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Reversal Strategies for Patients with Acute Medical & Intracranial Bleeding

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Disclosures

- Katelyn Dervay:
  - Boehringer Ingelheim - Tampa General Hospital [Tampa General Hospital is a study site for both idarucizumab & andexanet alpha, no personal financial relationship or benefit]
  - Portola Pharmaceuticals - Tampa General Hospital [Tampa General Hospital is a study site for both idarucizumab & andexanet alpha, no personal financial relationship or benefit]

- All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Objectives

1. Discuss the indications and clinical considerations for anticoagulation reversal in the acute care setting.
2. Describe the clinical pharmacology of available anticoagulants and reversal agents.
3. Evaluate potential agents and strategies for reversal of anticoagulants, including warfarin, unfractionated heparin, low molecular weight heparin, pentasaccharides, direct thrombin inhibitors, and direct factor Xa inhibitors.

Anticoagulant Reversal for Urgent Surgery

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Evaluating the Risks

Bleeding risk vs. Thrombotic risk

Urgent surgery had increased rates of bleeding and thrombosis vs. elective surgery in the RE-LY trial

		Dabigatran 150 mg twice daily	Warfarin
Major bleeding	**Urgent**	**24 (17.6%)**	**24 (22.9%)**
	Elective	**51 (3.7%)**	**47 (3.3%)**
Life-threatening bleeding	**Urgent**	**15 (11%)**	**12 (11.4%)**
	Elective	**17 (1.2%)**	**16 (1.1%)**
Thromboembolism	**Urgent**	**10 (7.4%)**	**11 (10.5%)**
	Elective	**15 (1.1%)**	**15 (1%)**

Douketis JD, Healey JS, Brueckmann M, et al. *Thromb Res.* 2016;139:77-81.

Oral anticoagulant (OAC) use is common, increasing

- Atrial fibrillation (AF) is the most common indication for chronic OAC
  - U.S. prevalence estimated 2.7 to 6.1 million in 2010
  - Expected to reach 12.1 million by 2030
  - Nearly 40% do not receive guideline-supported anticoagulation
- Direct oral anticoagulant (DOAC) use is catching up to warfarin use for AF
  - warfarin > rivaroxaban > apixaban > dabigatran > edoxaban
- Approximately 10% of patients on OAC require interruption for surgery or invasive procedure each year

Barnes GD, et al. *Am J Med.* 2015;128:1300-5.

There are several things to consider when managing anticoagulation in the perioperative patient

- Consider the surgery
  - How urgent is the procedure? What's the surgical bleeding risk?
- Consider the anticoagulant
  - Which one? Time of last dose? How much is present?
- Consider the Patient
  - Renal function? Drug interactions? Indication for anticoagulation?

Nutescu EA et al. *Am J Health-Syst Pharm*. 2013; 70(21):1914-29.

Anticoagulation reversal strategy is influenced by the urgency of the surgery/invasive procedure

- Important, but can be delayed (> 24 hours)
  - Perhaps withholding the drug is all that's necessary?
- Urgent, needs to happen today (< 24 hours)
  - If low risk of bleeding, consider a less aggressive reversal strategy?
- Emergent, needs to happen immediately (< 1 hour)
  - Probably will need an aggressive reversal strategy

Nutescu EA et al. *Am J Health-Syst Pharm*. 2013; 70(21):1914-29.

Surgical bleeding risk is affected by several factors

- Patient's history of bleeding
- Patient's medications associated with increased bleeding risk
- Patient's conditions associated with increased bleeding risk
- Whether patient's anticoagulation will be fully reversed
- The risk of bleeding with the surgery/invasive procedure itself

Nutescu EA et al. *Am J Health-Syst Pharm*. 2013; 70(21):1914-29.

Procedure-related bleeding risk should consider both national data and local expertise

- Data from non-anticoagulated patients may underestimate
  - Amount of blood loss
  - Risk of bleeding into a critical/non-compressible site
- Published estimates may not reflect local practice
  - Data on bleeding rates may be outdated
  - Newer techniques/devices may be available

Bleeding Risk from Selected Procedures

Minimal	Low	High
Minor dental procedures	Laparoscopic surgery	Neuraxial anesthesia
Minor skin procedures	Coronary angiography	Neurosurgery
Cataract extraction	Vascular surgery	Cardiac surgery
Endoscopy	Orthopedic surgery	Lung resection
Pacemaker/defibrillator implantation	Intra-abdominal surgery	Kidney or prostate biopsy

Bell BR, Spyropoulos AC, Douketis JD. *Hematol Oncol Clin North Am.* 2016;30:1073-1084.

Ideal Time to Stop Anticoagulants Before Surgery

Anticoagulant	Time Frame
UFH	At least 4 to 6 hours
LMWH	At least 24 hours
Fondaparinux	At least 3 to 4 days
Warfarin	At least 5 days or until INR < 1.5 May consider INR 1.5-1.8 for low-risk procedures
Dabigatran	CrCl ≥ 50mL/min: at least 24 hours for low-risk procedure at least 48 hours for high-bleed-risk CrCl < 50mL/min: at least 48 hours for low-risk procedure at least 96 hours for high-risk procedure
Rivaroxaban, Apixaban, and Edoxaban	At least 24 hours for low-bleed-risk procedure At least 48 hours for moderate to high-bleed-risk procedure

UFH = unfractionated heparin; LMWH = low molecular weight heparin; CrCl = creatinine clearance

Bell BR, Spyropoulos AC, Douketis JD. *Hematol Oncol Clin North Am.* 2016;30:1073-1084.

Consider the consequences of interrupting anticoagulation

- What is the perioperative thromboembolic risk?
  - Indication for anticoagulation?
- Will bridging before surgery be necessary?
  - Will there be time?
- Will bridging after surgery be necessary?
  - Enteral access?
  - Postoperative hemostasis?

Ideal Time to Restart Anticoagulants After Surgery*

Anticoagulant	Time Frame
UFH, LMWH, and Fondaparinux	At least 24 hours after low-bleeding risk surgery At least 48 to 72 hours after high-bleeding risk surgery
Warfarin	At least 12 to 24 hours after surgery
DOACs	At least 24 hours after low-bleed-risk surgery At least 48 to 72 hours after high-bleed-risk surgery

***Adequate hemostasis should be achieved before restarting anticoagulants**

Douketis JD, Spyropoulos AC, Spencer FA, et al. *Chest.* 2012;141 (2 Suppl):e326S-50S.

Case: CL is a 38-year-old woman

- Worsening abdominal pain over past few months
  - Fluctuating, comes in waves, taking longer to resolve each time
  - Thought it might be bad heartburn, but antacids no longer helping
- Had C-section 3 months ago
  - Developed venous thromboembolism in left calf one month later
  - On dabigatran 150 mg BID
  - Her creatinine clearance is 55 mL/minute
- Surgical team recommends laparoscopic cholecystectomy

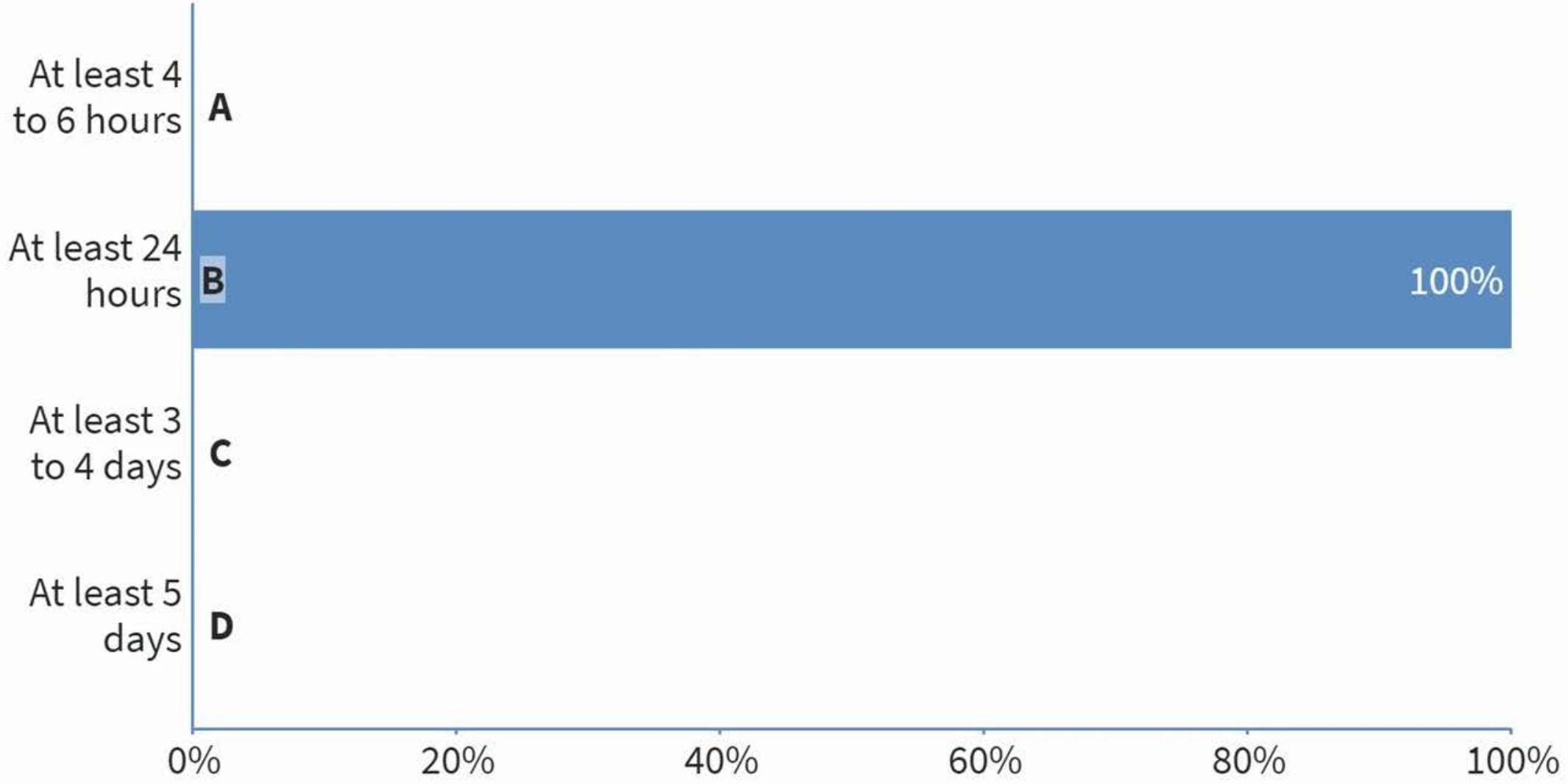
Time for a Poll

Web voting

Text voting

How long should you recommend holding CL's dabigatran prior to her surgery?

Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**



Assessing Coagulation Status

Laboratory testing

Pop quiz! Name a coagulation lab test for:

- Warfarin:
- Unfractionated heparin (UFH):
- Low molecular weight heparin (LMWH):
- Fondaparinux:

Laboratory Tests for DOACs

	Preferred tests	Other lab tests that may be of value
Dabigatran	dTT ECT	TT – If normal, rules out drug presence
		aPTT – If prolonged, rules in drug presence If normal, not useful
Rivaroxaban **Edoxaban**	Calibrated anti-FXa	Non-calibrated anti-FXa – If normal, can rule out drug presence
		PT – If prolonged, can rule in drug presence If normal, not useful Local laboratory calibration is recommended
		aPTT – If prolonged, can rule in drug presence If normal, not useful Less sensitive than PT
Apixaban	Calibrated anti-FXa	Non-calibrated anti-FXa – If normal, can rule out drug presence

aPTT = activated partial thromboplastin time; dTT= dilute thrombin time; ECT = ecarin clotting time; PT = prothrombin time; TT = thrombin time

Samuelson BT, et al. *Chest.* 2017;151(1):127-138.

Consider how testing will be incorporated into emergency surgery/invasive procedures

- Is the test available at your institution?
  - Have appropriate calibrations been performed/validated?
- Is the turnaround time fast enough?
  - What if you can't wait for the results?
- How will you interpret and act on the results?
  - Is there an approved protocol/algorithm?

Consider activated charcoal, but be mindful of contraindications and imminent surgery

- Consider using if DOAC was taken in past 2 hours
  - May consider up to 6 hours after last apixaban dose
  - Single dose of 25-100 g
- Consider aspiration risk
  - Can patient protect his/her own airway?
  - Risk of emesis with anesthesia, emergency surgery?
- Consider integrity of GI tract
  - Is patient having emergency bowel surgery?
  - Is patient at risk for GI perforation?

Heidbuchel H, et al. *Europace.* 2015;17:1467-1507.

Ward C, et al. *Thromb J.* 2013;11(1):27.doi: 10.1186/1477-9560-11-27.

If reversal is required for urgent surgery/invasive procedure, choose an appropriate reversal agent

- Vitamin K
- Protamine
- Idarucizumab
- Fresh Frozen Plasma (FFP)
- Prothrombin complex concentrate (PCC)
- Activated prothrombin complex concentrate (aPCC)

Reversing Parenteral Anticoagulants

Protamine for UFH and LMWH
PCC for fondaparinux

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Non-Urgent Perioperative Management

- Give the last dose:
  - UFH: 4 to 6 hours prior to surgery
  - LMWH: 24 hours prior to surgery
- Resume UFH or LMWH after surgery:
  - 24 hours after non-high-bleeding-risk surgery
  - 48 to 72 hours after high-bleeding-risk surgery

Douketis JD, Spyropoulos AC, Spencer FA, et al. *Chest.* 2012;141 (2 Suppl):e326S-50S.

Protamine sulfate neutralizes UFH

- Alkaline protein that binds with acidic heparin
  - Mild anticoagulant by itself, becomes inert when bound to heparin
- Works rapidly
  - Onset of action is usually within 5 minutes
- Administer by slow IV injection to avoid infusion reactions
  - Maximum 5 mg/min recommended
- Risk of anaphylaxis/cardiovascular collapse low, but increases with:
  - Fish allergy, high/repeated doses, vasectomy, severe left ventricular dysfunction

Garcia DA, Baglin TP, Weitz JI, Samama MM. *Chest.* 2012;141 (2 Suppl):e24S-43S.

Consider the amount of heparin remaining in the body when determining the protamine dose

- Determine number of UFH units infused over past 2 to 3 hr
  - Give 1 mg protamine for every 100 units heparin infused
  - Maximum dose = 50 mg, Maximum rate = 5 mg/min
- If heparin drip has been running at 1500 units/hr for 2 to 3 hr:
  - Give ≈ 30 to 45 mg of protamine
  - If > 60 minutes since heparin exposure, consider ½ to ¼ dose
  - aPTT and bleeding can also guide dosing/repeat dosing

Garcia DA, Baglin TP, Weitz JI, Samama MM. *Chest.* 2012;141 (2 Suppl):e24S-43S.

