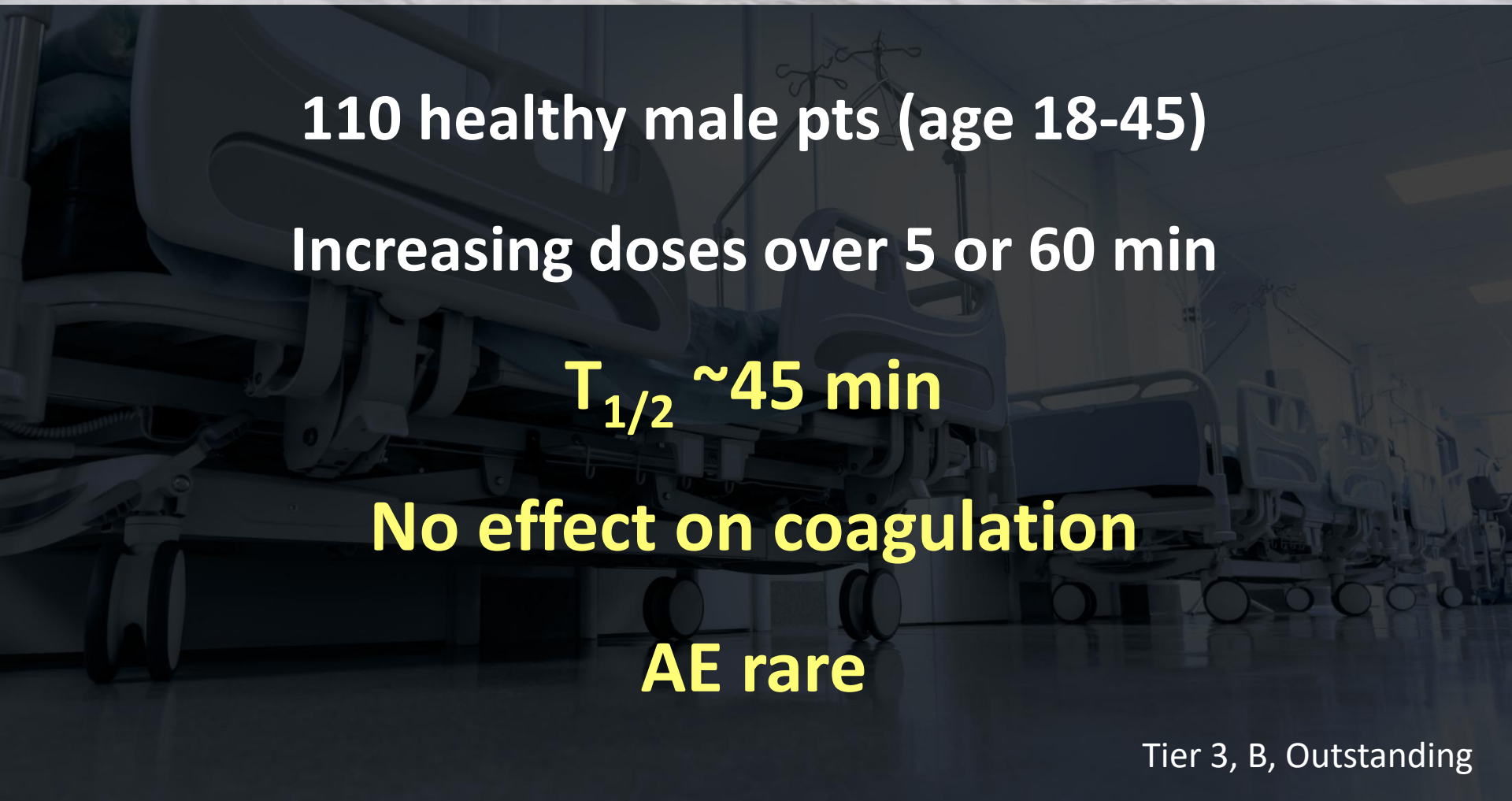
Tier 2: RCT in Core Clinical Journal

Tier 3: RCT

Tier 4: Clinical Trial

A randomized study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran

Glund S, et al. *Thromb Haemost* 2015;113(5):943-51.



110 healthy male pts (age 18-45)

Increasing doses over 5 or 60 min

$T_{1/2}$ ~45 min

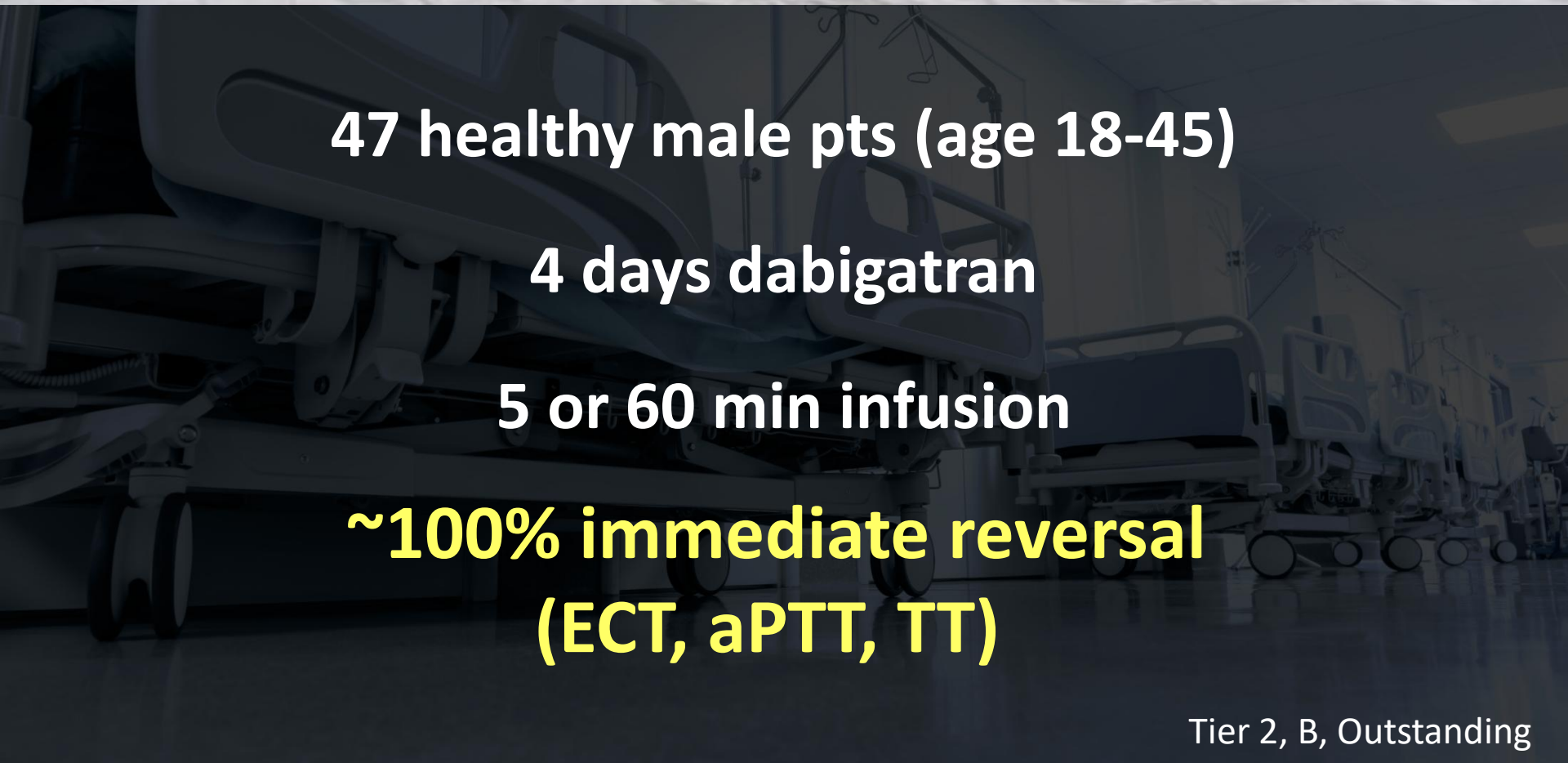
No effect on coagulation

AE rare

Tier 3, B, Outstanding

Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial

Glund S, et al. *Lancet* 2015;386(9994):680-90.



47 healthy male pts (age 18-45)

4 days dabigatran

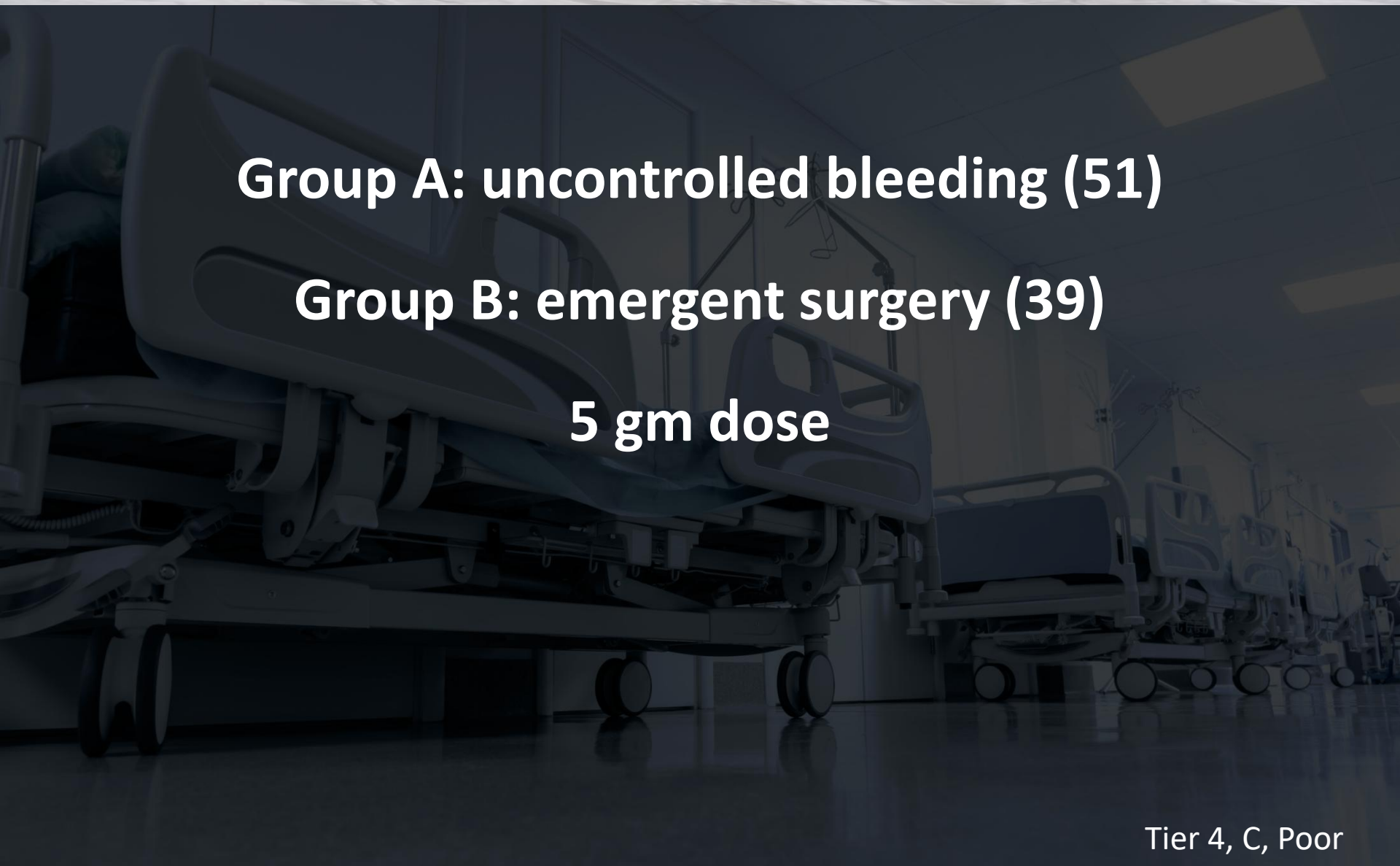
5 or 60 min infusion

~100% immediate reversal (ECT, aPTT, TT)

Tier 2, B, Outstanding

Idarucizumab for Dabigatran Reversal

Pollack CV Jr, et al. *N Engl J Med* 2015;373(6):511-20.