Protamine sulfate is less effective for reversing LMWH than UFH

- Neutralizes anti-FIIa activity more than anti-FXa activity
  - Will maximally neutralize only 60-75% of anti-FXa activity
- If last dose enoxaparin given within 8 hours:
  - Give 1mg protamine for every 100 anti-FXa units (max 50mg)
  - 1mg enoxaparin = 100 anti-FXa units
- If last dose enoxaparin given beyond 8 hours ago:
  - Give 0.5mg protamine for every 1mg enoxaparin

Garcia DA, Baglin TP, Weitz JI, Samama MM. *Chest.* 2012;141 (2 Suppl):e24S-43S.

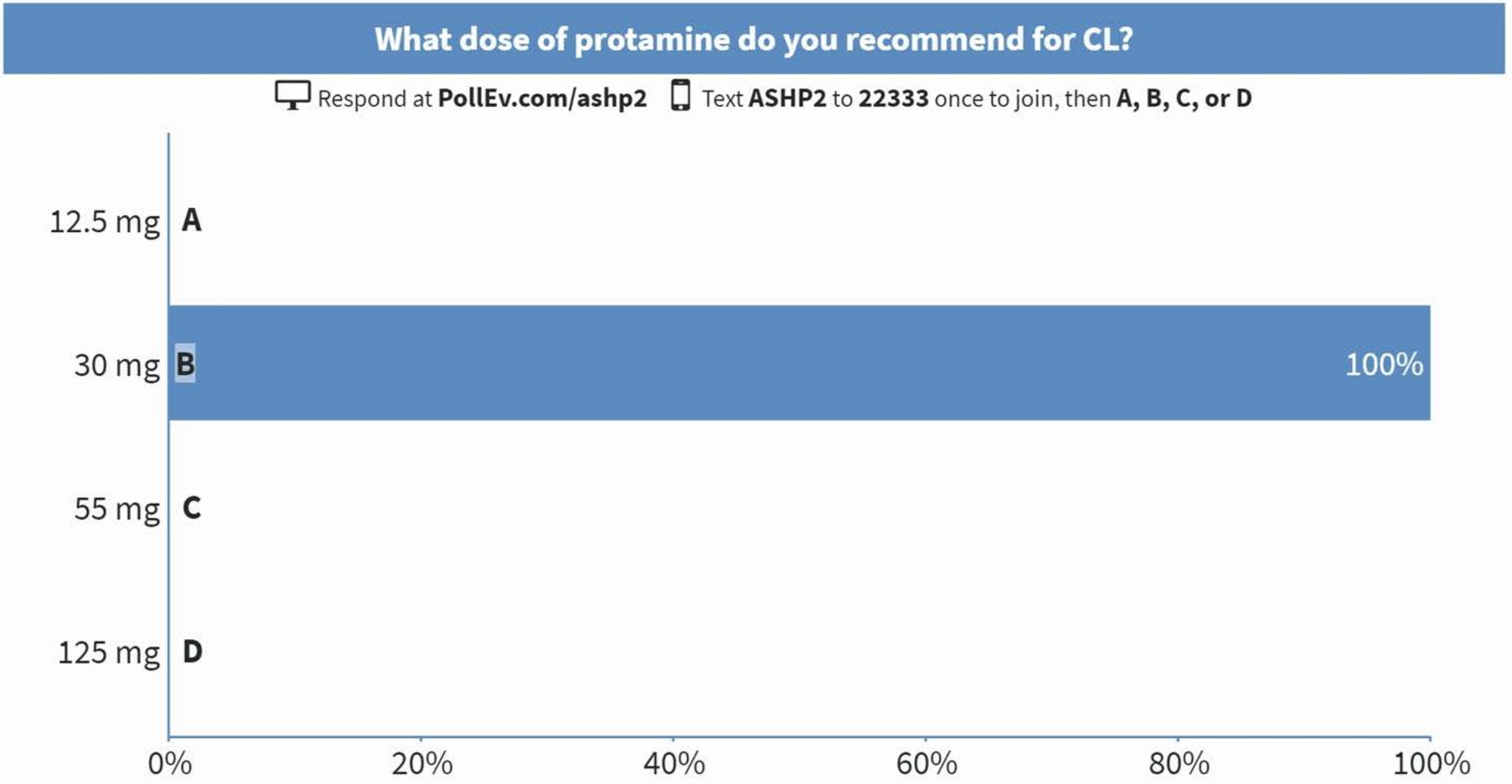
Protamine will not effectively reverse fondaparinux

- If given in past 3-4 days, anticoagulant effect may be present
  - Half-life of 17 to 21 hours
  - Renal elimination
- Ciraparantag and andexanet alfa probably will have a role in reversal

Garcia DA, Baglin TP, Weitz JI, Samama MM. *Chest.* 2012;141 (2 Suppl):e24S-43S.

The case of CL continues

- Receives UFH for bridging
  - No bolus, 3,300 units infused over past 3 hours
  - aPTT is currently 60 seconds
- Clinical condition abruptly worsens
  - Experiencing worsening abdominal pain, rising transaminases
  - Surgery team recommends immediate cholecystectomy
- CL weighs 87kg


What dose of protamine do you recommend for CL?
Respond at PollEv.com/ashp2
Text ASHP2 to 22333 once to join, then A, B, C, or D
12.5 mg
A
30 mg
B
100%
55 mg
C
125 mg
D
0%
20%
40%
60%
80%
100%

Reversing Warfarin

Vitamin K, Fresh Frozen Plasma (FFP), Prothrombin Complex Concentrate (PCC)

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Warfarin – American College of Chest Physicians (ACCP) Recommendations

- Stop 5 days prior to surgery/procedure
  - Consider longer time for patients with low clearance (e.g., elderly)
- Consider bridging if moderate to high thromboembolic risk
  - Evaluate history of mechanical heart valve, atrial fibrillation, VTE
- Attain an INR < 1.5
  - INR 1.5 to 1.8 may be okay for minor procedures
- Resume warfarin 12 to 24 hours after surgery
  - Once adequate hemostasis has been achieved

Douketis JD, Spyropoulos AC, Spencer FA, et al. *Chest.* 2012;141 (2 Suppl):e326S-50S.

Vitamin K plus clotting factor replacement is the gold standard to reverse warfarin for urgent surgery

- Vitamin K monotherapy if surgery can be delayed 18-24 hours:
  - 2.5 to 5 mg PO or slow IV infusion
- If more rapid reversal is required, IV route is preferred
  - 2.5 to 5 mg slow IV infusion K PLUS either PCC or FFP
- Vitamin K helps to sustain the more rapid hemostatic effects of clotting factor replacement

Douketis JD, Berger PB, Dunn AS, et al. *Chest.* 2008;133:299-339S.

Douketis JD, Spyropoulos AC, Spencer FA, et al. *Chest.* 2012;141 (2 Suppl):e326S-50S.

PCC is preferable to FFP for reversal of warfarin for urgent surgery/invasive procedures

- Less volume
- More rapid correction of INR
- Head-to-head trial demonstrated superiority of 4-factor PCC (n=181)
  - More effective hemostasis: 78 (90%) vs. 61 (75%)
  - More rapid INR correction: 48 (55%) vs. 8 (10%)
  - Similar safety profile, but not powered to detect differences

Goldstein JN, Refaai MA, Milling TJ Jr, et al. *Lancet.* 2015;385(9982):2077-87.

To determine 4-factor PCC dose, you'll need the patient's INR and actual body weight

INR	4F-PCC dose	Max dose
2 to 3.9	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
> 6	50 units/kg	4500 units

Kcentra (R) [package insert]. Kankakee, IL: CSL Behring LLC; 2017.

Reversing the Direct Oral Anticoagulants (DOACs)

Idarucizumab for dabigatran
PCCs for rivaroxaban, apixaban, and edoxaban

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Pharmacokinetic Properties of the DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
t_{max} (hours)	1 to 3 (delayed by food)	2 to 4 (delayed by food)	3 to 4	1 to 2
Half-life (hours)	12 to 17	5 to 9 (11 to 13 elderly)	12	10 to 14
Renal elimination (%)	80	36	27	50
Dialyzable	Yes	No	No	No
Protein binding (%)	35	92-95	87	55
Drug interactions	P-gp	P-gp and CYP3A4	P-gp or CYP3A4	P-gp
Dosing frequency	Once or twice daily	Once or twice daily	Twice daily	Once daily

P-gp = P-glycoprotein

Options to Reverse Dabigatran

- Idarucizumab
- Activated Prothrombin Complex Concentrate (aPCC)
- Prothrombin Complex Concentrate (PCC)
- Hemodialysis

Idarucizumab reversed dabigatran-associated anticoagulation in the RE-VERSE AD trial

- Group B, Urgent Surgery, n=202
  - Laboratory test-guided reversal was rapid, complete
  - 97.5% underwent intended procedure
  - 93.4% achieved normal periprocedural hemostasis
  - Dabigatran restarted an average of 3.5 days after idarucizumab

Pollack CV Jr, Reilly PA, van Ryn J, et al. *N Engl J Med*.2017;377(5):431-441.

Questions about idarucizumab still remain

- Rebound dabigatran concentrations observed at 12 hours
  - Concentrations not measured between 4 and 12 hour mark
  - Is there a need to repeat dose?
- Thrombotic events occurred
  - 10 patients by day 30, 15 patients by day 90
  - Are there strategies to lower this risk?
- Cases of incomplete reversal have been reported
  - Should laboratory assessment guide repeat dosing?
  - Should PCC or aPCC be added based on lab or clinical findings?

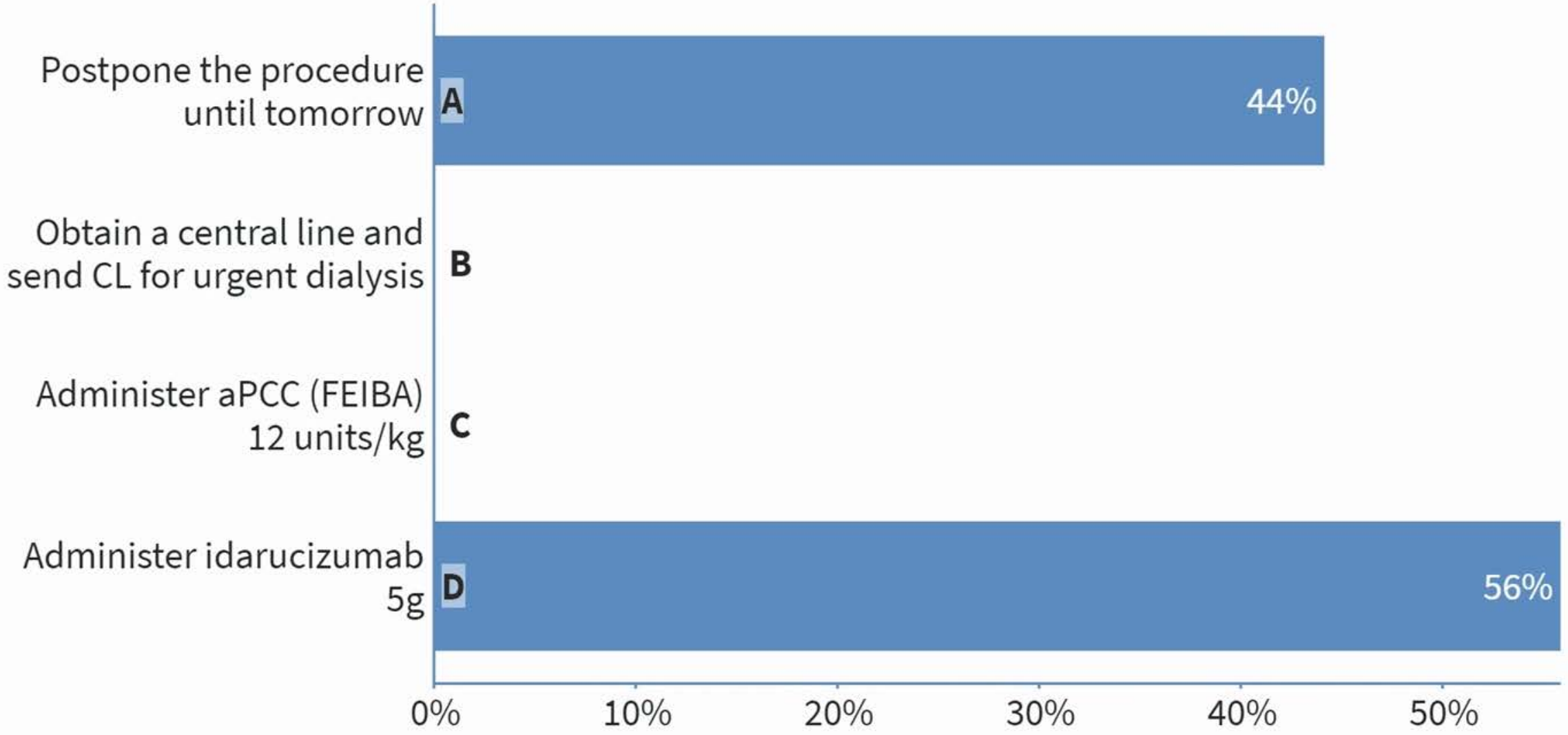
Steele AP, Lee JA, Dager WE. *Clinical Toxicol.* 2017. Jul 13:1-3. doi: 10.1080/15563650.2017.1349911. [Epub ahead of print].

The case of CL continues

- That night, after her surgery, the team informs CL there was a stone that slipped into her common bile duct
- The team would like to retrieve the stone via endoscopic retrograde cholangiopancreatography (ERCP) in the AM
- Due to a miscommunication, CL is accidentally administered her home dabigatran 150 mg dose at 0800
- The ERCP is planned for 1200
- You discover the error during pre-rounds at 1015

Which one of the following strategies is most appropriate to reduce CL's bleeding risk?

Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**



PCC or aPCC can be considered for rapid reversal of rivaroxaban, apixaban, or edoxaban

- Consider lower end of dosing range in patients with low-bleeding risk and/or high-thrombotic risk
  - aPCC: 8 to 50 units/kg
  - PCC: 25 to 50 units/kg

Key Takeaways

- Key Takeaway #1
  - Rapid reversal of anticoagulation can be costly and risky, but also necessary. The risks of harm from delayed surgery, surgical bleeding, and thrombosis after reversal of anticoagulation should be considered in decision making.
- Key Takeaway #2
  - The anticoagulant reversal plan for urgent surgery should consider the anticoagulant drug's half-life, barriers to elimination (e.g., organ dysfunction), time of last dose, available coagulation labs, available reversal agents, and plan for restarting/bridging anticoagulation therapy.
- Key Takeaway #3
  - Pharmacists can play a key role in crafting local guidelines, developing optimal workflows, and educating staff to ensure rapid, safe, and efficient reversal of anticoagulant therapy.

Reversal Strategies for Trauma Patients

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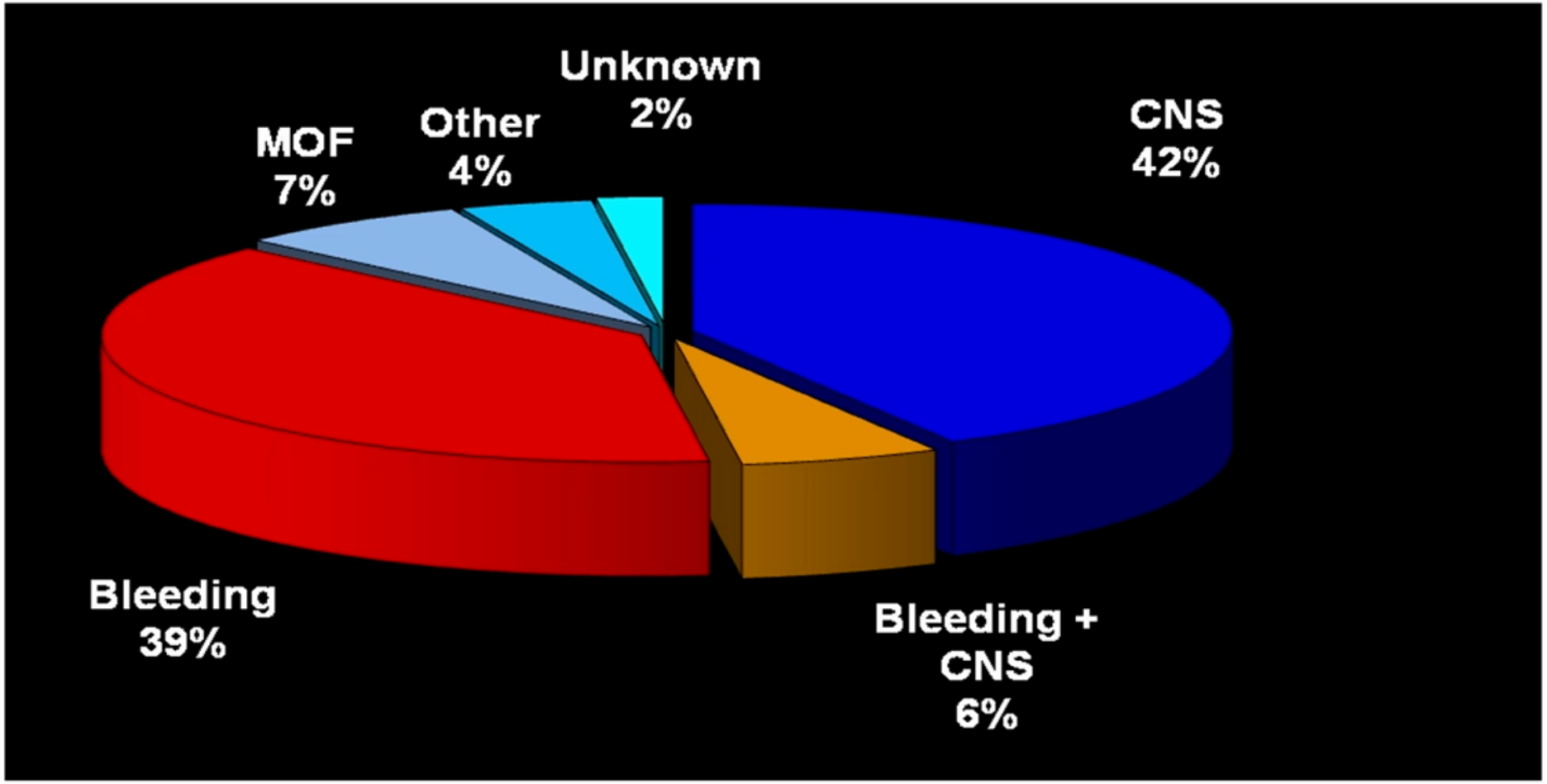
- 19 yo male motorcycle crash vs. car, level 1 trauma
- Systolic blood pressure reported as 85 mm Hg and repeat 79 mm Hg
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
- R wrist open fracture, pneumothorax L chest, positive focused assessment with sonography in trauma (FAST)

Photo credit: Kate Kokanovich

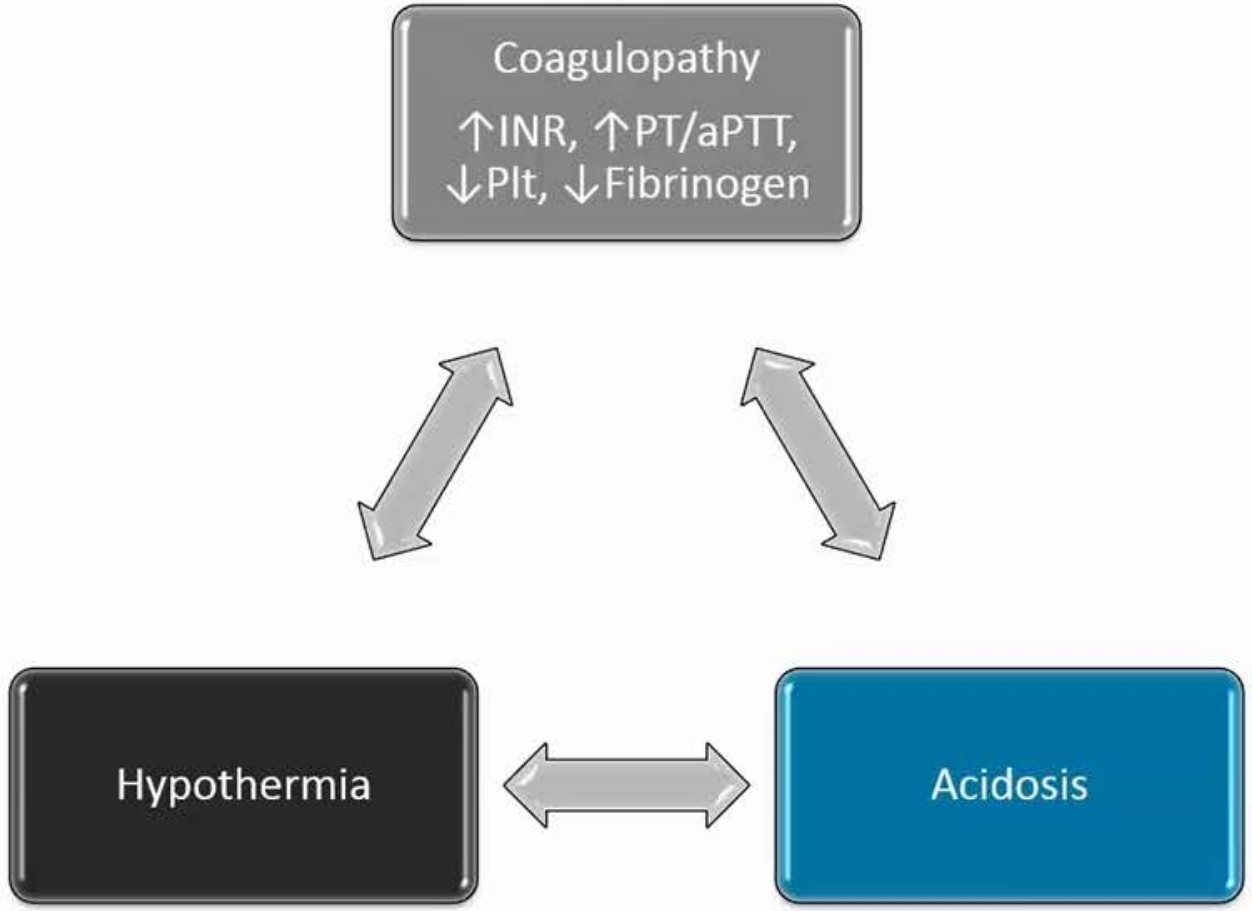
Bleeding is the Major Cause of Death in Trauma



MOF: Multiple organ failure

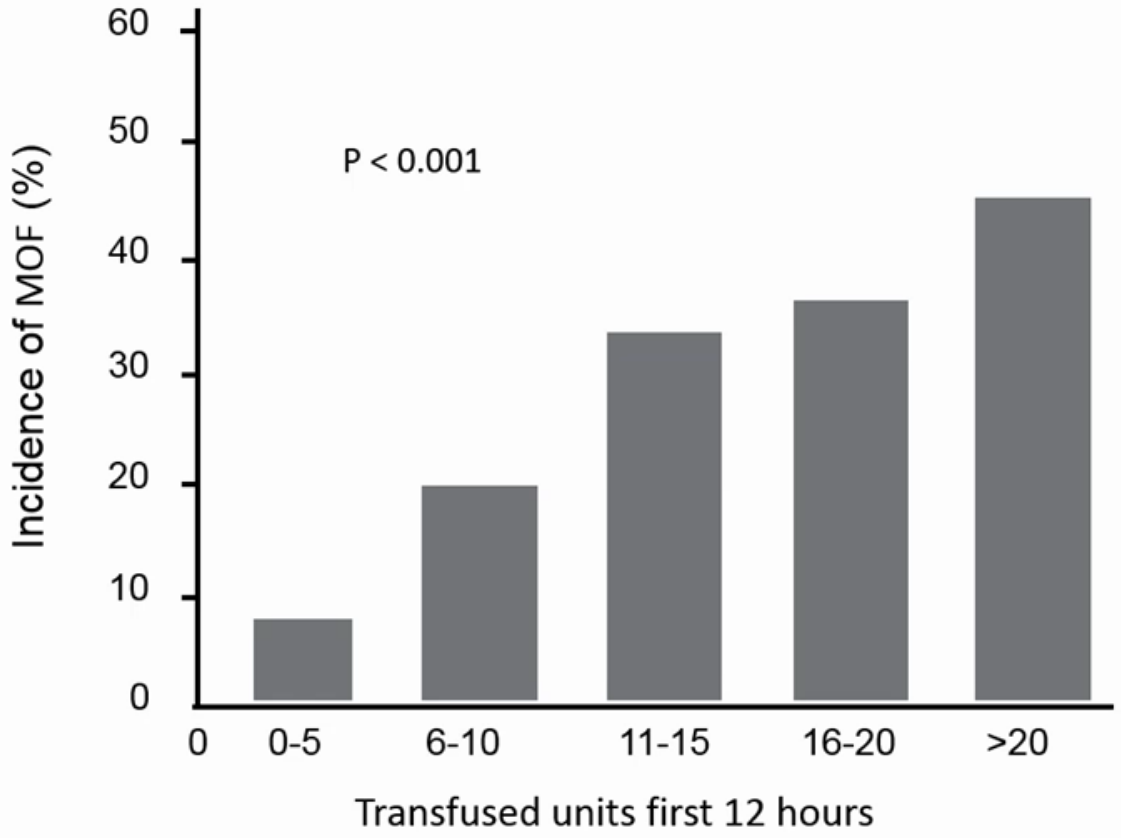
Sauaia A et al. *J Trauma* 1995;38:185-93.

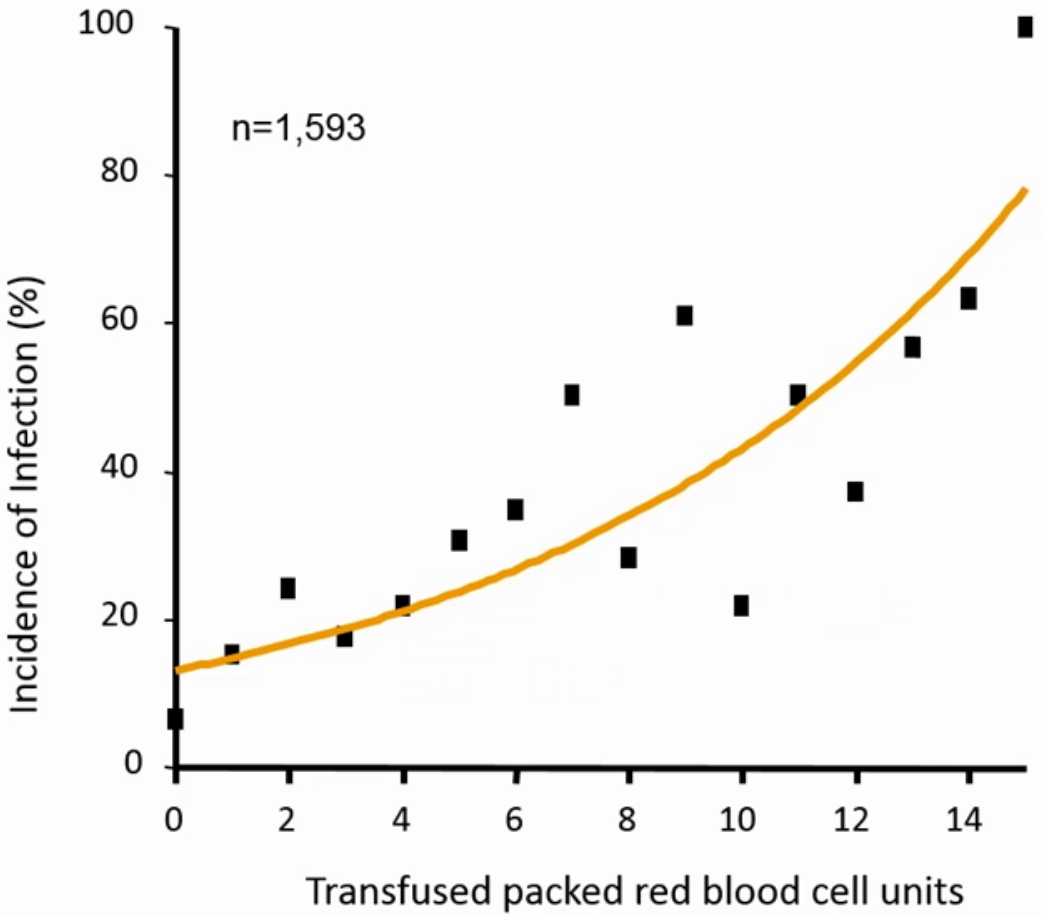
Lethal Triad → High Mortality Rate



Nunez TC, et al. *Curr Opin Crit Care* 2009;15 :536-541.

More Blood, More Problems





Moore FA, et al. *Arch Surg* 1997;132:620-4.
Claridg JA, et al. *Am Surg* 2000;68:566-72.