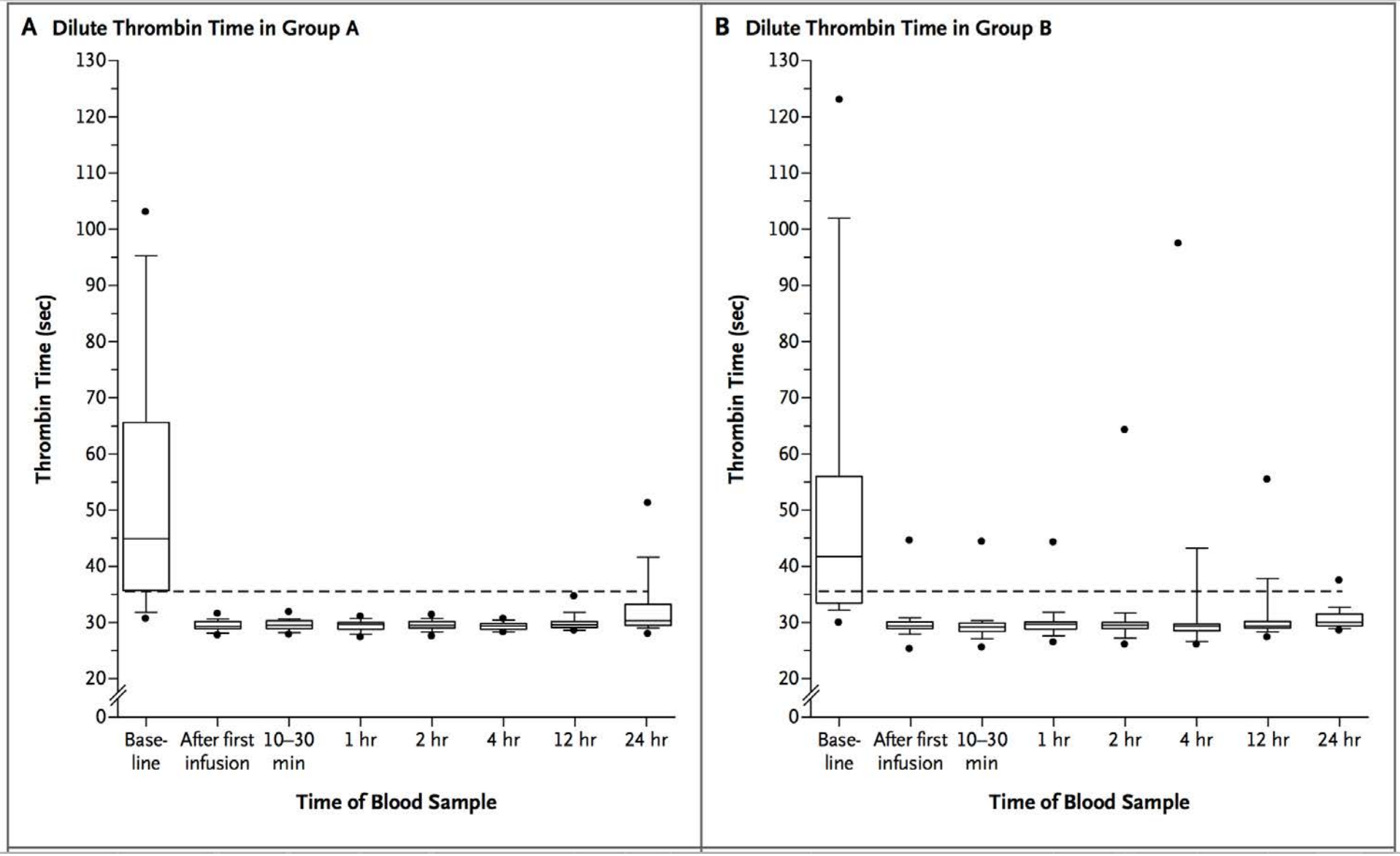


Group A: uncontrolled bleeding (51)

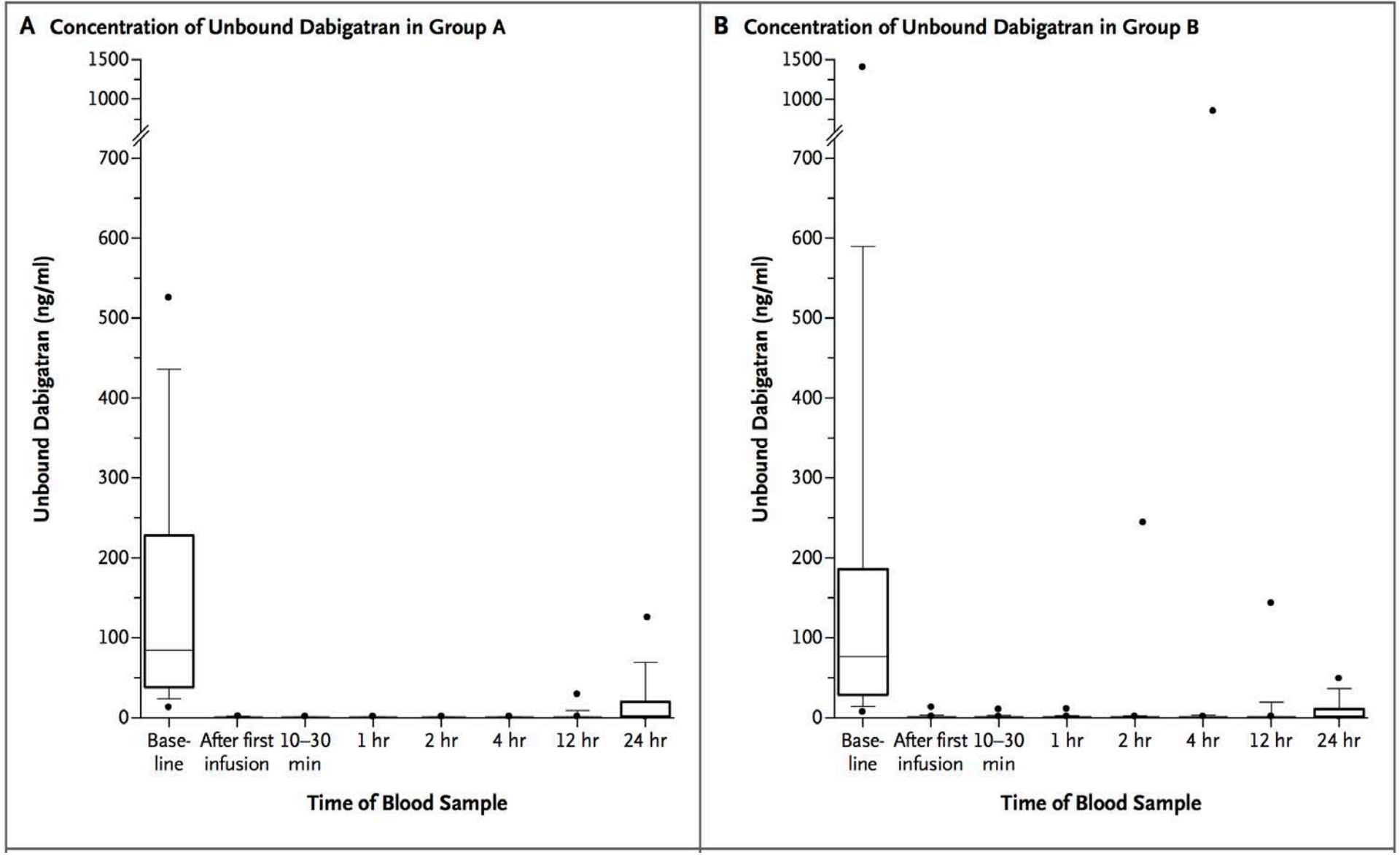
Group B: emergent surgery (39)

5 gm dose

Tier 4, C, Poor

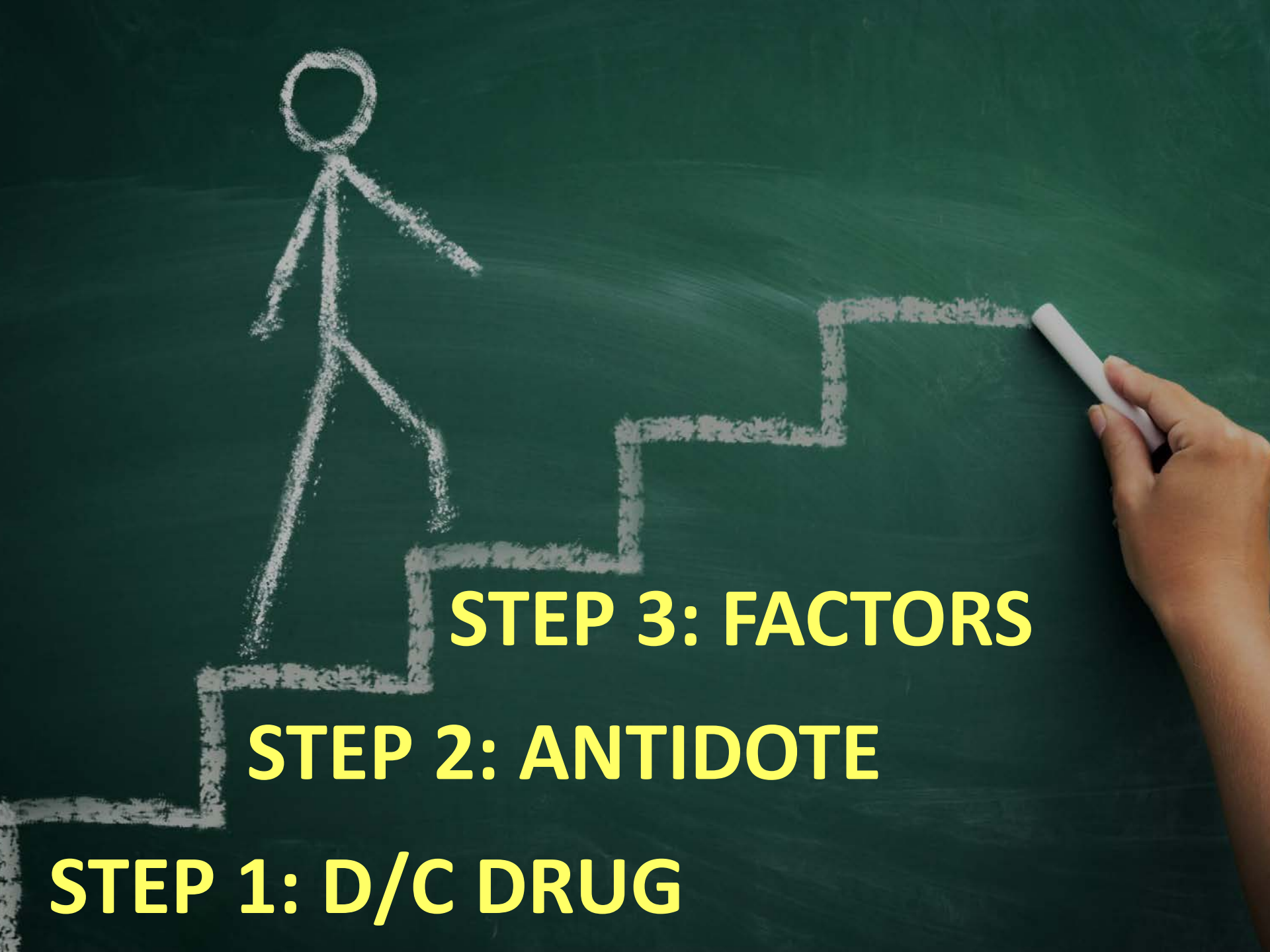


Pollack CV Jr, et al. *N Engl J Med* 2015;373(6):511-20.