Tranexamic Acid (TXA)

- Hyperfibrinolysis in trauma
  - Dysfunction from severe shock and major tissue trauma
  - Present in 2.5-7% of all trauma patients

- TXA
  - Causes reversible competitive inhibition of the plasminogen-fibrin lysine binding site → prevents fibrin breakdown

Schochl H, et al. *Hamostaseologie* 2012;32:22-7

CRASH-2 Trial

- Randomized, placebo controlled trial
- 40 countries, 274 hospitals, n = 20,211 with or at risk for bleeding
- Randomization – uncertainty principle
- SBP < 90 mm Hg or HR > 110 bpm or thought to be at risk of significant hemorrhage
- TXA 1 g over 10 minutes, then 1 g over 8 hours or placebo

Crash-2 trial collaborators. *Lancet.* 2010;376:23-32.

CRASH-2 Trial Results

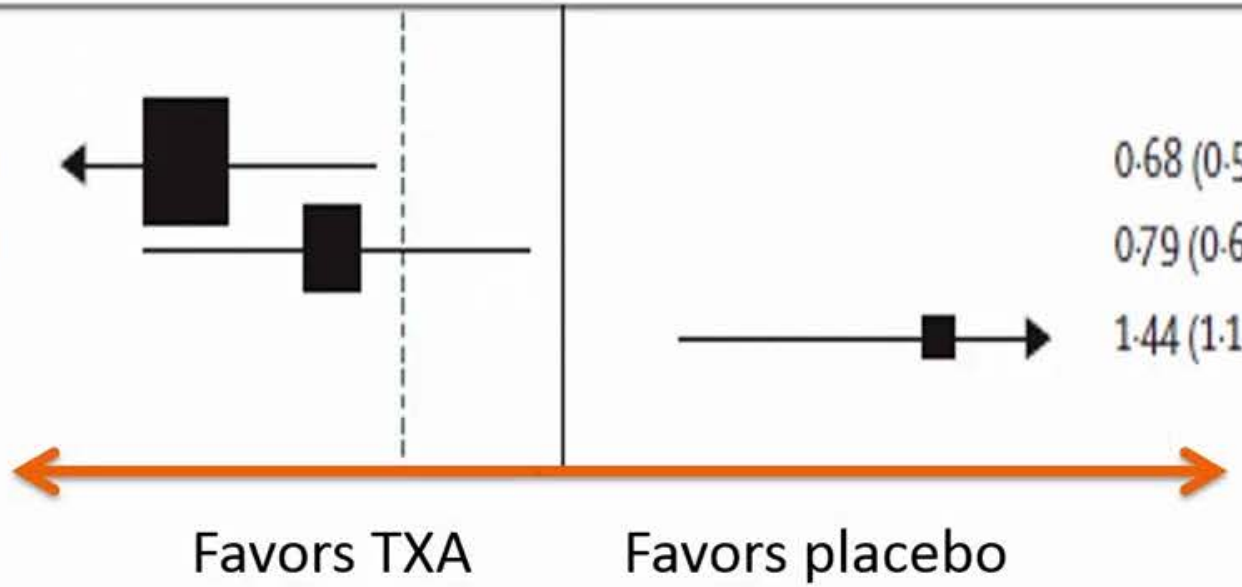
- Death in the hospital within 4 weeks of injury

	TXA (n=10,060)	Placebo (n=10,067)	RR (95% CI)	p-value
Any cause of death	1463 (14.5%)	1613 (16.0%)	0.91 (0.85–0.97)	0.0035
Bleeding	489 (4.9%)	574 (5.7%)	0.85 (0.76–0.96)	0.0077
Vascular occlusion	33 (0.3%)	48 (0.5%)	0.69 (0.44–1.07)	0.096
Multi-organ failure	209 (2.1%)	233 (2.3%)	0.90 (0.75–1.08)	0.25
Head injury	603 (6.0%)	621 (6.2%)	0.97 (0.87–1.08)	0.60
Other causes	129 (1.3%)	137 (1.4%)	0.94 (0.74–1.20)	0.63

Crash-2 trial collaborators. *Lancet.* 2010;376:23-32.

Mortality Subgroup Analysis

	Tranexamic acid allocated	Placebo allocated	Risk ratio (95% CI)
Time to treatment (h)			
≤1	198/3747 (5·3%)	286/3704 (7·7%)	0·68 (0·57–0·82)
>1–3	147/3037 (4·8%)	184/2996 (6·1%)	0·79 (0·64–0·97)
>3	144/3272 (4·4%)	103/3362 (3·1%)	1·44 (1·12–1·84)
χ^2=23·516; p<0·0000			



Reprinted from The Lancet 2010; 376: 23-32, *Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial*. Copyright 2010 with permission from Elsevier.

Limitations to Study Results

	TXA (n=10,060)	Placebo (n=10,067)
Blood products transfused	5067 (50.4%)	5160 (51.3%)
Mean units transfused	6.06 (SD ± 9.98)	6.29 (SD ±10.31)
Systolic blood pressure (mm Hg)		
≤ 75	15.5%	15.9%
76-89	16%	16.8%
≥ 90	68.4%	67.1%
Heart rate (bpm)		
< 77	8.7%	8.6%
77-91	17.1%	17.5%
92-107	25.3%	25.2%
> 107	48.3%	48%

Crash-2 trial collaborators. *Lancet.* 2010;376:23-32.

Controversy with CRASH-2

- Design
- Lack of modern trauma systems
- Lack of laboratory monitoring of coagulation function
- No injury severity scores
- Need for an antifibrinolytic agent since only half required blood transfusion
- Number needed to treat 67

- *New York Times* Article "Cheap drug is found to save lives"
- Death avoidance paper
- World Health Organization essential medicines list

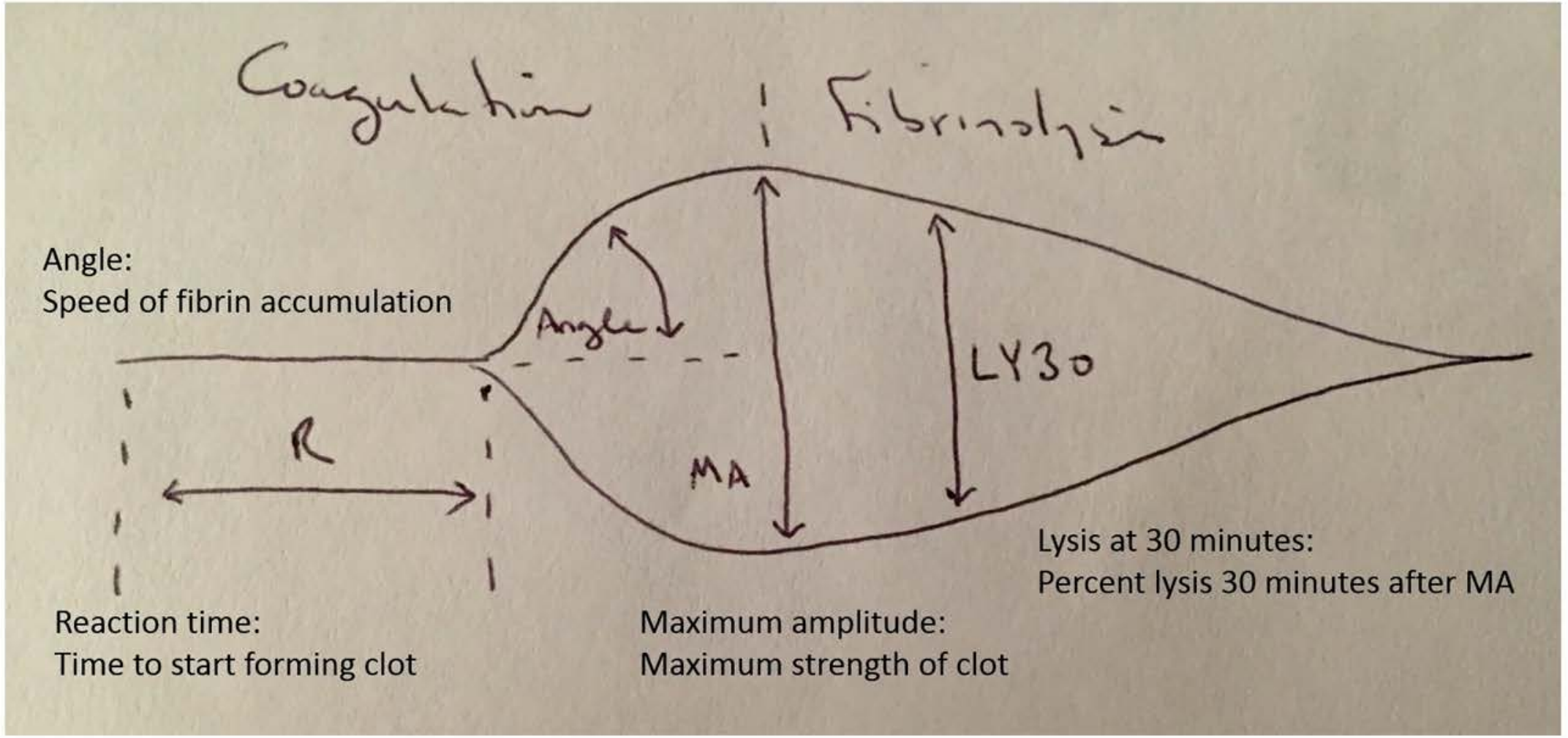
Binz S, et al. *J Blood Transfus*. 2015;2015:874920.

CRASH-2 Collaborators. *Lancet* 2011;377:1096-1101.

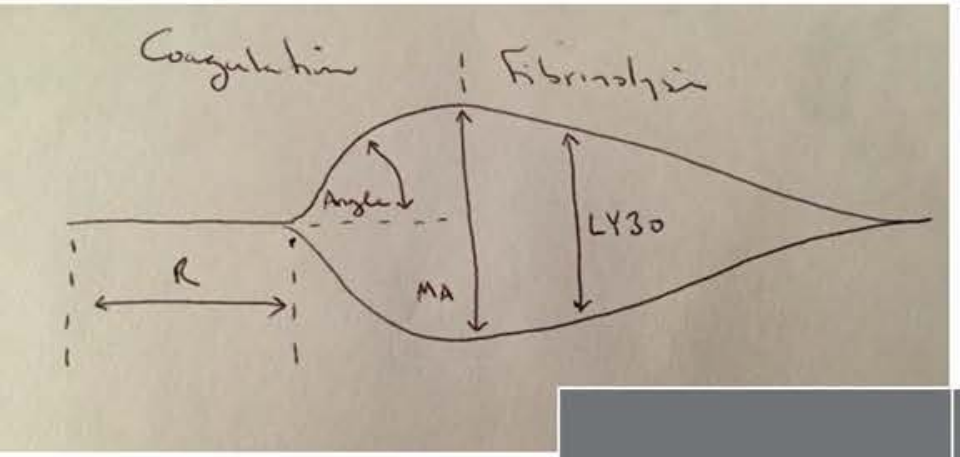
Ker K et al. *BMC Emerg Med* 2012;12:3.

McNeil DG. The New York Times. March 20, 2012; World Health Organization. WHO model list of essential medicines,20th list. March 2017. http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1.

Thromboelastometry (TEG)



Hemorrhagic TEG Changes



Components	Normal Values	Derangement	Problem
R Time	5 – 10 minutes	Prolonged	Coagulation Factors
Angle	53 – 73 degrees	Decreased	Fibrinogen
MA	50 – 70 mm	Decreased	Platelets
LY30	0 – 8%	Narrowed	Excess fibrinolysis

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs)

- Retrospective, consecutive patients Jan 2009-Dec 2012
- Received at least 1 unit of red blood cells within 24 hours of injury
- 2009
  - TXA administered at physician discretion
- 2010 and after
  - TXA administered to those requiring emergent transfusion or based on thromboelastogram data (documented hyperfibrinolysis)
- Loading dose was given, continuation was at discretion

Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.

MATTERs Results

- TXA lowered unadjusted mortality
  - 17.4% (n = 293) vs. 23.9% no TXA (n = 603), p = 0.03
- TXA lowered unadjusted mortality in patients requiring massive transfusion 14.4% (n = 125) vs. 28.1% no TXA (n = 196), p = 0.004
  - TXA independently associated with survival
    - Odds Ratio 7.228 (95% CI 3-17)
    - Number needed to treat 7

Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.

Thromboembolism Risk

Study	TXA	Placebo
CRASH-2 (any vasoocclusive event)	1.7%	2%
MATTERs		
Pulmonary embolism (PE)	2.7%	0.3%*
Deep vein thrombosis (DVT)	2.4%	0.2%*
Massive transfusion + PE	3.2%	0%*
Massive transfusion + DVT	1.6%	0.5%
Swendsen, et al. (PE/DVT)	11.5%	0%*
Cole, et al. (Shock patients: PE/DVT)	8%	2%*

*Statistically significant difference

Shakur H et al. *Lancet* 2010;376(9734):23-32.
Morrison JJ, et al. *Arch Surg* 2012;147(2):113-9.
Swendsen H, et al. *J Trauma Treat* 2013; 2(4):1000179.
Cole E, et al. *Ann Surg* 2015;261:390-4.

TXA Questions

- Unknown mechanism
  - Anti-fibrinolysis vs. anti-inflammatory
- Is there more to the pathophysiology of trauma-induced coagulopathy
- Hyperfibrinolysis determination
  - Lysis at 30 minutes (LY30) 3% or greater predicts requirement for massive transfusion/risk of mortality
  - Hyperfibrinolysis (18%), physiologic (18%), shutdown (64%)
- Correct dose
- Pre-hospital use (STAAMP trial, The PATCH study, ….)

Roberts I, et al. *Crit Care* 2014;18:685.
Binz S, et al. *J Blood Transfus* 2015:874920.
Chapman MP, et al. *J Trauma Acute Care Surg* 2013;75:961-7.
Moore HB, et al. *J Trauma Acute Care Surg* 2013;77:811-7.
Wafaisade, et al. Crit Care 2016;20:143.
Huebner BR, et al. Wilderness Environ Med 2017;28:S50-60.

MASSIVE TRANSFUSION PROTOCOL (MTP)

if ... your patient has these VS in the *FIELD* or *ED*

- SBP ≤ 70

OR

- SBP 71-90 *AND* HR ≥108

AND

Any of these in the ED:

- Penetrating Torso Injury
- Major Pelvic Fracture
- FAST ⊕ >1 Body Region

ACTIVATE MTP

Transfuse RBC 4 Units *and* FFP 2 Units

$CaCl_2$ 1 gm IV

Order *Citrated Rapid TEG*

Continue to component transfusion based on *TEG Results*

if patient is bleeding

ACT	Angle	MA	LY30
>128 sec	<65°	<55 mm	≥5%
FFP 2 Units	Cryo 10 Units	Platelets 1 Unit	TXA 1 gm

Re-assess via *Citrated Rapid TEG*

- 19 yo male motorcycle crash vs. car, level 1 trauma
- Systolic blood pressure reported as 85 mm Hg and repeat 79 mm Hg
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
- R wrist open fracture, pneumothorax L chest, positive focused assessment with sonography in trauma (FAST)

Photo credit: Kate Kokanovich

Which management is the most appropriate for resuscitation?

Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**

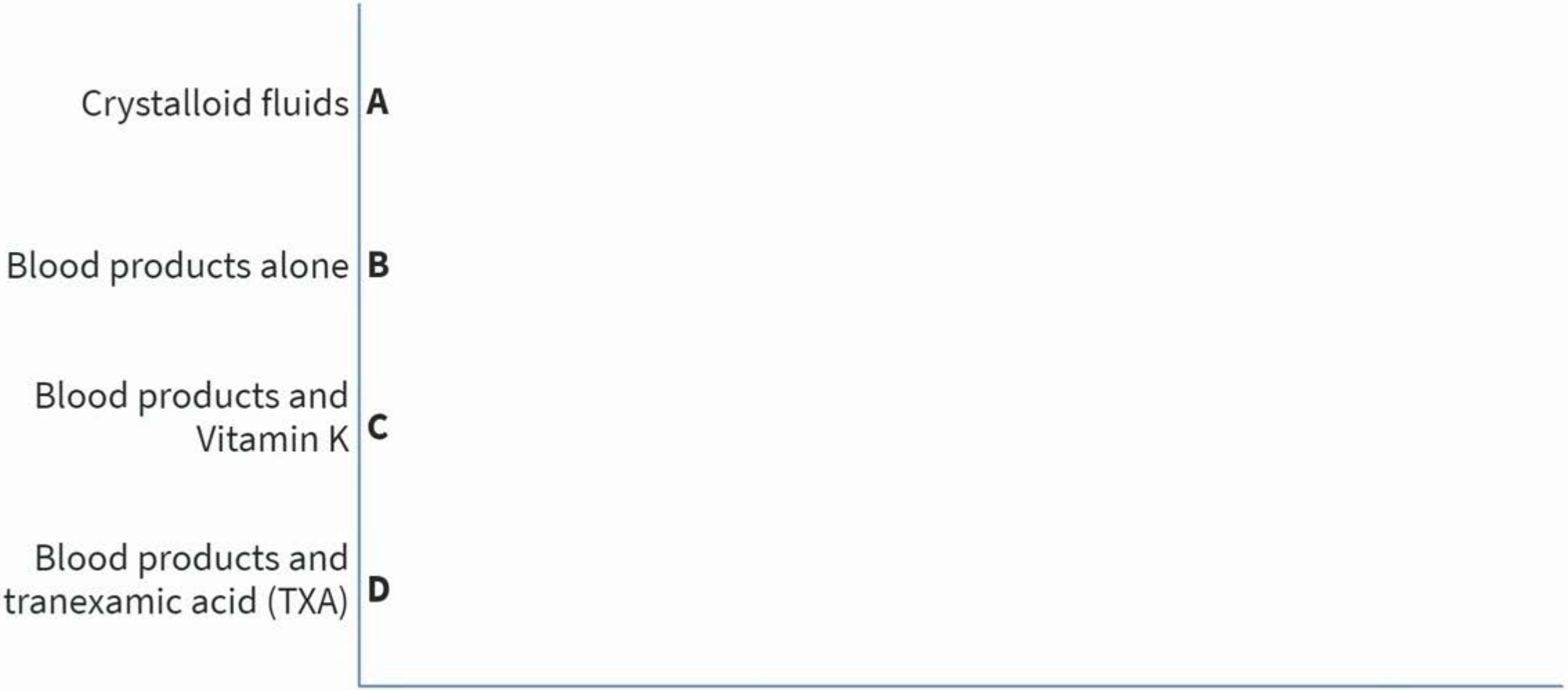
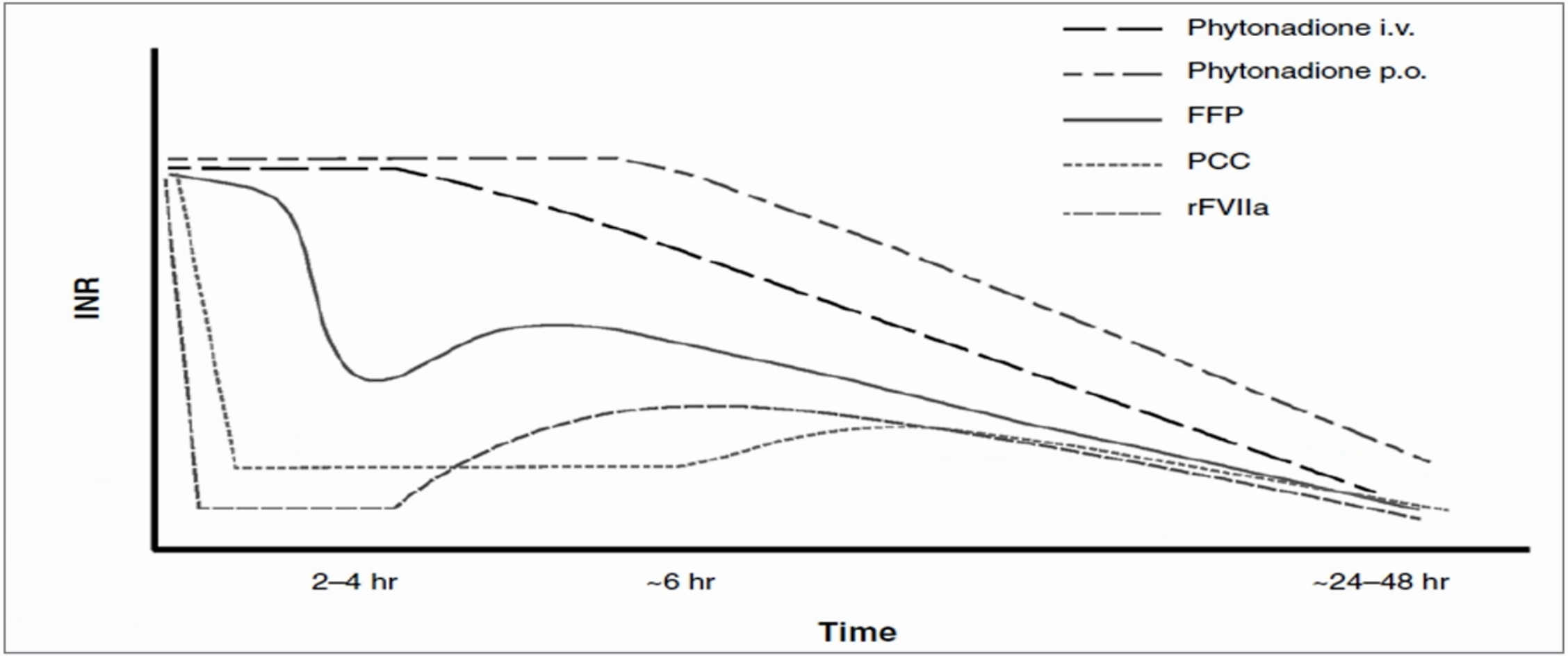


Photo credit: Kate Kokanovich

- The patient's family arrives and you find out the patient has factor V Leiden mutation
- He is on warfarin as an outpatient (unknown time of last dose)
- INR = 3.2
- SBP is 75 mm Hg

Other Reversal Agents and Onset



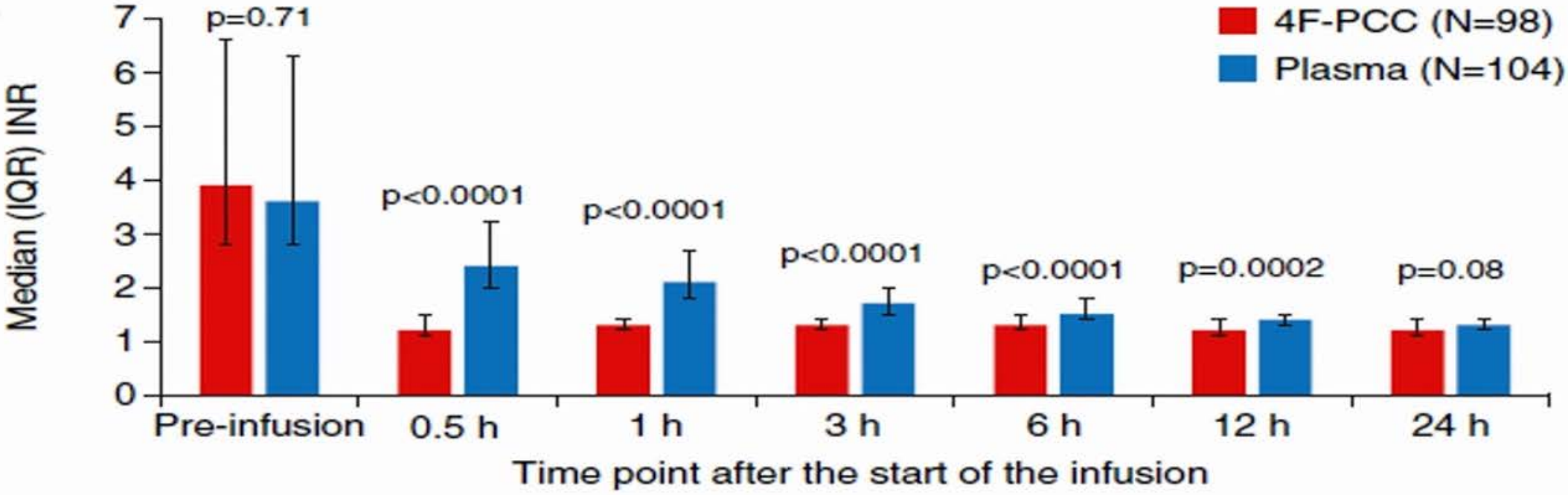
Originally published in Dager WE. Developing a management plan for oral anticoagulant reversal. *Am J Health-Syst Pharm.* 2013; 70(suppl 1):S21-31.

Characteristics of Fresh Frozen Plasma vs. 4-Factor PCC

	FFP	PCC
Blood typing required	YES	NO
Thawing time	30-45 min	0
Infection risk	YES	YES*
Thrombosis risk	YES	YES
Transfusion-related lung injury (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

Phase IIIb multicenter, open label (Part 1)



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

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

Vitamin K Antagonists

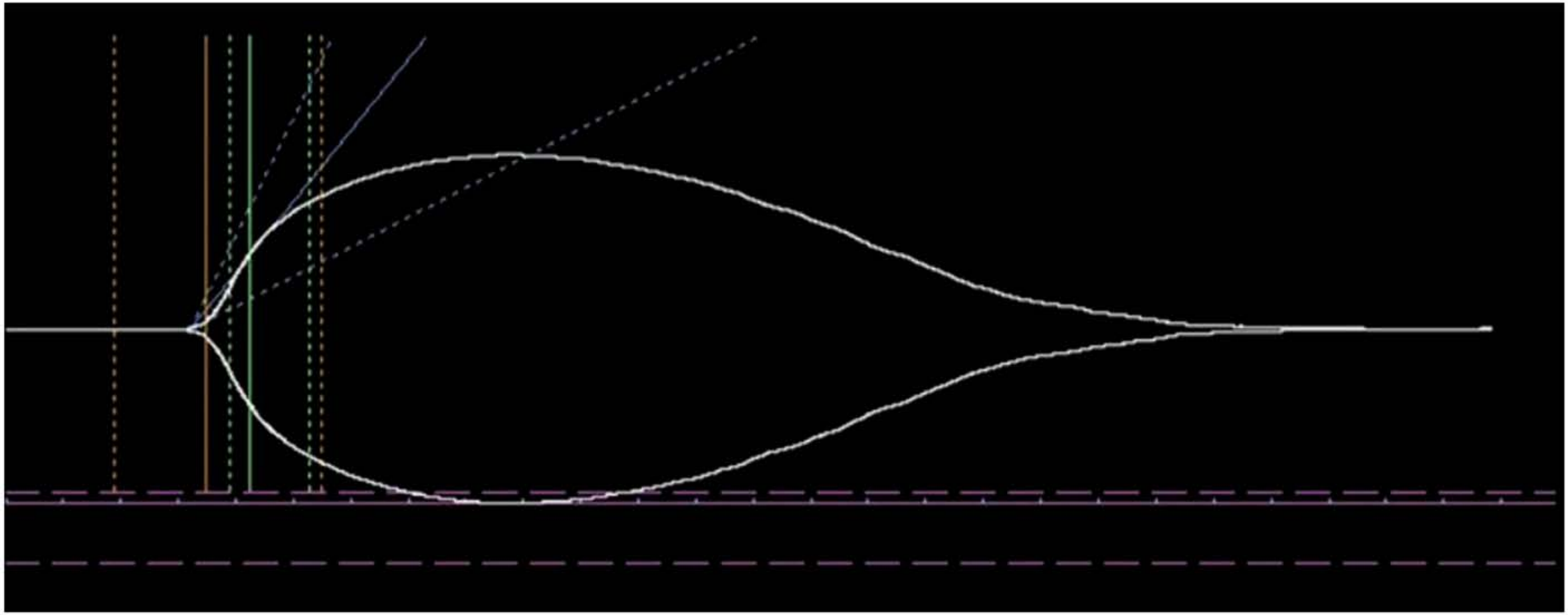
- 30-50% reduction in clotting factor activities leads to therapeutic effect
  - FVII – 6 hours
  - FIX – 24 hours
  - FX – 36 hours
  - FII – 50 hours
  - Protein C – 8 hours
  - Protein S – 30 hours

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

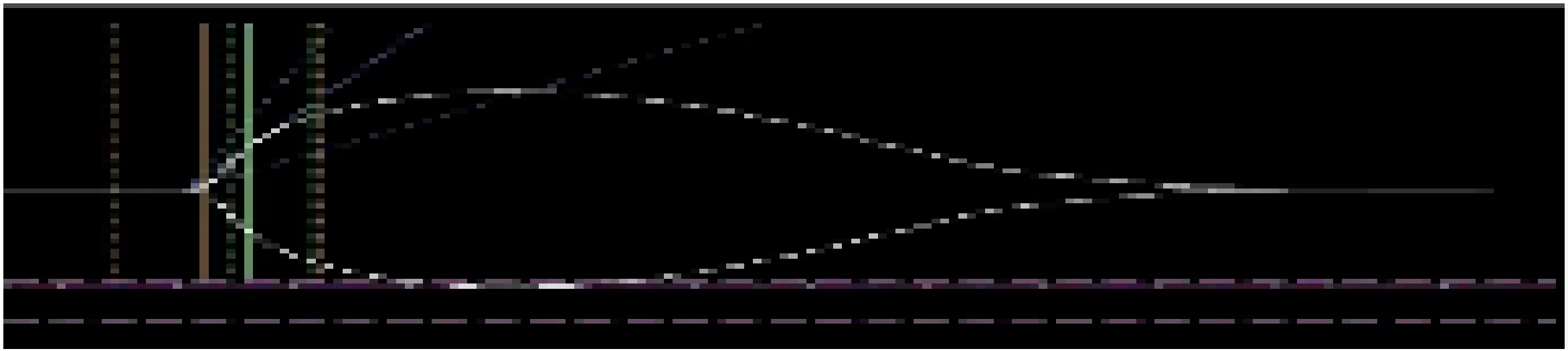
ISI = International Sensitivity Index

How do you interpret INR in a coagulopathic, hypotensive, trauma patient?