Pollack CV Jr, et al. *N Engl J Med* 2015;373(6):511-20.


Good
Bad


STEP 3: FACTORS
STEP 2: ANTIDOTE
STEP 1: D/C DRUG

FACTORS

S

N

T

T

VII

IX

X

II


Frozen Plasma
DO NOT
HIV Ag/Ab,HIV RNA,
HCV RNA,HBV DNA
Negative for
Syphilis,HBsAg,HCV Ab,

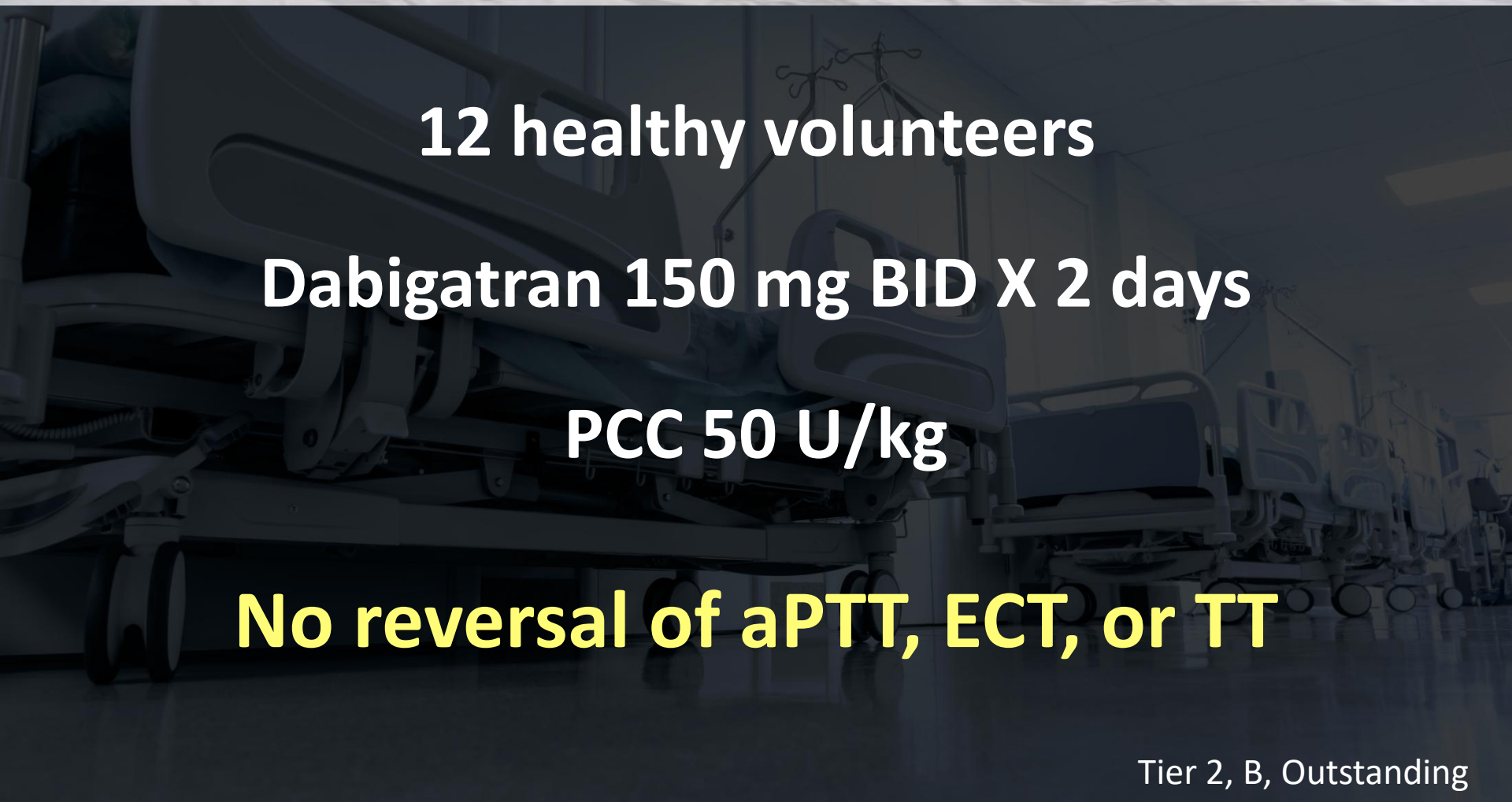
FFP

	Recombinant Factor VIIa	3-Factor PCC	4-Factor PCC *	FEIBA
VII	✓ (activated)		✓	✓ (activated)
IX		✓	✓	✓
X		✓	✓	✓
II		✓	✓	✓

* Also contains Protein C, Protein S, ATIII, and heparin

Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects

Eerenberg ES, et al. *Circulation* 2011;124(14):1573-9.



12 healthy volunteers

Dabigatran 150 mg BID X 2 days

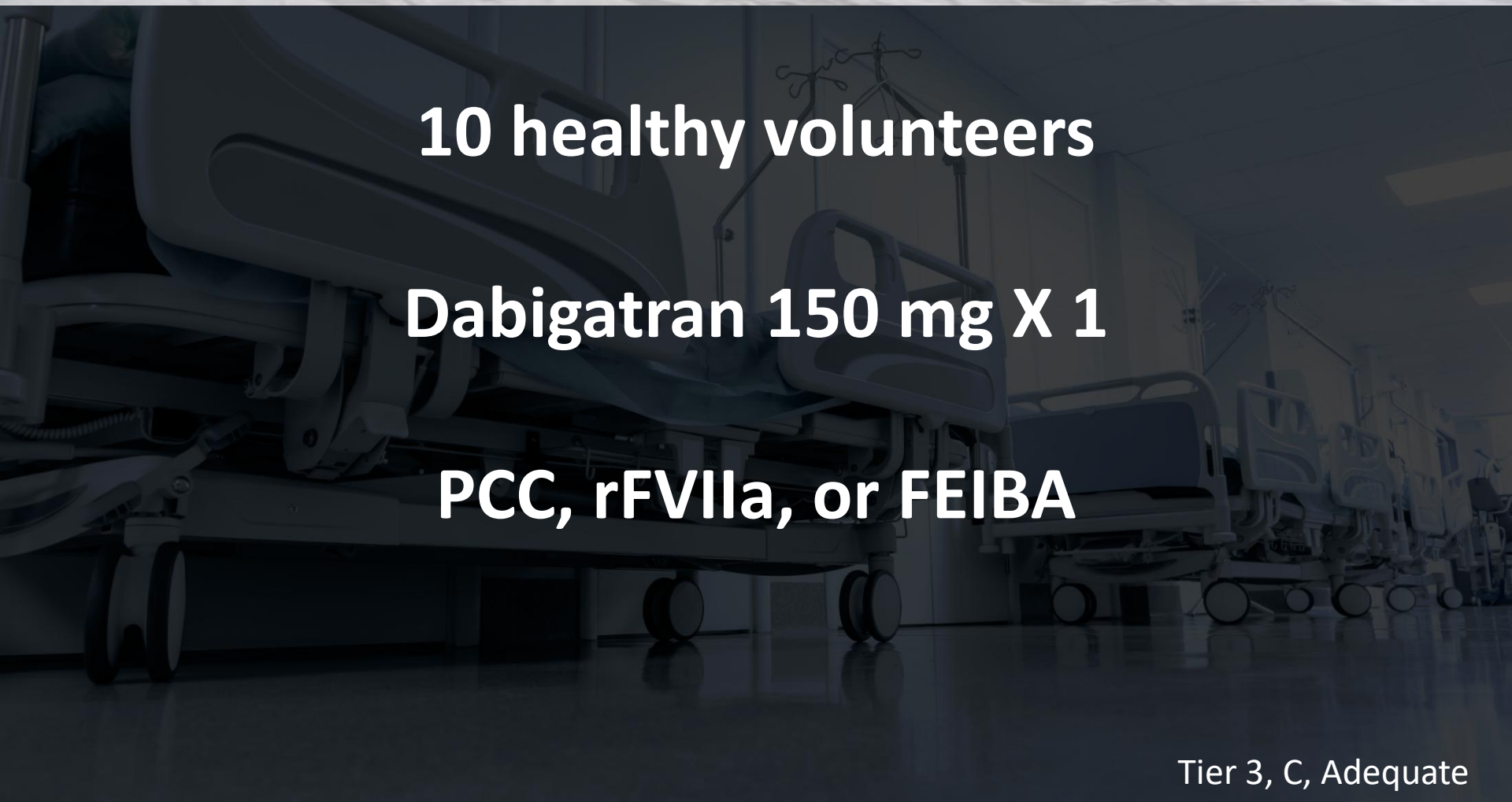
PCC 50 U/kg

No reversal of aPTT, ECT, or TT

Tier 2, B, Outstanding

Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers

Marlu R, et al. *Thromb Haemost* 2012;108(2):217-24.



10 healthy volunteers

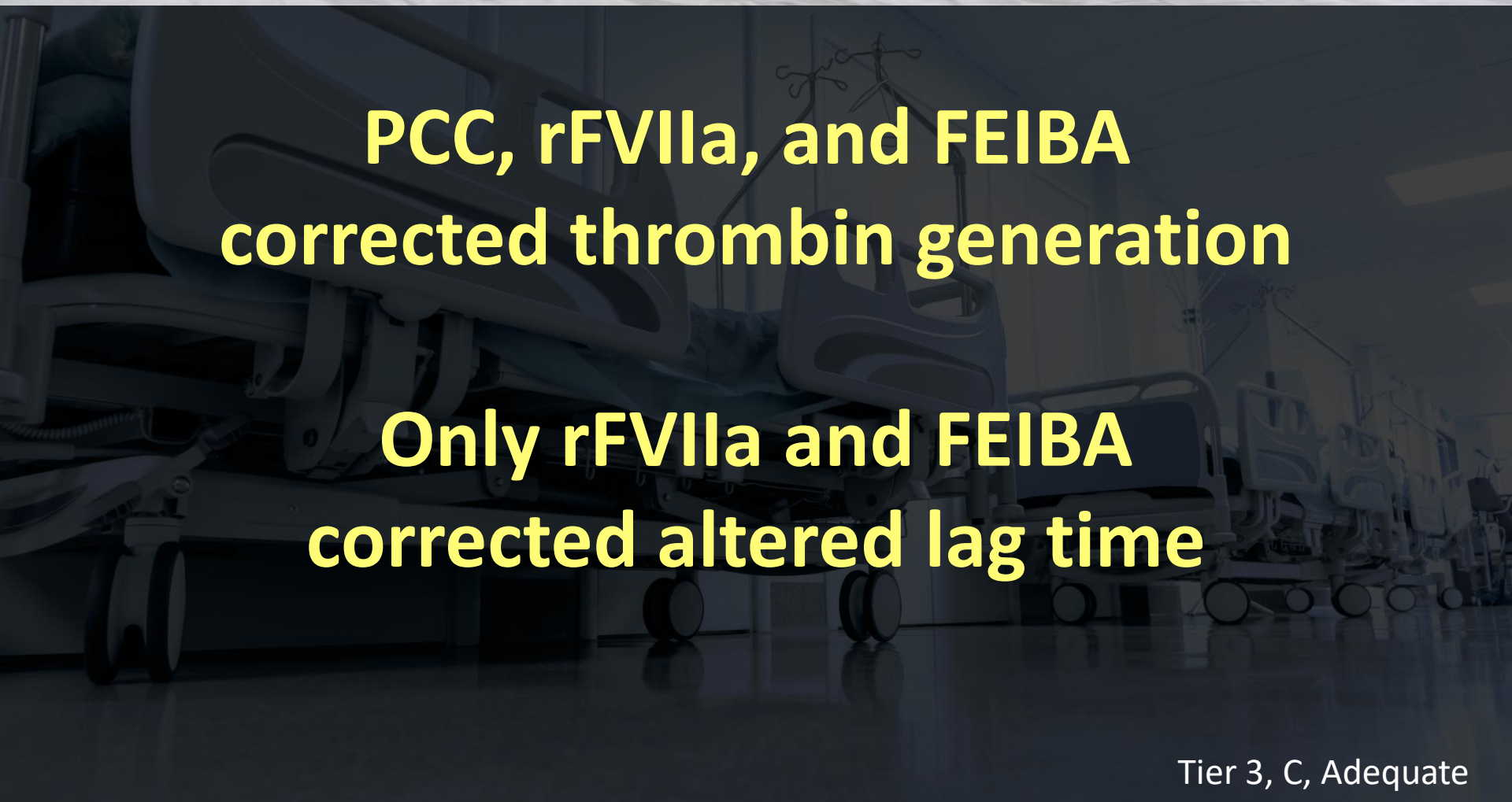
Dabigatran 150 mg X 1

PCC, rFVIIa, or FEIBA

Tier 3, C, Adequate

Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers

Marlu R, et al. *Thromb Haemost* 2012;108(2):217-24.