Thromboelastogram Results



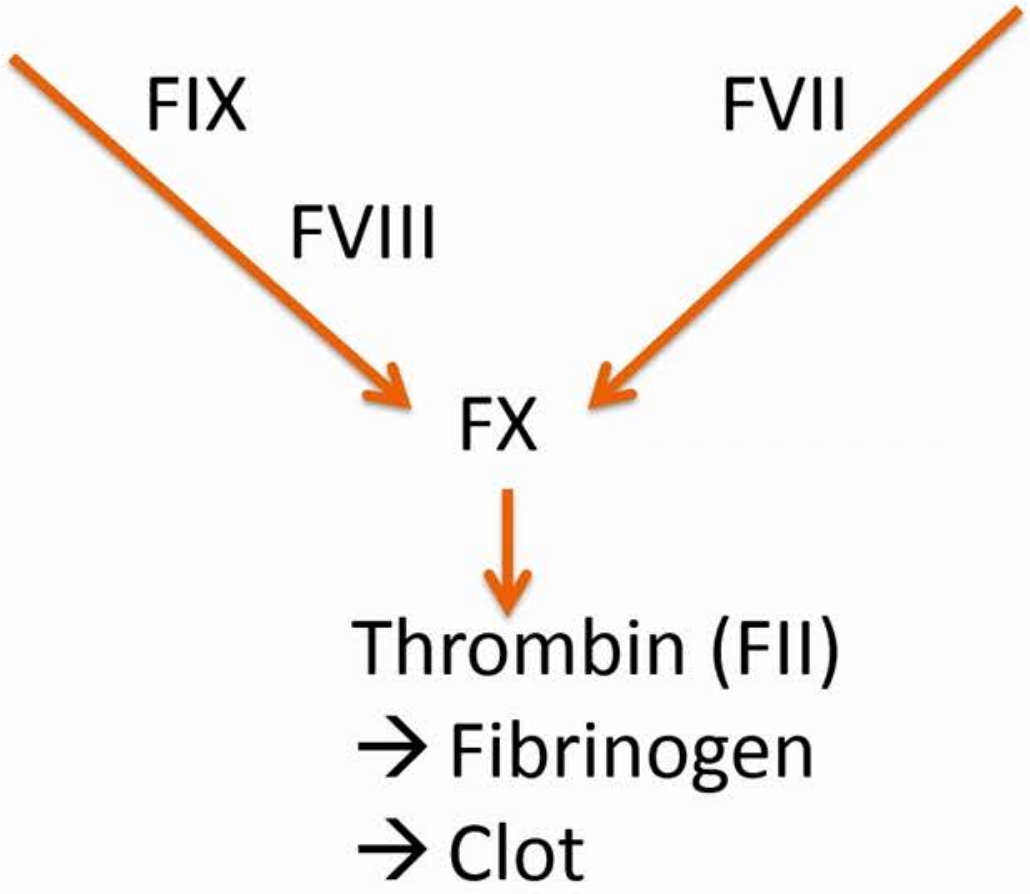
Thromboelastography Results



- 52 yo male motor vehicle crash, rollover, level 2 trauma
- Systolic blood pressure reported as 95 mm Hg, heart rate 135 bpm
- No obvious extremity deformities, abdominal distension, seat belt sign
- Report that level of consciousness decreasing
- History of hemophilia B per wife

Hemophilia

- A – Factor VIII
- B – Factor IX
- With inhibitors
- von Willebrand Disease



Bleeding Severity Based on Clotting Factor Level

Severity	Clotting Factor Level	Bleeding Episodes
Severe	< 1 IU/dL (<0.01 IU/mL) or < 1% of normal	Spontaneous bleeding into joints or muscles
Moderate	1-5 IU/dL (0.01-0.05 IU/mL) or 1-5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5-40 IU/dL (0.05-0.4 IU/mL) or 5-40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

Srivastava A et al. Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH). *Haemophilia* 2013; 19:e1-47.

Goal Clotting Factor Activity in Trauma

- Charts for suggested plasma clotting factor peak levels based on severity of bleed
- Life-threatening (CNS, throat/neck, GI)
  - Hemophilia A recommend desired level 80-100 IU/dL
    - Dose: [kg x desired rise in factor level (IU/dL)] x 0.5 = units
    - Each unit FVIII/kg will raise level by ~ 2 IU/dL
  - Hemophilia B recommend desired level 60-80 IU/dL
    - Dose: [kg x desired rise in factor level (IU/dL)] = units
    - Each unit FIX/kg will raise level by ~ 1 IU/dL (some variation based on age and product)

Srivastava A et al. Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH). *Haemophilia*. 2013; 19:e1-47.

Remember ≥ 50 units/kg

- Ex: FVIII units = [80 kg x 100 IU/dL desired] x 0.5 = 4000 units
- Ex: FVIII units = 50 units/kg x 80 kg = 4000 units

- Ex: FIX units = [80 kg x 80 IU/dL desired]/1 = 6500 units
- Ex: FIX units = 75 units/kg x 80 kg = 6400 units

Assuming factor activity < 1% of normal in life-threatening bleeding or hemodynamically unstable trauma → treat before full evaluation

Srivastava A et al. Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH). *Haemophilia.* 2013; 19:e1-47.

Concentrated Clotting Factor Products

FVIII

- Kogenate (recombinant)
- Humate-P (with von Willebrand factor, human)
- Alphanate (with von Willebrand factor, human)

FIX

- Benefix (recombinant)
- Mononine (human)

rFVIIa

Recombinant activated FVII (bypass factor)

90 mcg/kg

Blood Products

Product	Components	Hemophilia Type	Recommendation
Cryoprecipitate	VIII, XIII, VWF, fibrinogen	A	Preferred for A over FFP 1 mL cryo = 3-5 IU FVIII
Fresh Frozen Plasma (FFP)	All coagulation factors	B, A (if cryo unavailable)	1 mL FFP = 1 unit factor activity (starting dose 15-20 mL/kg) Difficult to achieve FVIII > 30 IU/dL or FIX > 25 IU/dL

Srivastava A et al. Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH). *Haemophilia.* 2013; 19:e1-47.

Pharmacologic Agents

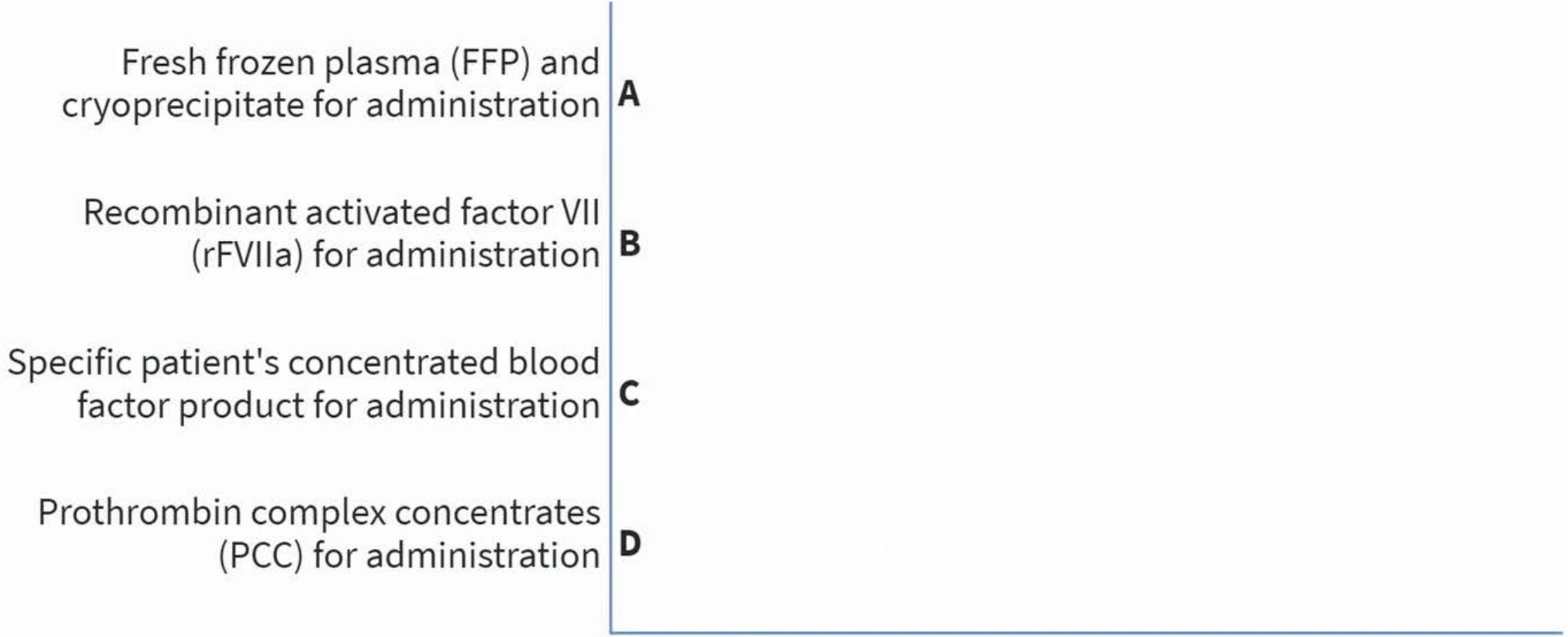
Medication	Mechanism	Hemophilia Type	Recommendation
Desmopressin (DDAVP)	Promote release of VWF and increases FVIII	A	Mild/moderate to raise FVIIIa (avoid factor expense) 0.3 mcg/kg IV or SC boost FVIII 3-6 fold
TXA	Anti-fibrinolytic	A or B Adjunct, oral administration → promotes clot stability	Contraindicated (thromboembolic risk) Hematuria (dissolution of clots → obstructive uropathy) Thoracic surgery → insoluble hematomas FIX receiving PCC
Aminocaproic Acid	Anti-fibrinolytic (shorter half-life, less potent than TXA)		Myopathy risk
Emicizumab	Monoclonal antibody	A (with inhibitors)	Bridges aFIX and aFX to restore the function of missing activated FVIII

Srivastava A et al. Treatment Guidelines Working Group, on behalf of the World Federation of Hemophilia (WFH). *Haemophilia* 2013; 19:e1-47.; ; Oldenburg J, et al. *N Engl J Med* 2017;377:809-1.

- 52 yo male motor vehicle crash, rollover, level 2 trauma
- Systolic blood pressure reported as 95 mm Hg, heart rate 135 bpm
- No obvious extremity deformities, abdominal distension, seat belt sign
- Report that level of consciousness decreasing
- History of hemophilia B per wife

Which of the following products would you prepare for administration as soon as possible after this patient's arrival at the emergency department?

Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**



Key Takeaways

- Key Takeaway #1
  - Use of tranexamic acid (TXA) remains controversial but may be guided by thromboelastography
- Key Takeaway #2
  - Coagulopathy is complicated during trauma resuscitation. A patient history and thromboelastogram can guide anticoagulation reversal therapies
- Key Takeaway #3
  - Concentrated clotting factors are preferred to blood products to achieve desired factor levels in hemophilia patients with trauma

Anticoagulation Reversal Strategies for Patients with Acute Medical or Intracranial Bleeding

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Massachusetts General Hospital
Assistant Professor of Emergency Medicine
Harvard Medical School
Boston, Massachusetts

@PharmERToxGuy

ashp Certification Resources

ashp MIDYEAR 2017
Clinical Meeting & Exhibition

65 y/o male

BP: 74/52 mm Hg

HR: 122 bpm

ashp Certification Resources

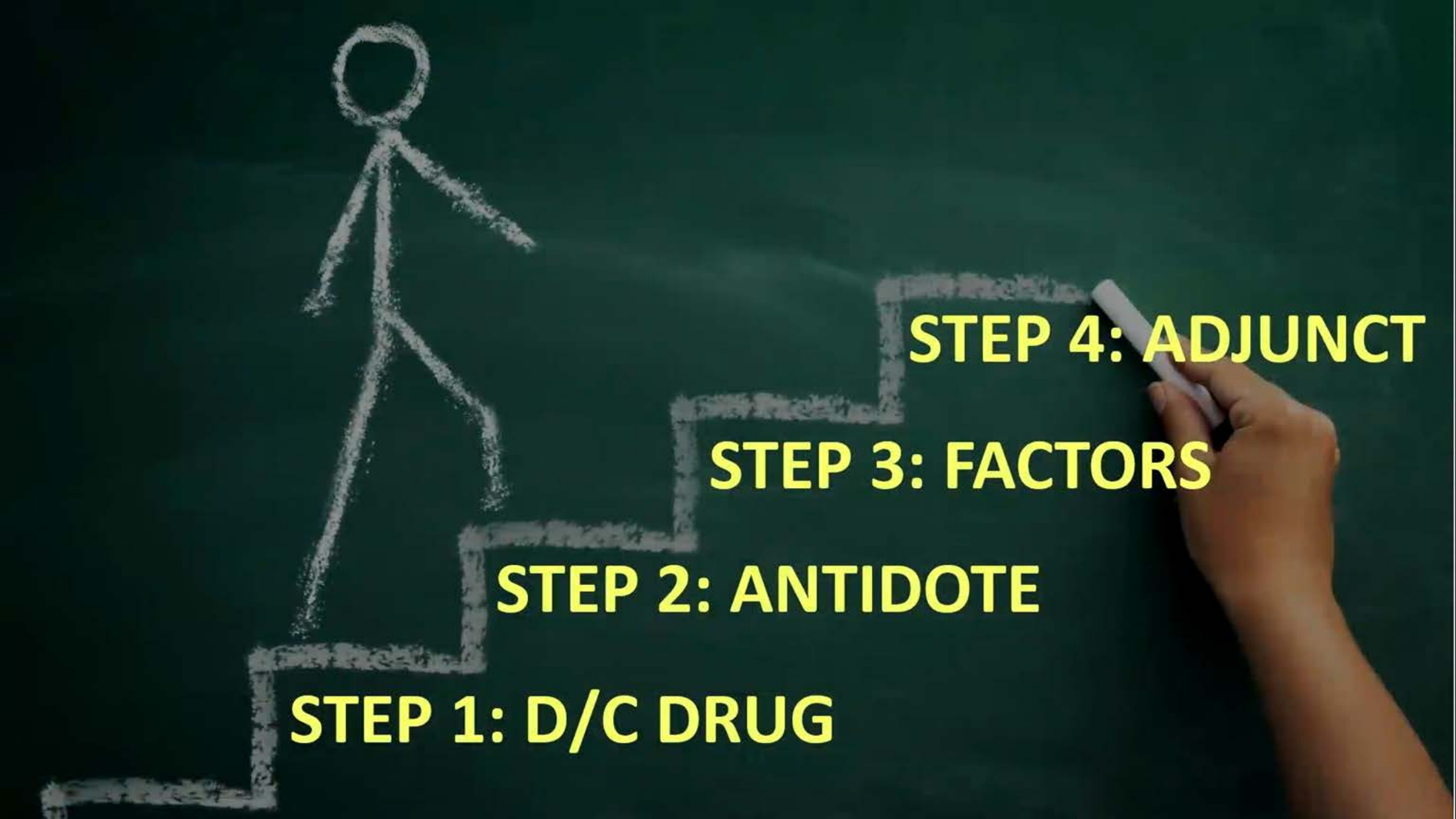
40 y/o male

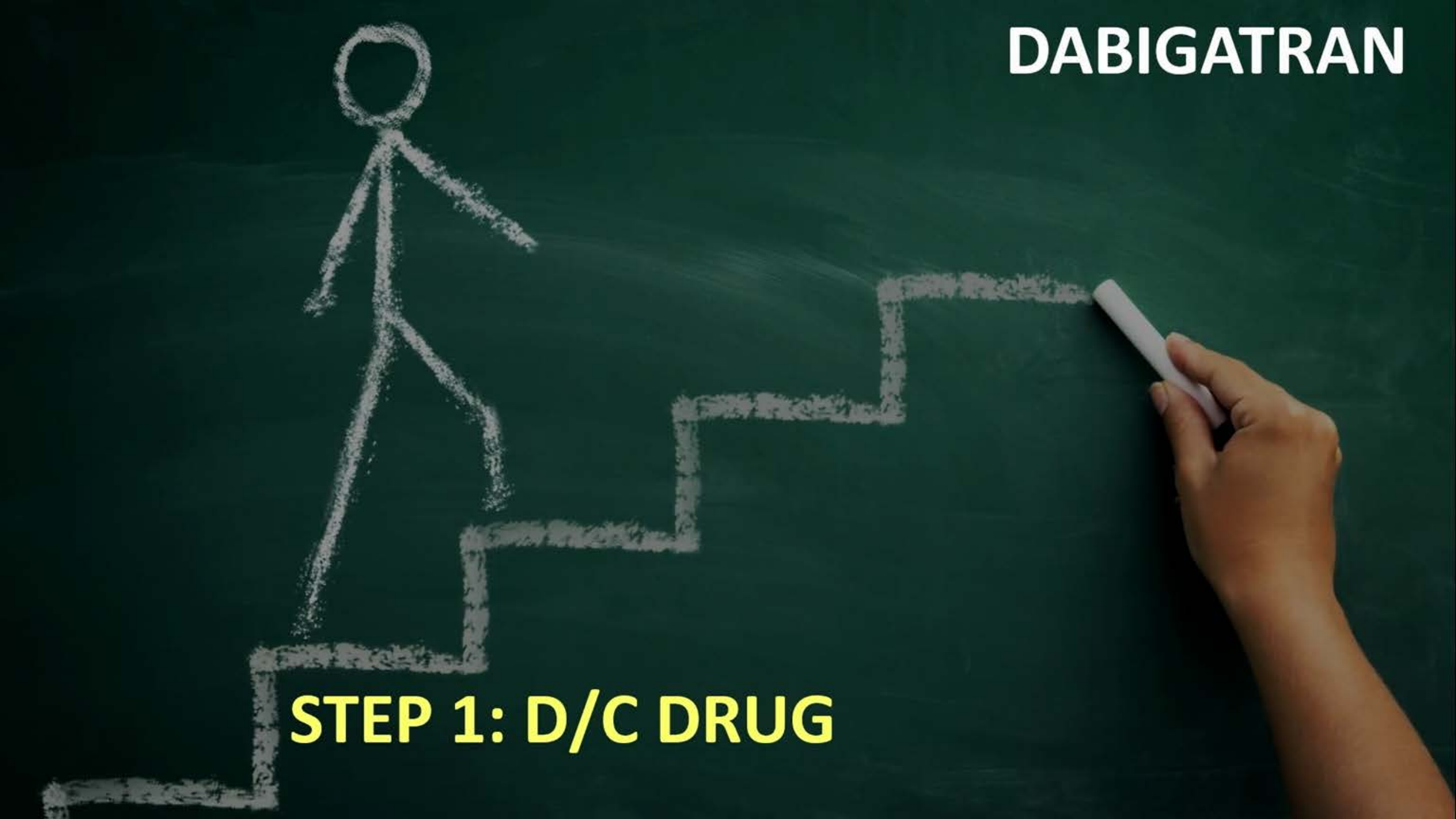
HTN, PE, CAD, CHF

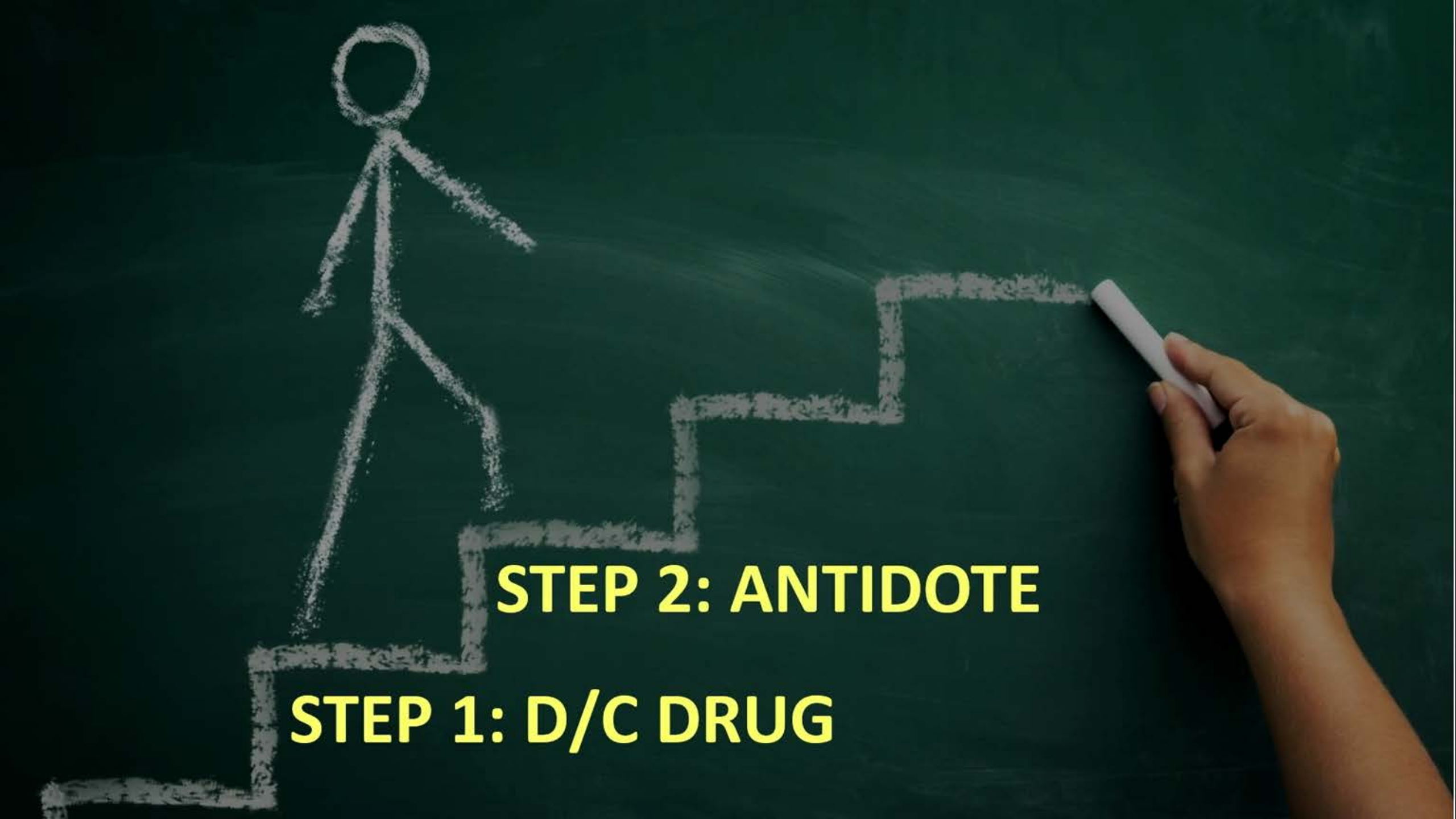
Time: 06:10

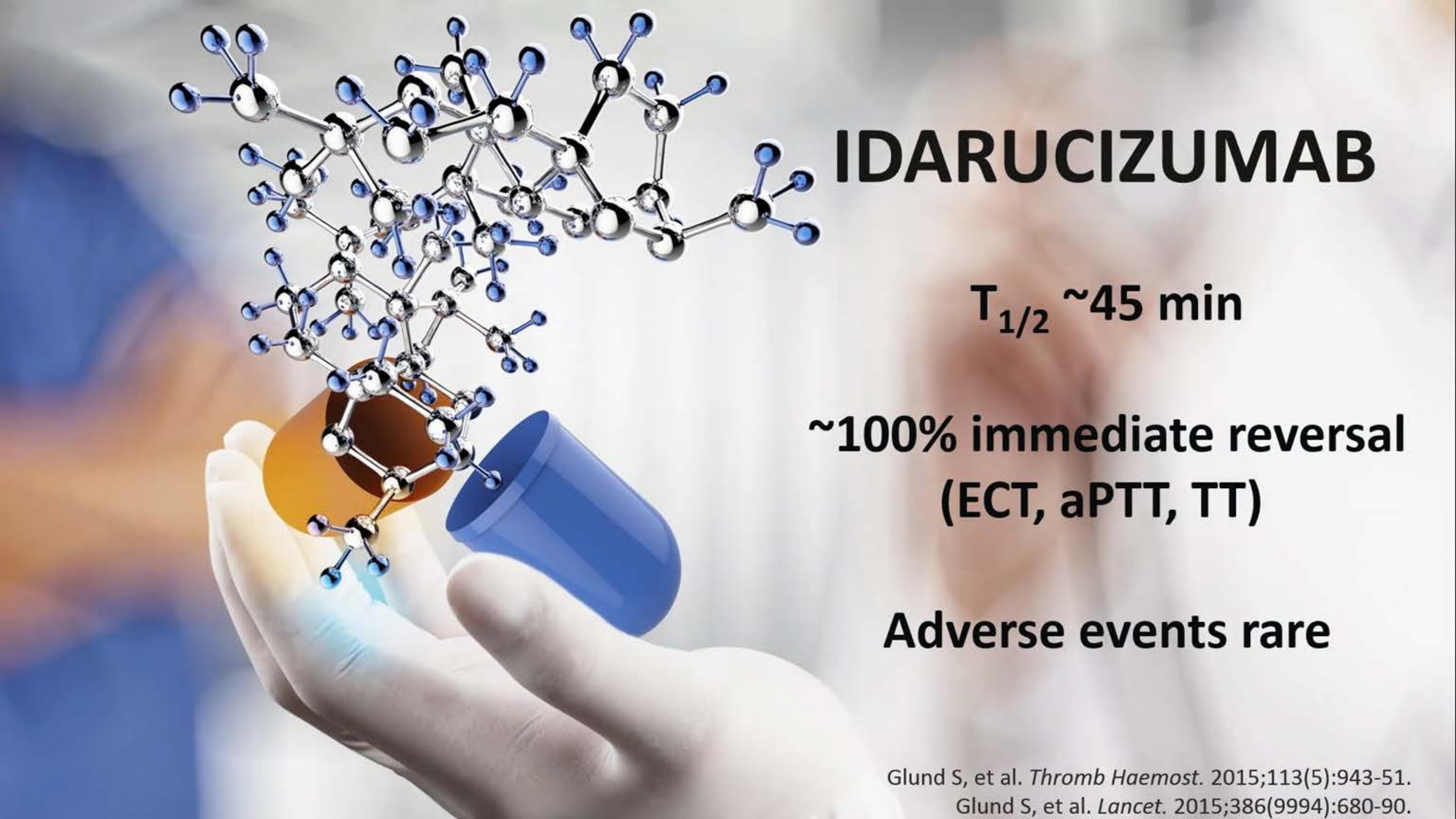
Time
07:08

INR 3.8


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


DABIGATRAN
STEP 1: D/C DRUG


STEP 2: ANTIDOTE
STEP 1: D/C DRUG



IDARUCIZUMAB

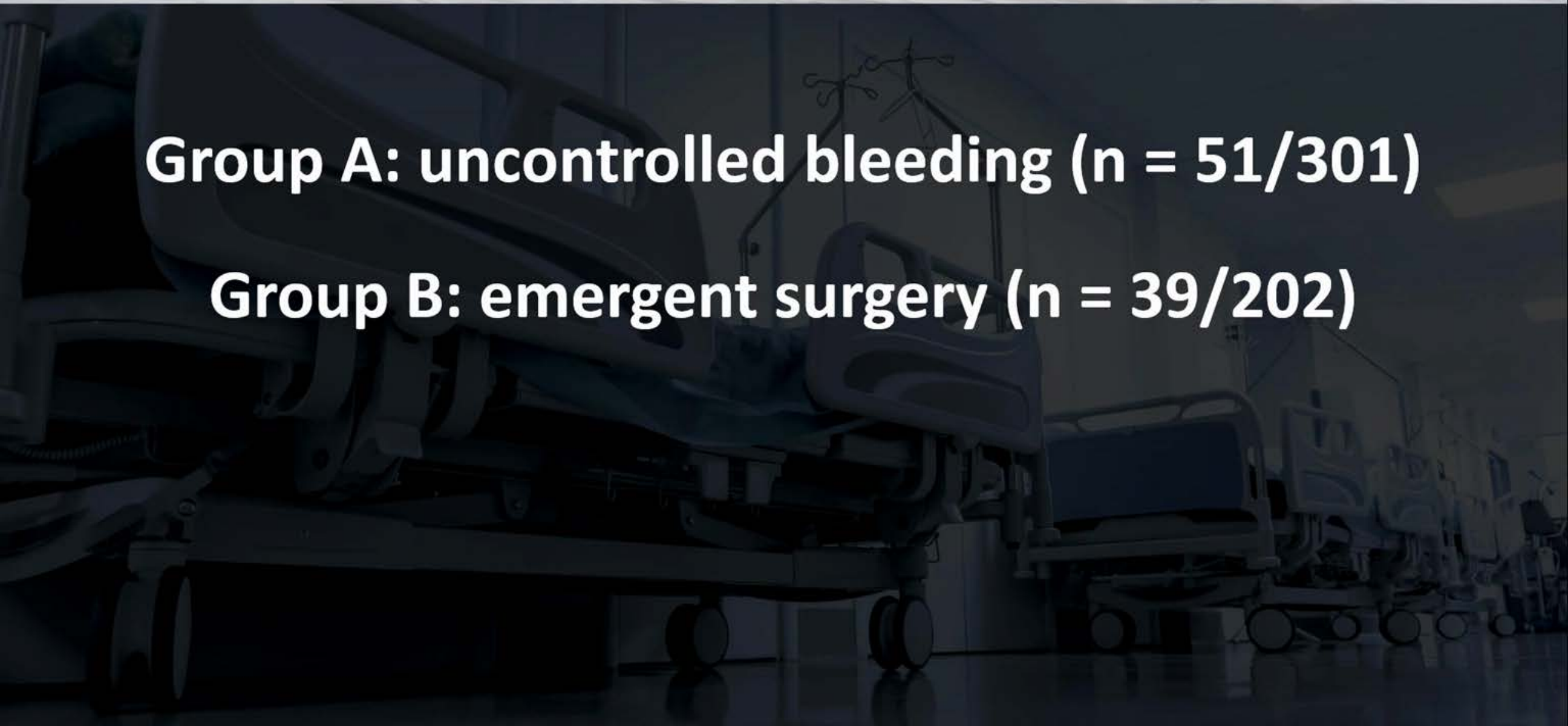
$T_{1/2}$ ~45 min

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

Adverse events rare

Glund S, et al. *Thromb Haemost.* 2015;113(5):943-51.
Glund S, et al. *Lancet.* 2015;386(9994):680-90.

Idarucizumab for Dabigatran Reversal



Group A: uncontrolled bleeding (n = 51/301)