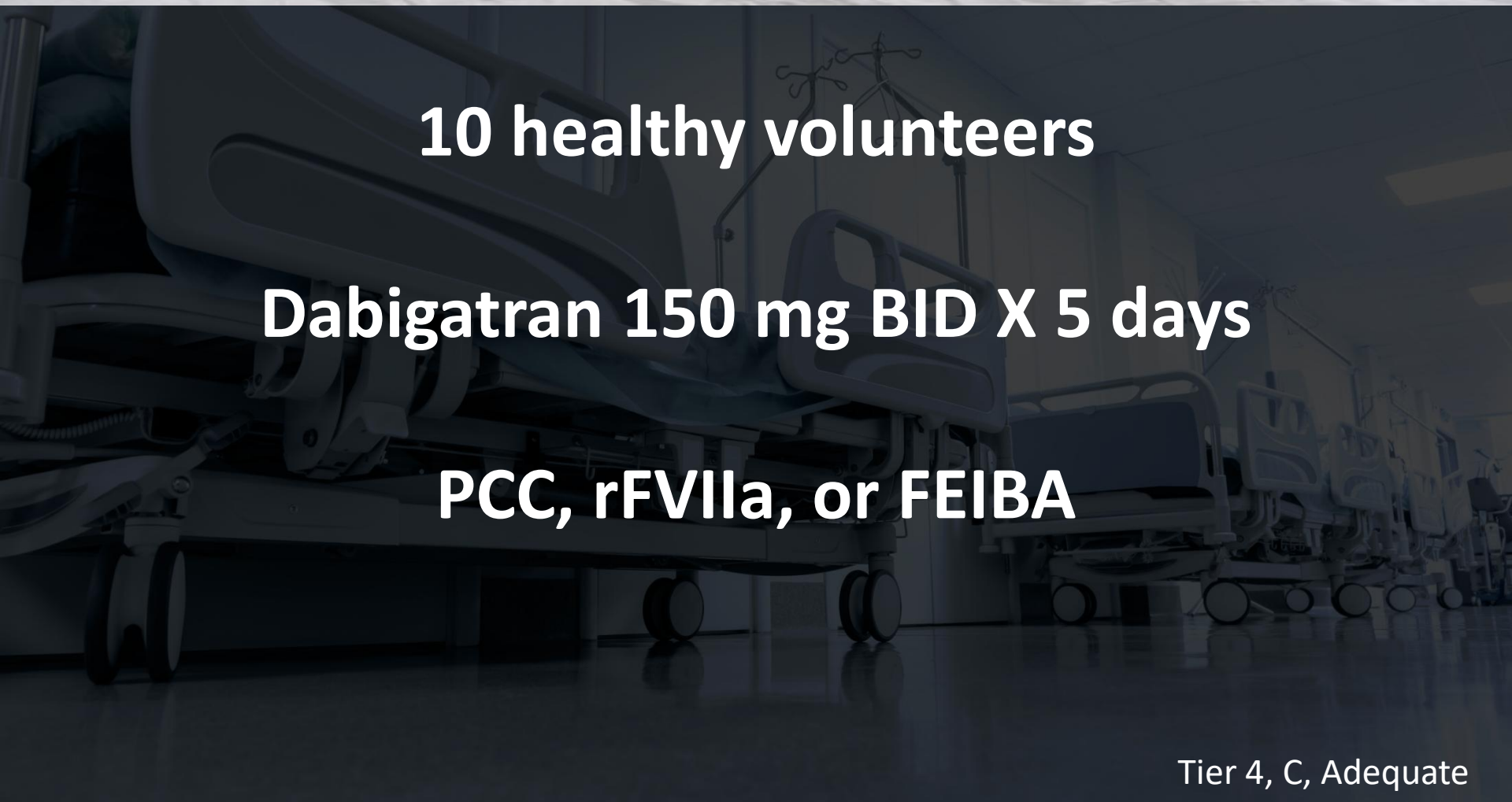
PCC, rFVIIa, and FEIBA corrected thrombin generation

Only rFVIIa and FEIBA corrected altered lag time

Tier 3, C, Adequate

Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers

Arellano-Rodrigo E, et al. *Tranfus Med Rev* 2015;29(4):242-9.



10 healthy volunteers

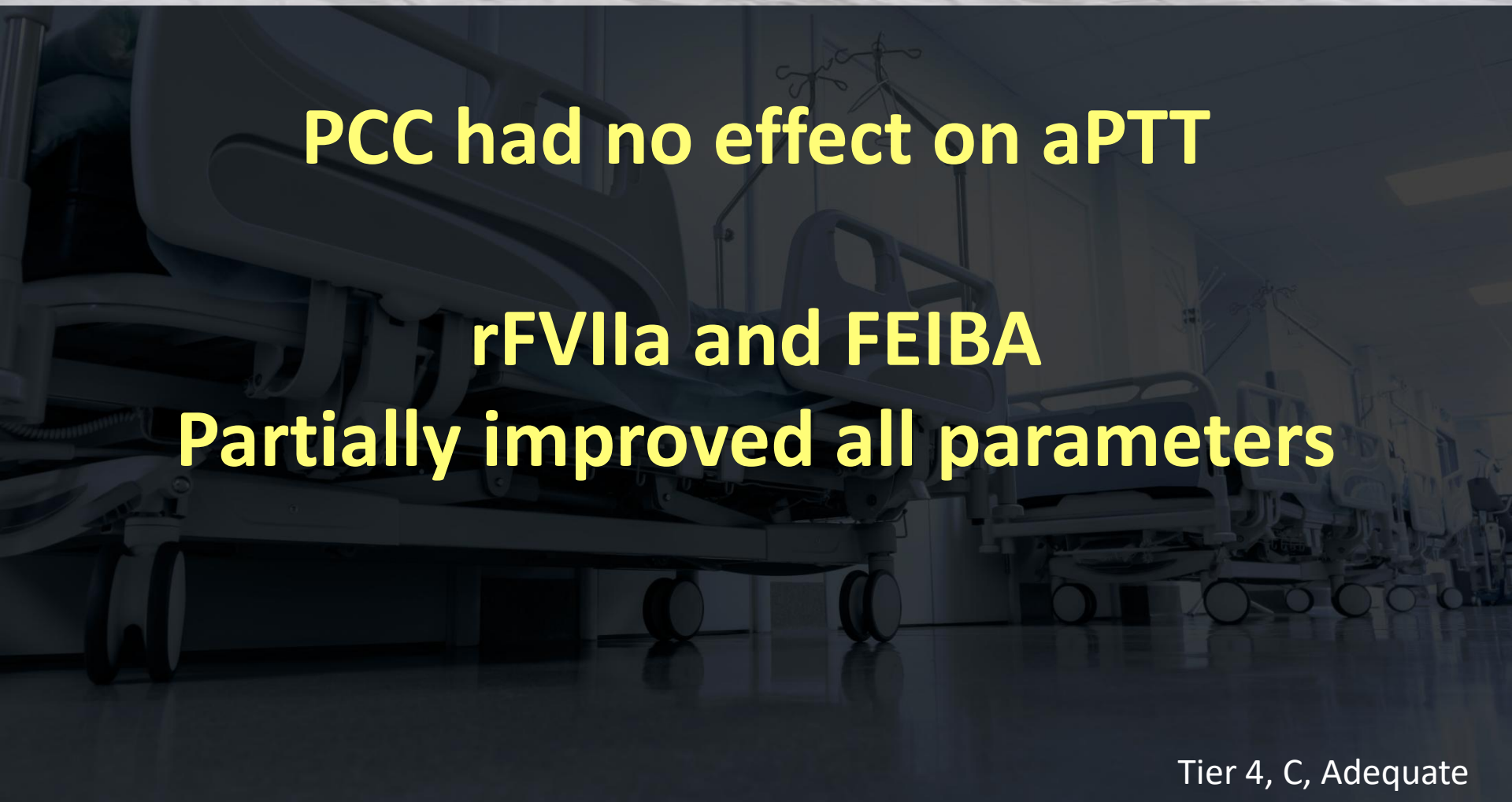
Dabigatran 150 mg BID X 5 days

PCC, rFVIIa, or FEIBA

Tier 4, C, Adequate

Coagulation Factor Concentrates Fail to Restore Alterations in Fibrin Formation Caused by Rivaroxaban or Dabigatran in Studies With Flowing Blood From Treated Healthy Volunteers

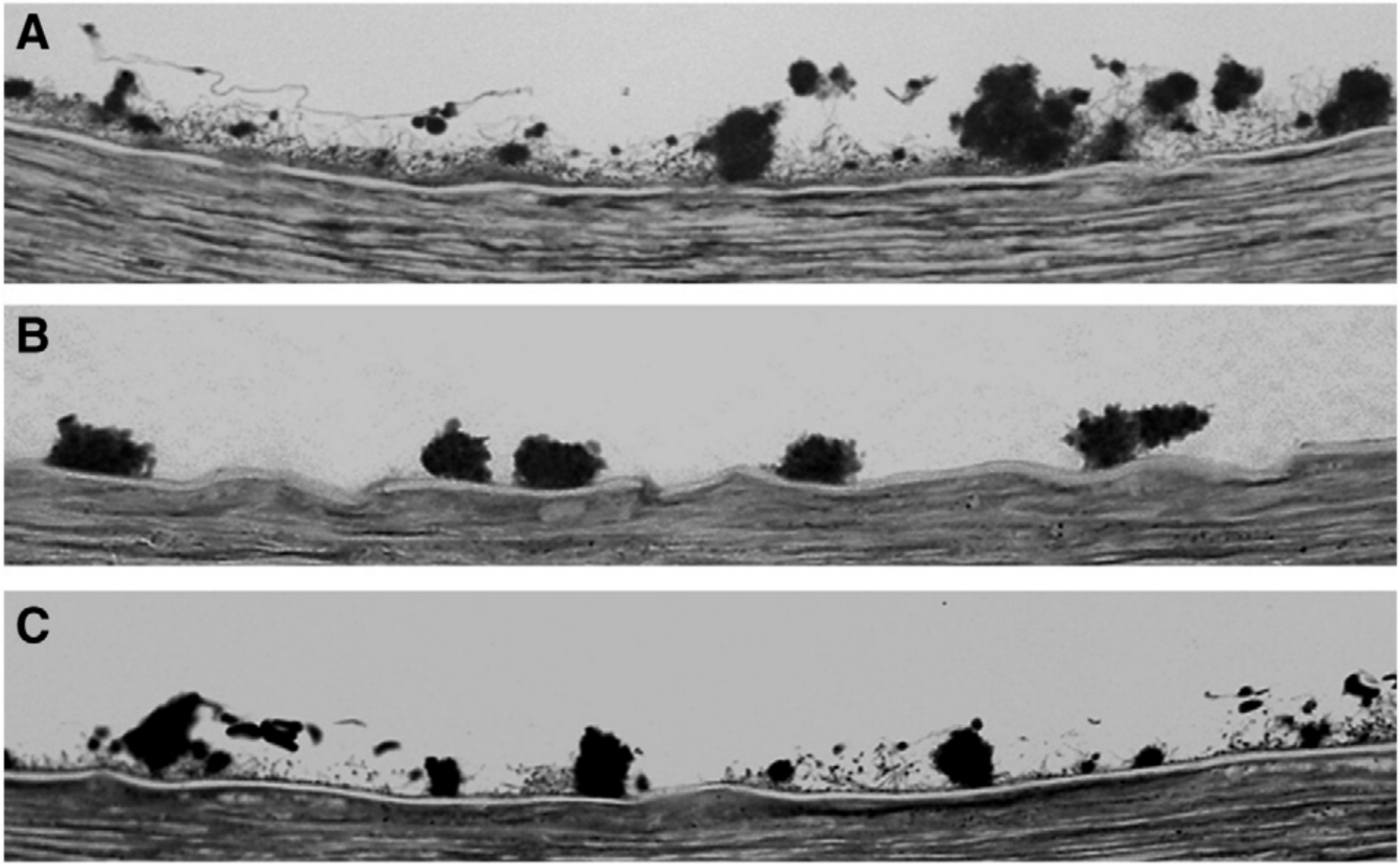
Arellano-Rodrigo E, et al. *Tranfus Med Rev* 2015;29(4):242-9.



PCC had no effect on aPTT

rFVIIa and FEIBA
Partially improved all parameters

Tier 4, C, Adequate



Arellano-Rodrigo, et al. *Transfus Med Rev* 2015;29:242-9.

Which of the following factor replacements is probably not effective in reversing dabigatran?

A aPCC (FEIBA)

B 4-factor PCC

C rFVIIa

D FFP

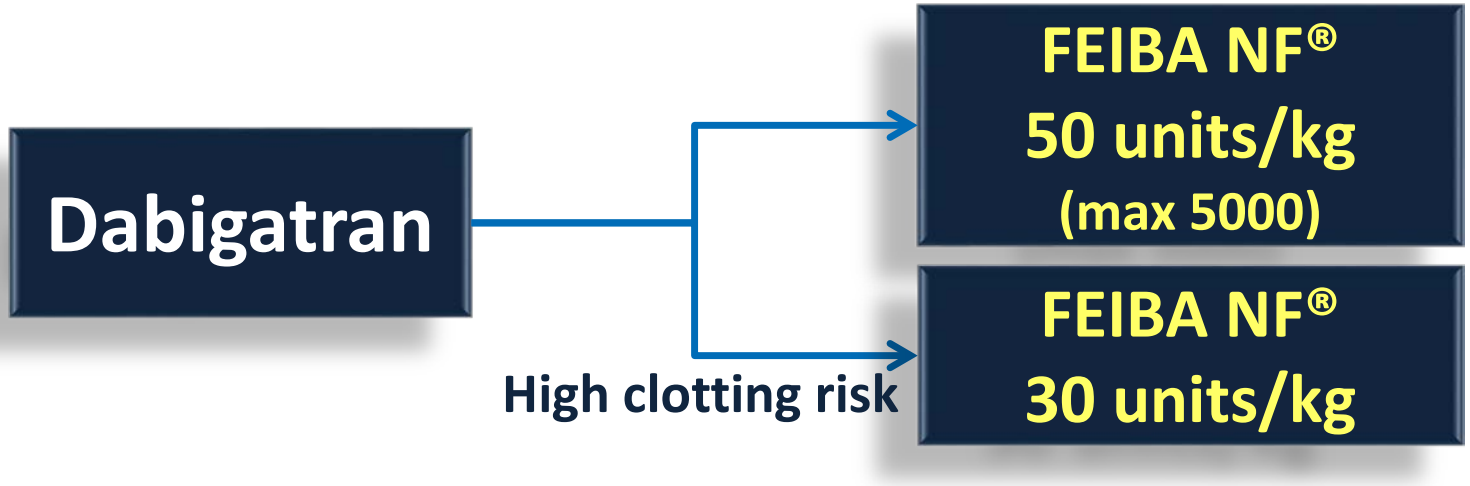
Which of the following factor replacements is probably not effective in reversing dabigatran?

A aPCC (FEIBA)

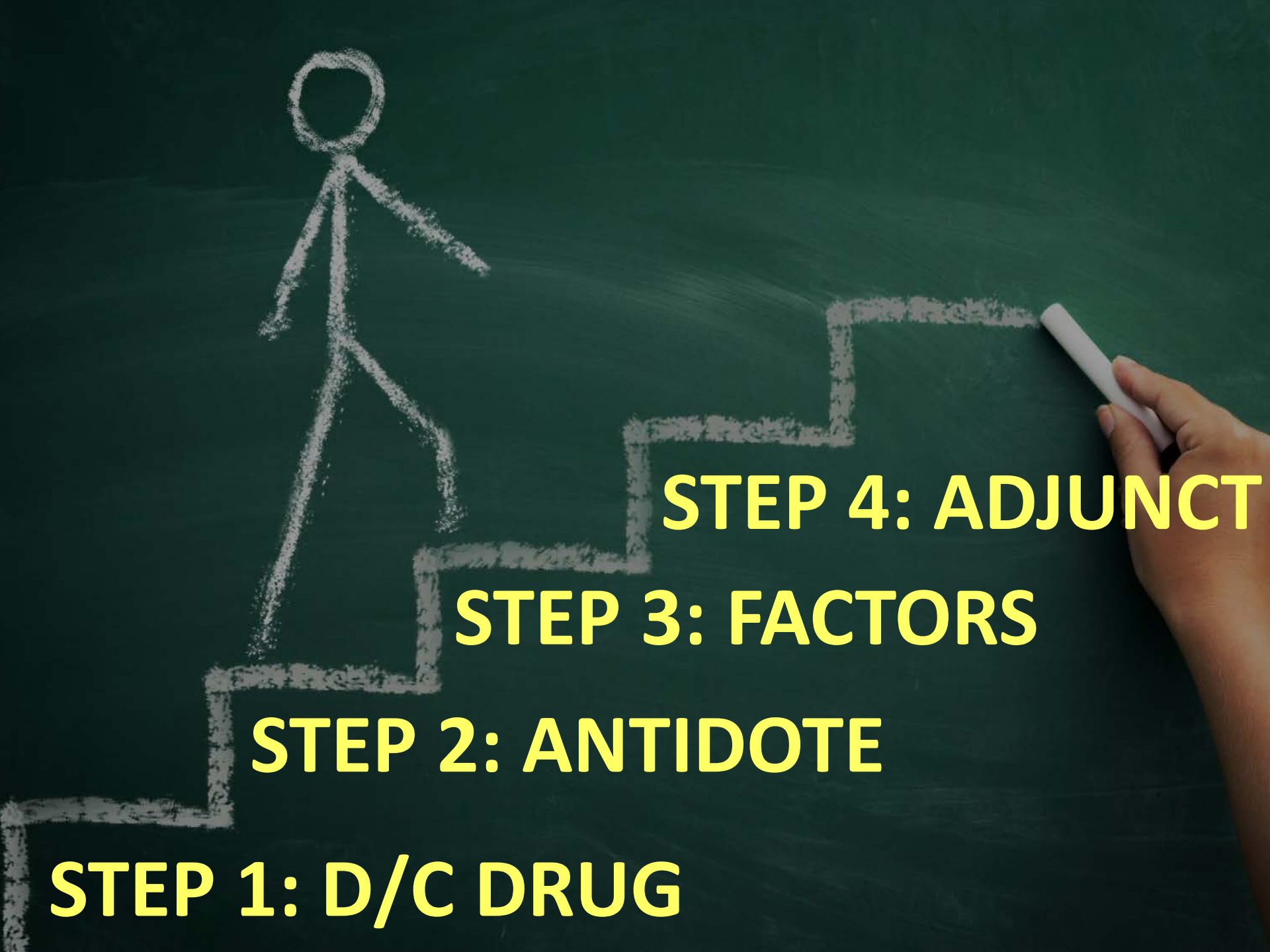
B **4-factor PCC**

C rFVIIa

D FFP



Do not repeat


STEP 4: ADJUNCT
STEP 3: FACTORS
STEP 2: ANTIDOTE
STEP 1: D/C DRUG

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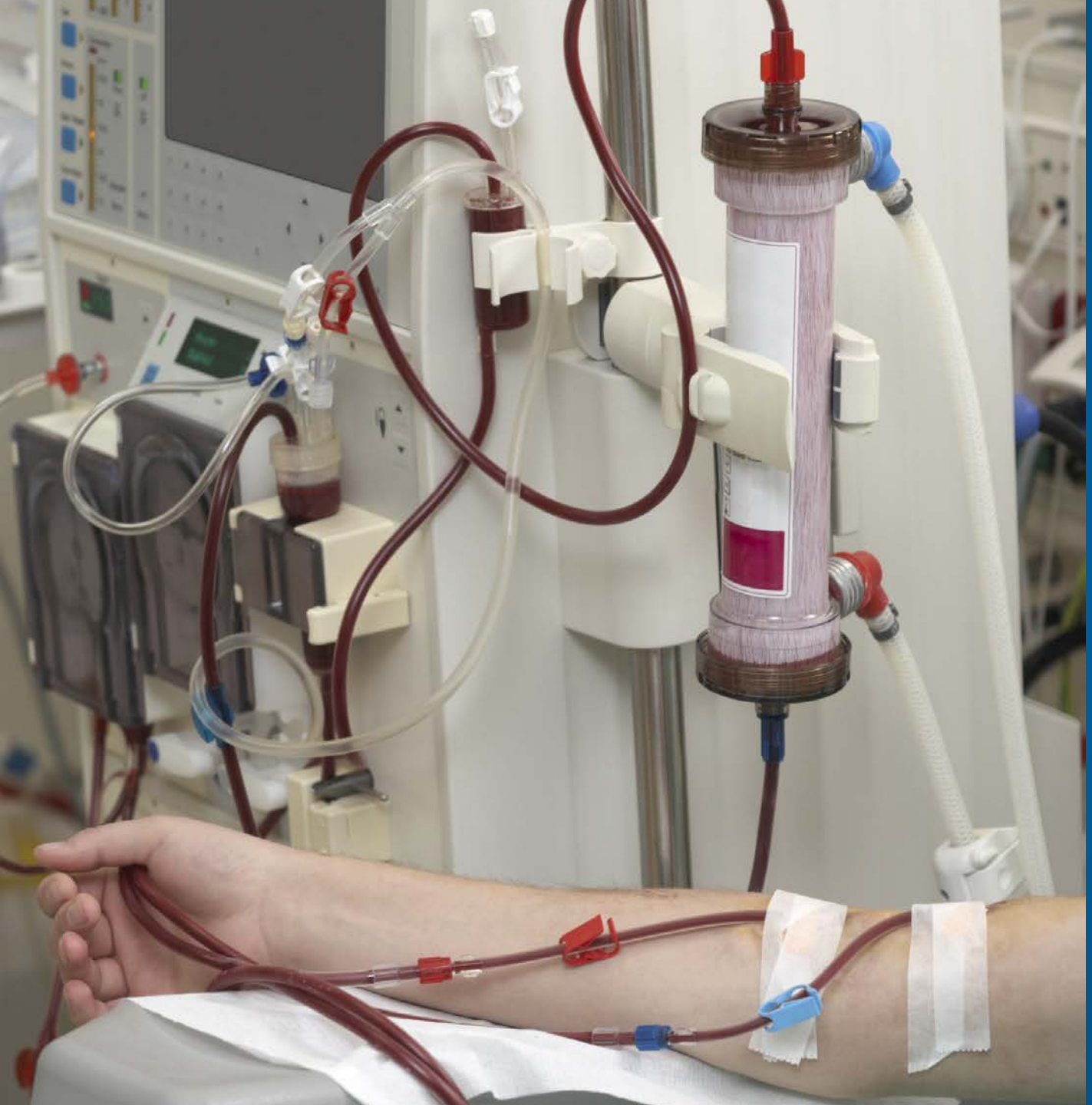
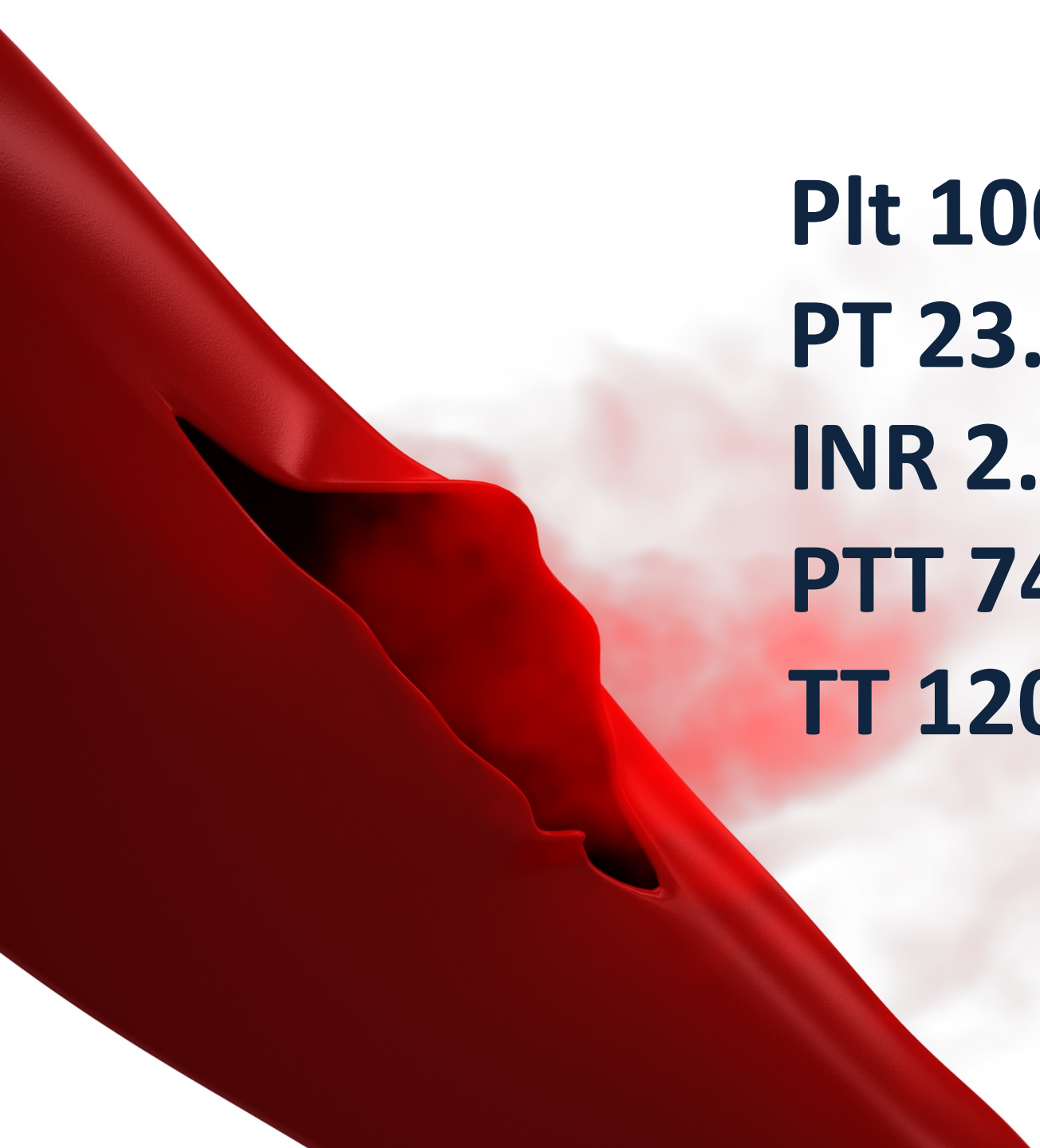


RRT

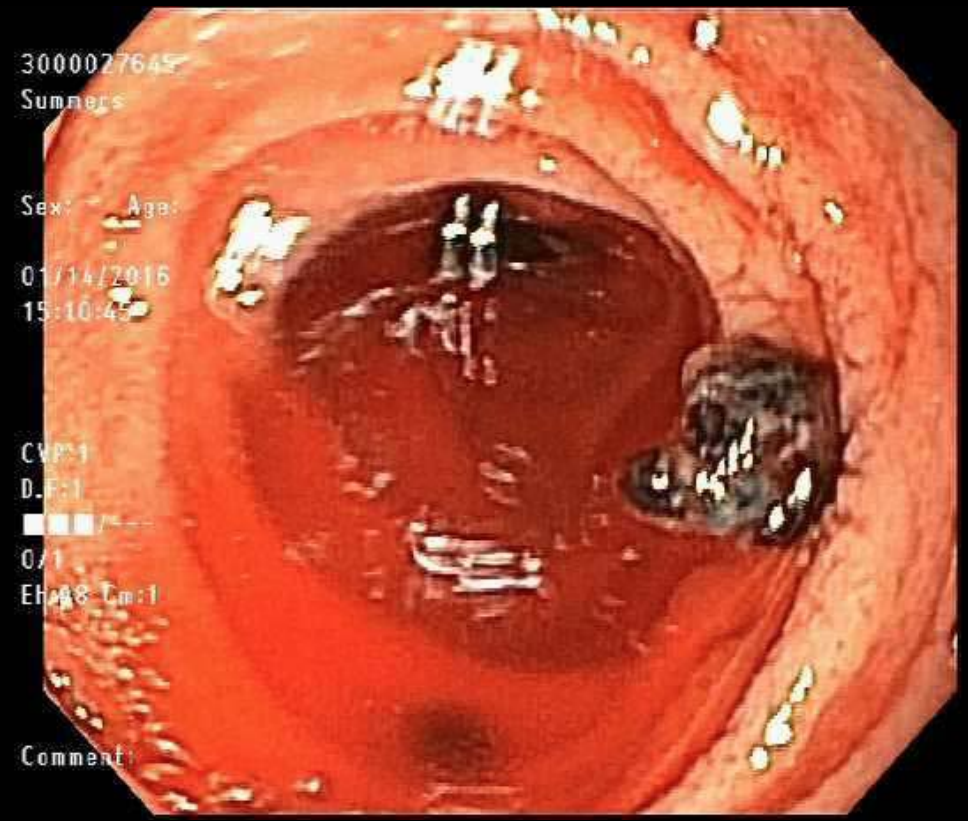
65 y/o m

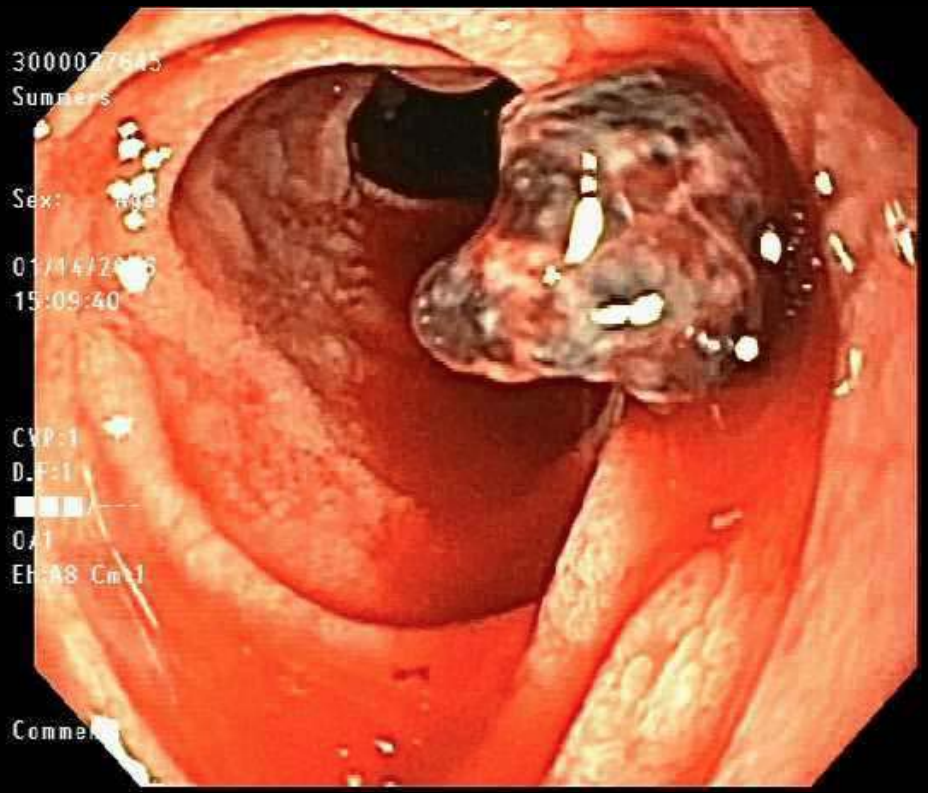
74/52 mm Hg

122 bpm



Plt 106	76
PT 23.4	13.3
INR 2.0	1.0
PTT 74	70
TT 120	24





Alhashem HM, et al. *Am J Emerg Med*. 2016 Jun 30. Epub ahead of print.

Summary

1. Routine coags can help
2. Idarucizumab role TBD
3. Factor replacement: aPCC or rFVIIa
4. Adjuncts: FFP, charcoal, RRT

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Zlatan Coralic, PharmD, BCPS
Emergency Medicine Clinical Pharmacist
Associate Clinical Professor
University of California San Francisco

@ZEDPharm

80 year old woman
AMS 40 min PTA

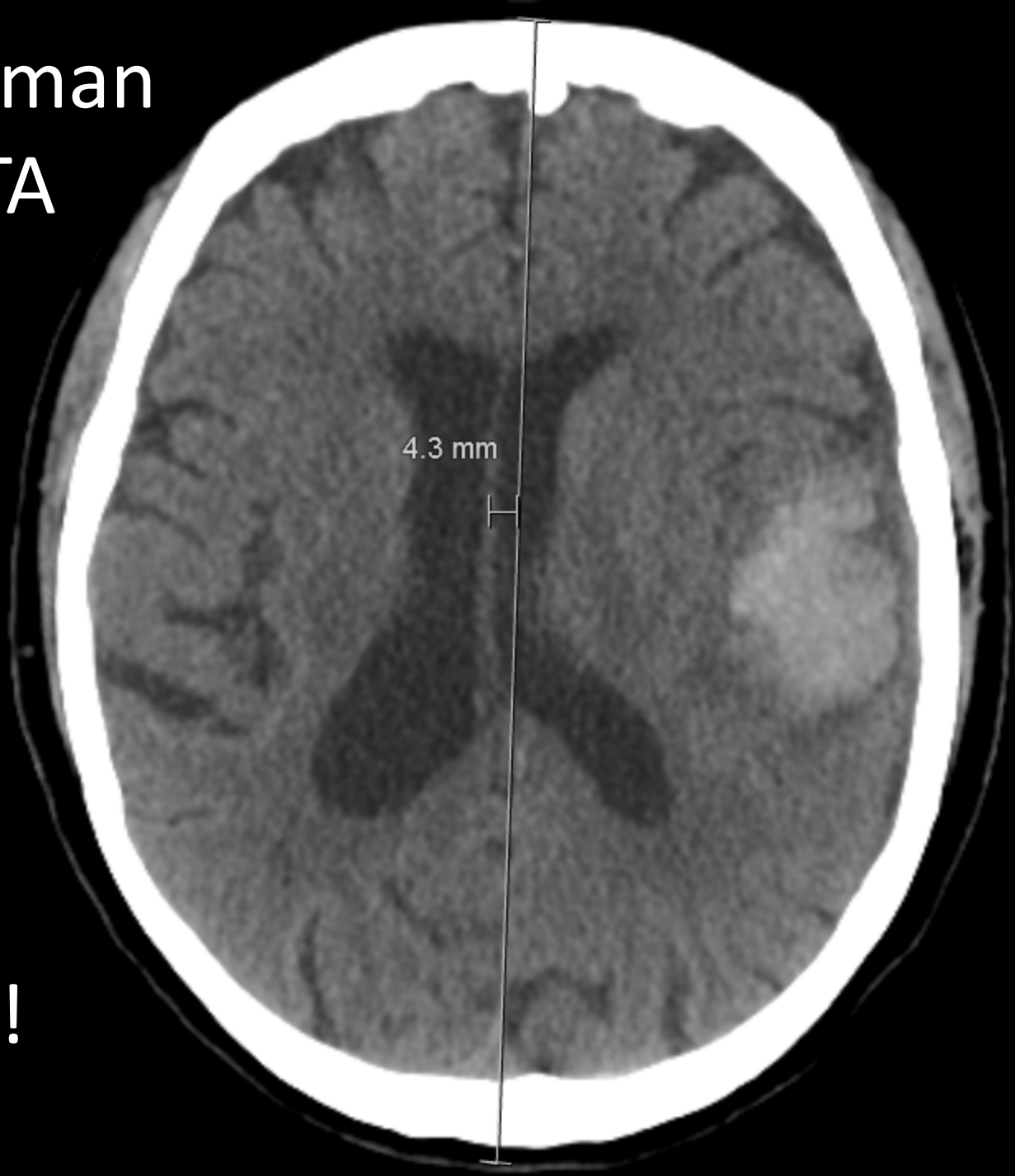
BP: 194/83
HR: 88
O2: 92%

CODE STROKE!

80 year old woman
AMS 40 min PTA

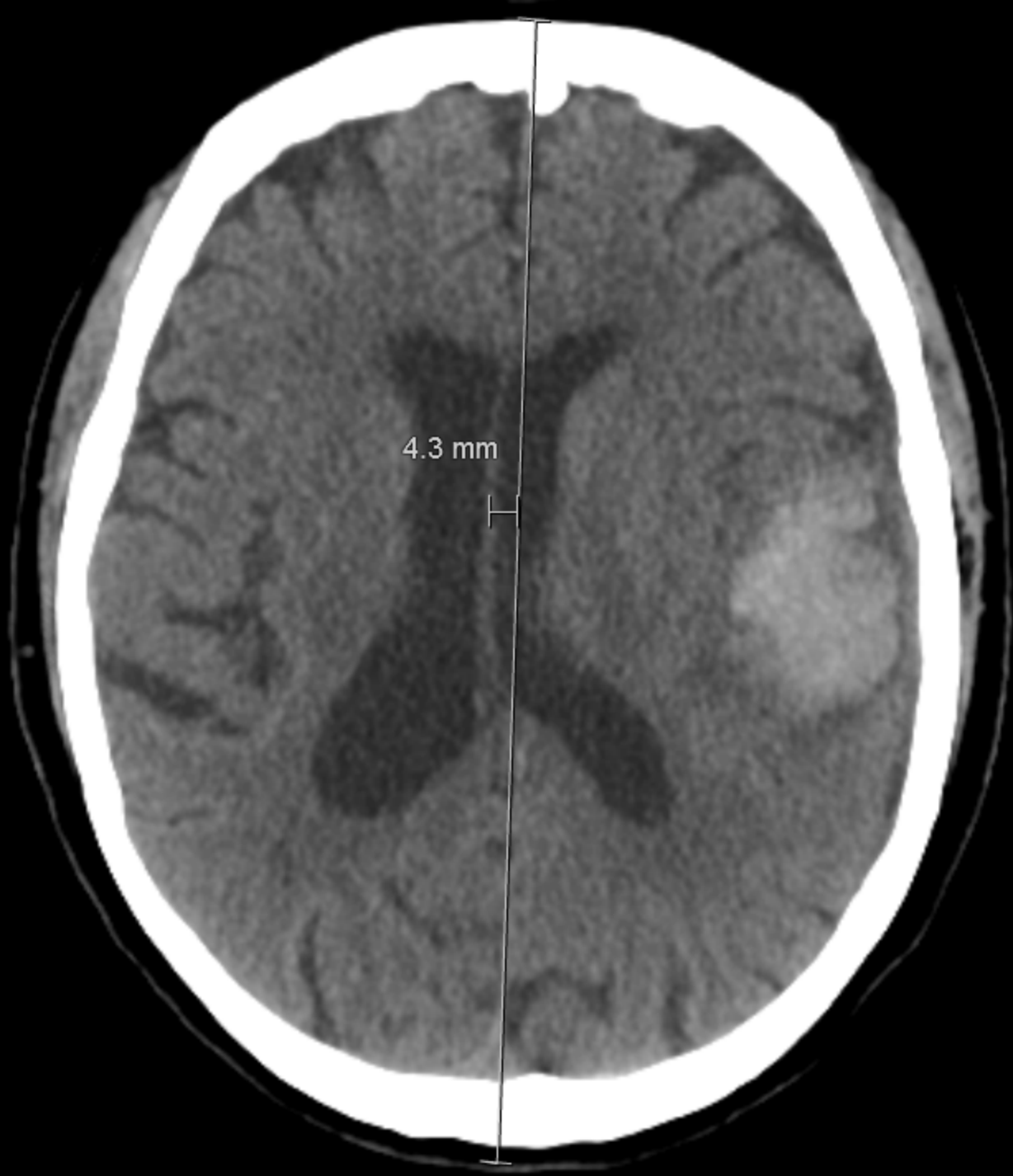
BP: 194/83
HR: 88
O2: 92

CODE STROKE!



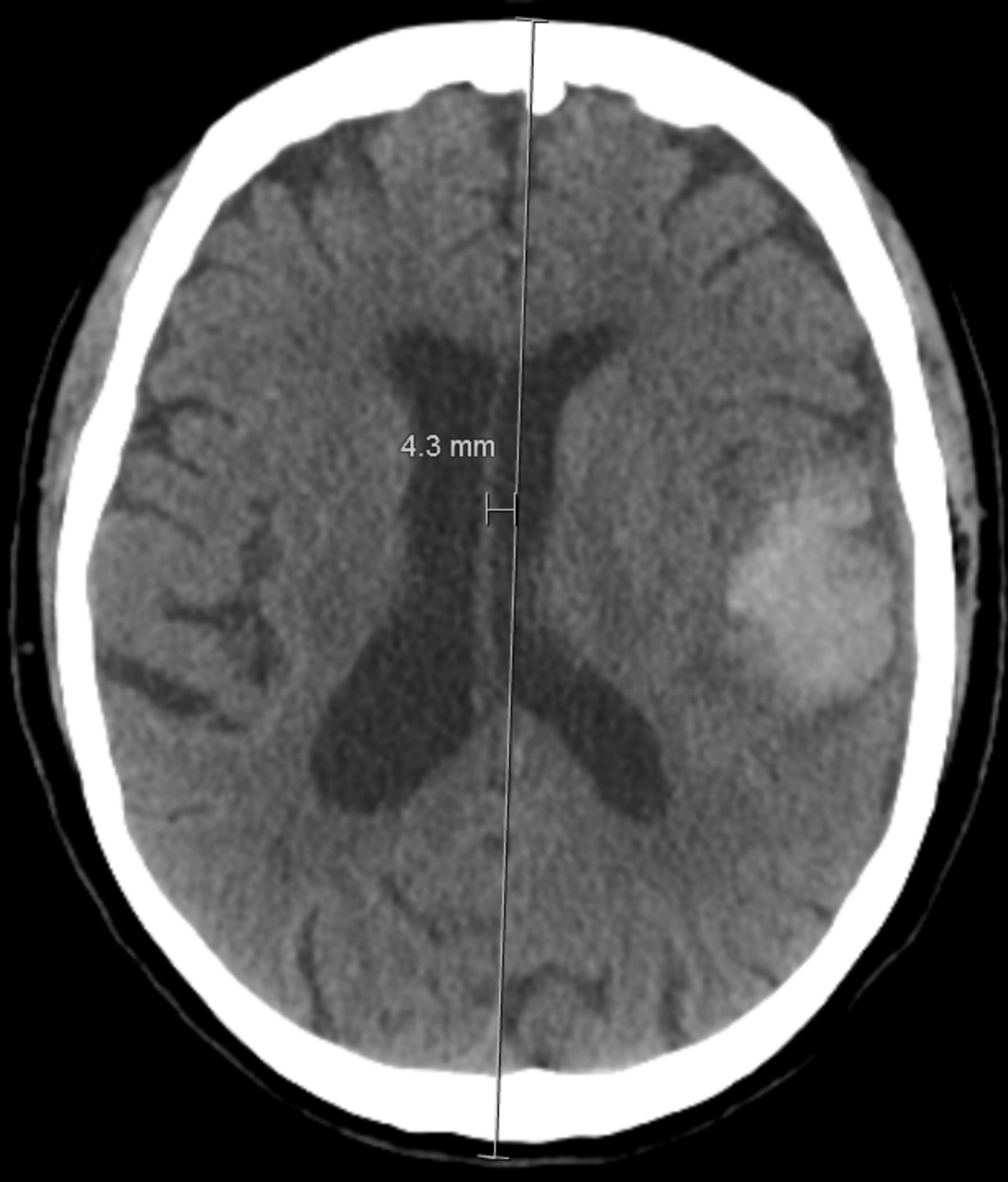
PMH:
DVTs, PE, IVC
STEMI, PCI

Med List:
Rivaroxaban
Aspirin
Metoprolol
Rosuvastatin
Metformin



SCr = 1.20
Plt = 273

aPTT = 32
PT = 13.8
INR = 1.1



What Do You Do Regarding Reversal?

A FFP

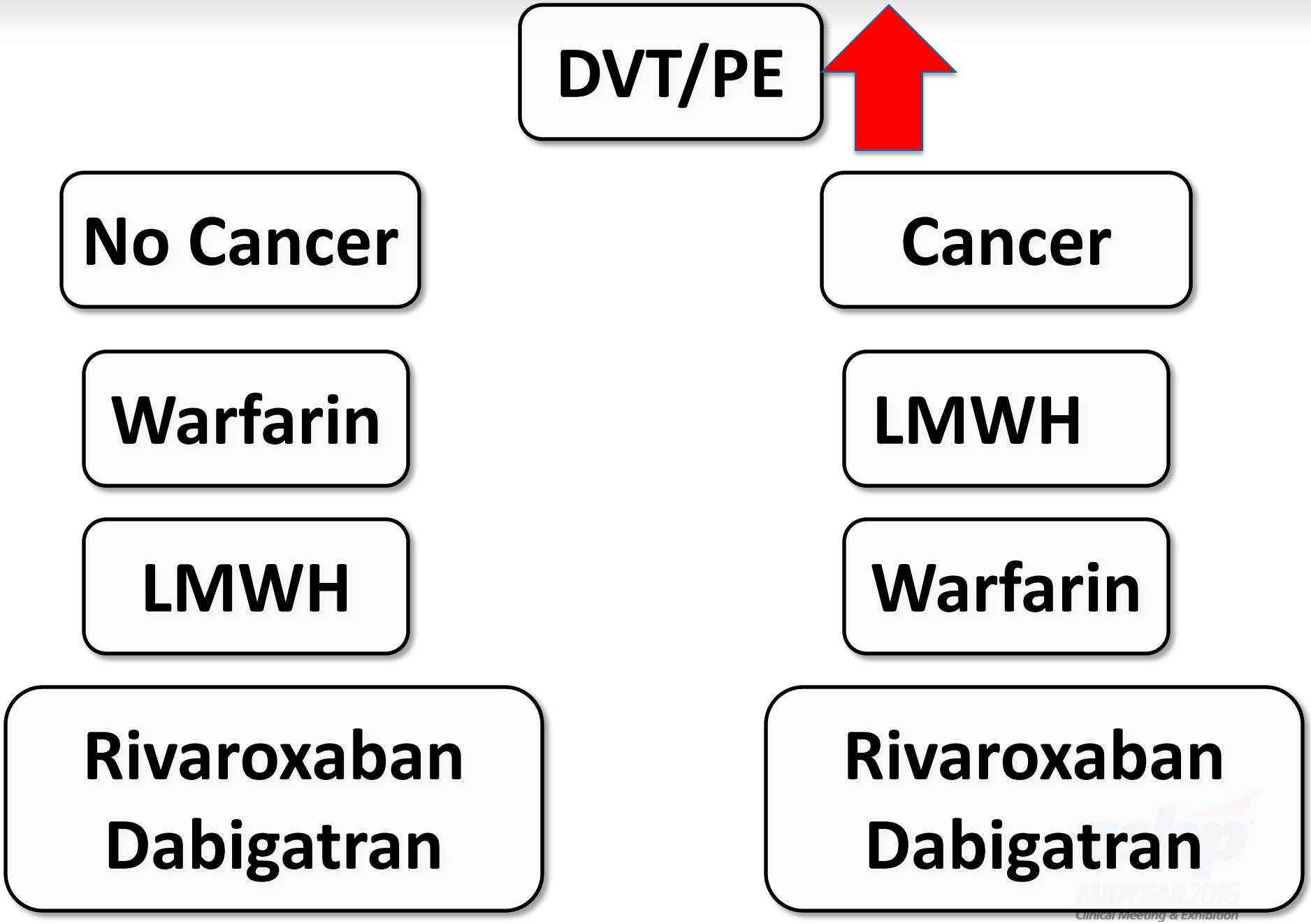
B 4-factor PCC

C FEIBA

D Do nothing

Anti Xa-reversal

- When to give?
- What to give?
- And then what?


DVT/PE
No Cancer
Warfarin
LMWH
Rivaroxaban
Dabigatran
Cancer
LMWH
Warfarin
Rivaroxaban
Dabigatran

DVT/PE

No Cancer

- Rivaroxaban
- Dabigatran
- Apixiban
- Edoxaban

Warfarin

LMWH

Cancer

LMWH

Warfarin

- Rivaroxaban
- Dabigatran
- Apixiban
- Edoxaban

Non-valve Afib ($CHA_2DS_2VASc \geq 2$)

Warfarin	I, A
Dabigatran Rivaroxaban Apixaban	I, B

AHA/ACC/HRS Afib Guidelines
Circulation. 2014 Dec 2;130(23):2071-104.

Post Marketing Data

Table 3. Dispensed oral anticoagulant prescripions 2014 Q4*		
	Prescriptions	Person-years
Rivaroxaban	1,758,016	505,560
Dabigatran	560,887	252,780
Apixaban	609,301	231,618
Warfarin	80,266,745	3,944,233
Data from IMS Health National Prescription Audit		

Adverse Events	Incidence of Warfarin, %	Incidence of NOACs, %	RR (95% CI)	I^2 Heterogeneity, %
Recurrent DVT	2.7	2.5	0.9 (0.8–1.1)	0
Death	1.7	1.5	0.9 (0.75–1.1)	0
MI	0.1	0.3	2.6 (1.1–5.6)	0
Major bleeding	1.8	1.1	0.6 (0.5–0.8)	44

NOAC, New oral anticoagulant; *RR*, relative risk; *CI*, confidence interval; *DVT*, deep venous thrombosis; *MI*, myocardial infarction.

Institute for Safe Medication Practices
Intern Emerg Med. 2015;10:499-506

Post Marketing Data

Table 5. Domestic, serious reports for 3 anticoagulant drugs, 2014									
		Direct to FDA		Death outcome		Embolic-thrombotic*		Hemorrhage*	
Drug	Total	Number, %		Number, %		Number, %		Number, %	
Rivaroxaban	3,331	525	15.8%	379	11.4%	1129	33.9%	1,647	49.4%
Dabigatran	3,592	188	5.2%	752	20.9%	721	20.1%	2,709	75.4%
Apixaban	1,014	95	9.4%	108	10.7%	224	22.1%	492	48.5%
*Standardized MedDRA queries (SMQ), broad scope									

Institute for Safe Medication Practices

Drug	Target	HL	PT/INR	aPTT
Rivaroxaban	Xa	~ 10h	"May be prolonged"	
Apixaban	Xa	~ 12h		
Edoxaban	Xa	~ 12h		
Dabigatran	DTI	~ 12h		

ECT – Ecarin Clotting Time
TT – Thrombin Time

Baumann-Kreuziger LM, et al. J Trauma Acute Care Surg 2012

Patients	Ingestion	Measurements	Outcomes
8 PCC / 9 states 203 adults 20 kids	Apixaban (11%) Rivaroxaban (89%) 211 therapy errors 12 suicide attempts	Normal INR: 80% PT: 87% PTT: 91% 50% suicide attempts had normal coags	Kids do OK All bleeds on chronic therapy: 8 GI bleeds 3 mouth/gums 1 bruise 1 urine 1 subdural (fall)

Ann Emerg Med. 2016;67:189-195.

How to Reverse Xa Inhibitors?

Historically

- FFP
- VIIa
- 3-Factor PCCs
- 4-Factor PCCs

In-vitro
Animal models
Healthy volunteers
Prothrombogenicity

BLACK BOX:
Premature discontinuation of [NOACs] increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if [NOACs] are discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Andexanet alfa

- Factor Xa decoy protein
- Recombinant, modified, human Xa
- No anticoagulant activity
- Potential reversal for
  - Apixaban
  - Rivaroxaban
  - Edoxaban
  - Enoxaparin

Rank	Status	Study
1	Completed	A Study in Older Subject to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Rivaroxaban **Condition:** Bleeding **Interventions:** Biological: Andexanet; Other: Placebo
2	Completed	A Study in Older Subjects to Evaluate the Safety and Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Apixaban **Condition:** Bleeding **Interventions:** Biological: Andexanet; Other: Placebo
3	Recruiting	A Study in Patients With Acute Major Bleeding to Evaluate the Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Direct and Indirect Oral Anticoagulants **Condition:** Bleeding **Intervention:** Biological: Andexanet

clinicaltrials.gov

Andexanet alfa

Patients	Intervention	Comparison	Outcomes
145 healthy volunteers 50 – 75 y.o	A: apixaban, or R: rivaroxaban X4 days + Andexanet bolus +/- infusion x2 hours n=101	A: apixaban, or R: rivaroxaban X4 days + Placebo n=44	**Anti-Xa decrease 92-97%** Effect **NOT** sustained U-shape drop & bounce
NCT02329327	*recruiting*		Hemostasis

N Engl J Med 373(25): 2413-2424.

Patients

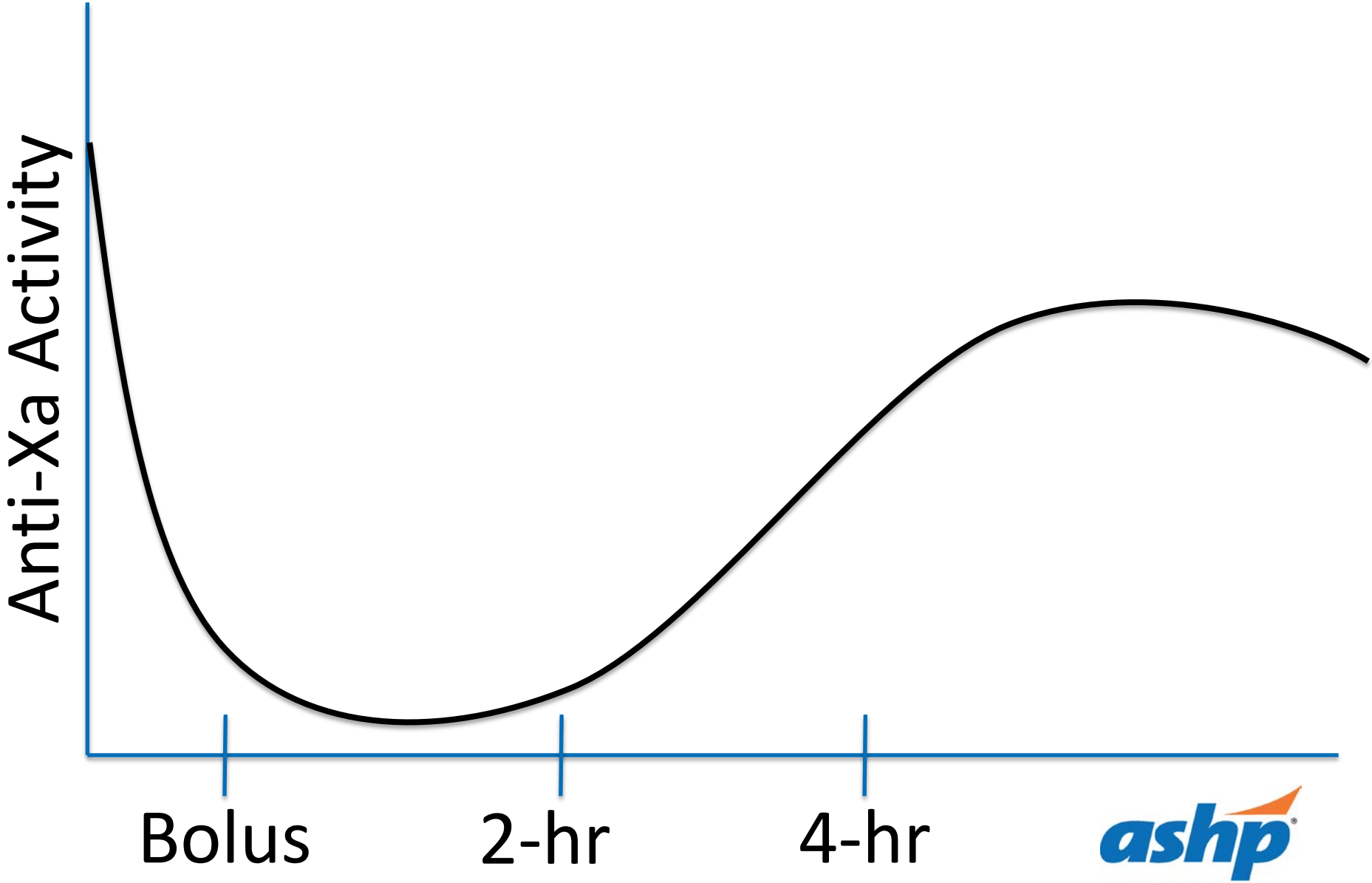
67 super sick patients

Acute major bleeding w/in 18 hours

GI: 49%
ICH: 42%
Other: 9%

~77 y.o

N Engl J Med 375(12): 1131-1141.



Patients	Intervention	Outcomes
67 super sick patients Acute major bleeding w/in 18 hours GI: 49% ICH: 42% Other: 9% ~77 y.o	**Andexanet bolus** **+** **2-hour infusion** *Riva: 26 pts* *Apix: 20 pts* *Enox: 1 pt* *Edox: 0 pt*	1. <u>PD Outcome</u> a) Anti-factor Xa activity: U-shape drop & bounce

N Engl J Med 375(12): 1131-1141.

Andexanet alfa

- Bolus (15-30 minutes) + 2-hour infusion

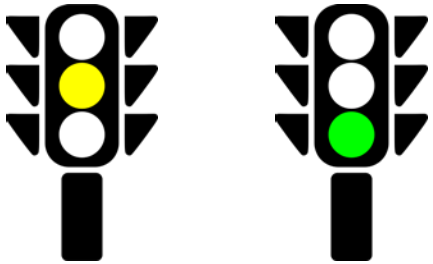
  400 mg bolus + 480 mg infusion

  800 mg bolus + 960 mg infusion

- Clotting?
- Deaths?
- Safety 47 -> 162
- Efficacy 67 -> 230

Key Takeaways

- NOAC use is increasing
- Rising concern with NOAC post-marketing data
- No universally accepted agent for reversal of anti-Xa inhibitors
- Andexanet alfa FDA approval pending more data



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Stop the Bloodshed: What a Pharmacist Needs to Know About Emergent Reversal of Anticoagulation

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Nicole Acquisto, PharmD, BCPS

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