Group B: emergent surgery (n = 39/202)

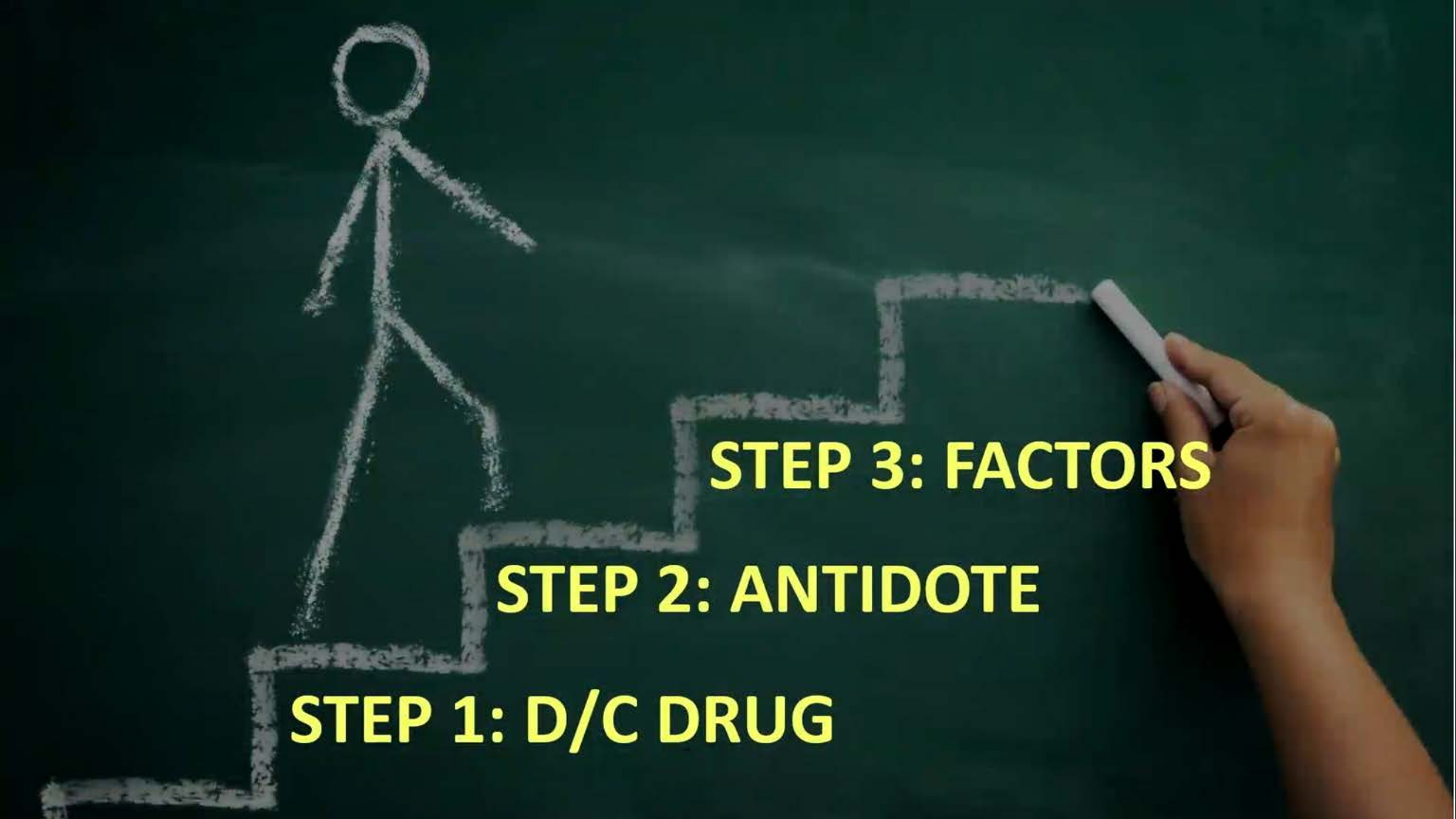
Interim Analysis	Full Analysis
Maximum reversal in 88-98%	Maximum reversal in 98%
Funded by Boehringer Ingelheim	Funded by Boehringer Ingelheim
No control group	No control group
Bleeding cessation 11.4 hrs	Bleeding cessation 2.5 hrs
25% normal dTT/ECT	10% normal dTT/ECT
5.5% thrombotic events	4.8% thrombotic events

Pollack CV Jr, et al. *N Engl J Med.* 2015;373(6):511-20.
Pollack CV Jr, et al. *N Engl J Med.* 2017;377(5):431-44.

Sustained bleeding

Repeat antidote dosing

Alhashem HM, et al. *Am J Emerg Med.* 2017;35:193.e3-e5.
Steele AP, et al. *Clin Toxicol*. 2017 Jul 13:1-3. [Epub]
Simon A, et al. *J Thromb Haemost.* 2017;15(7):1317-21.

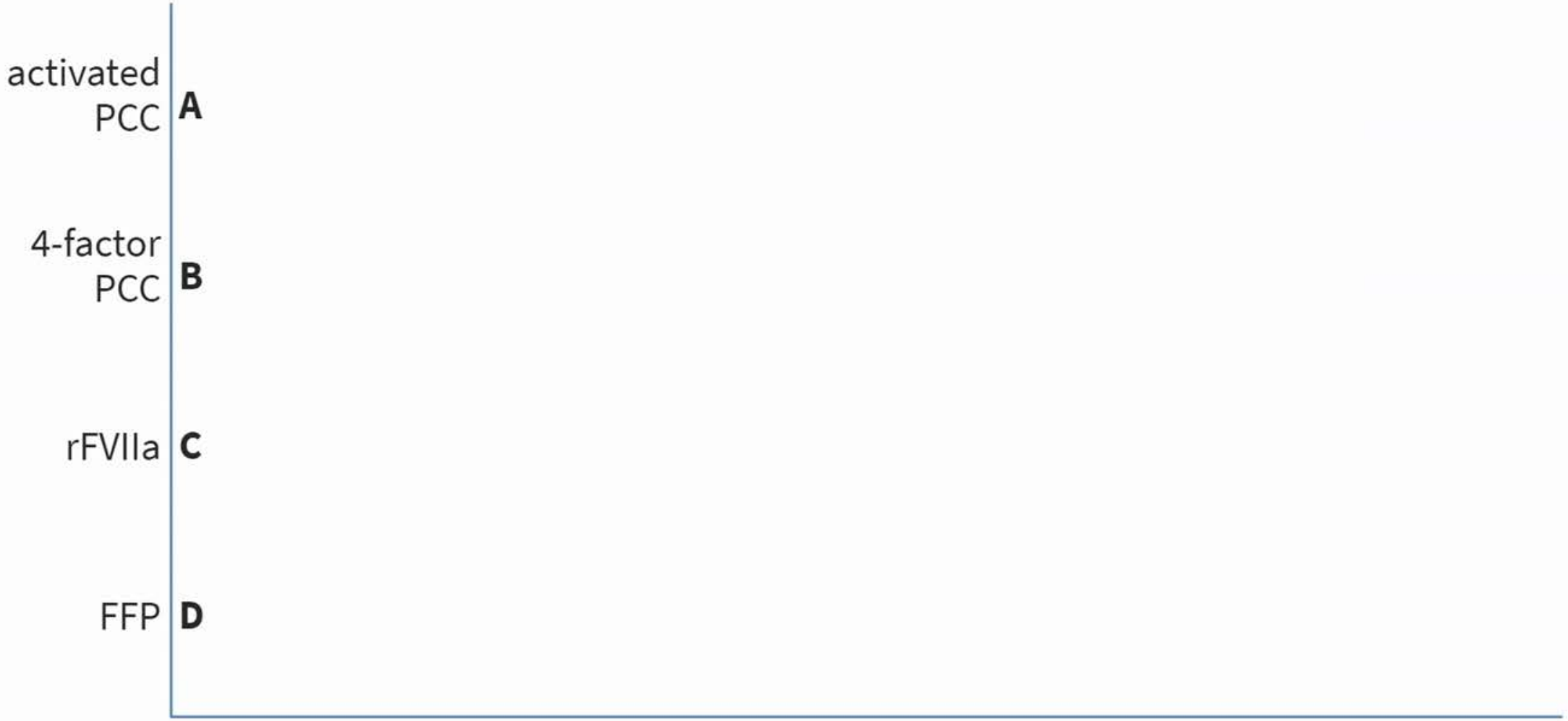

STEP 3: FACTORS
STEP 2: ANTIDOTE
STEP 1: D/C DRUG

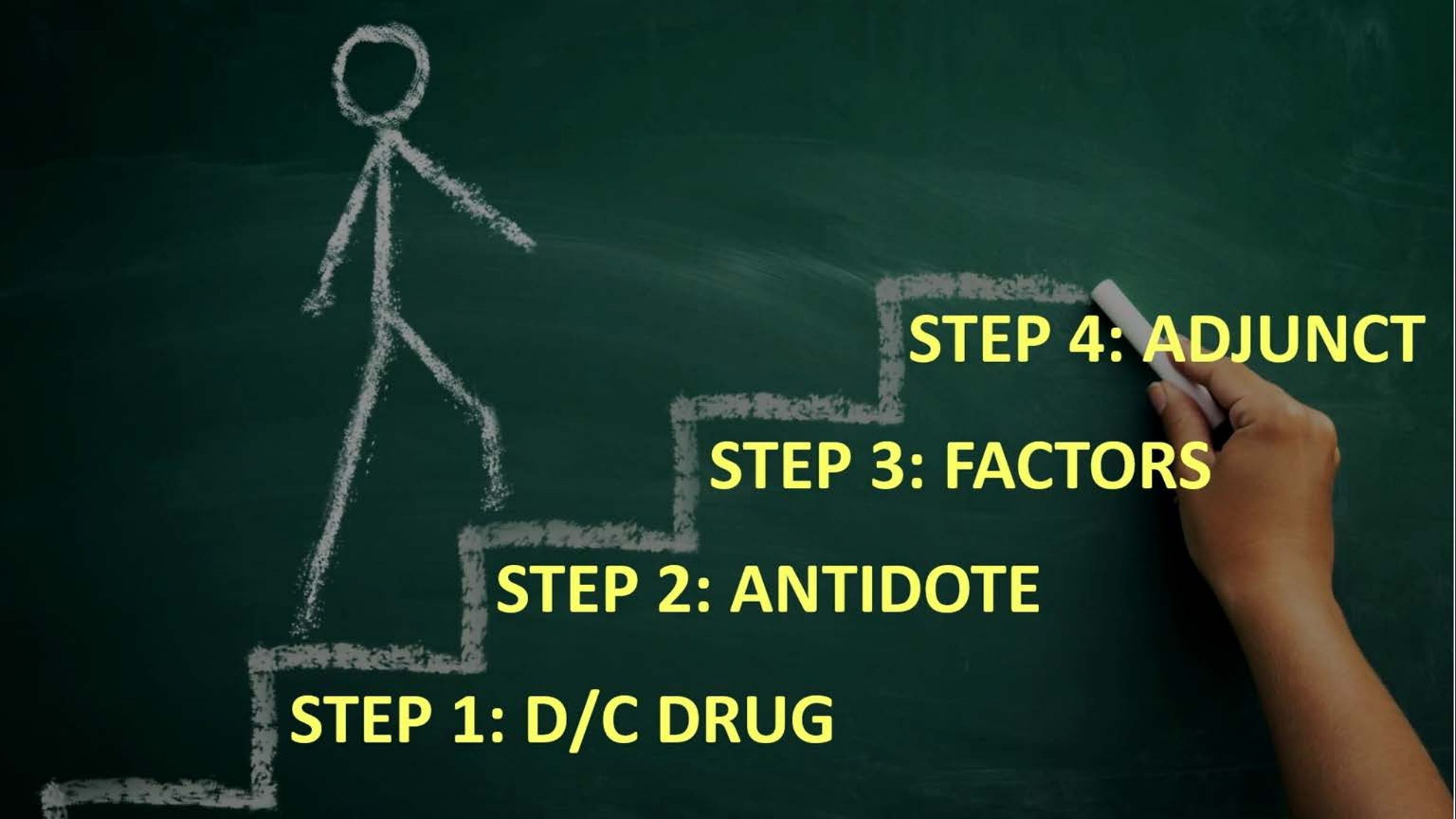
Citation	N	Drug	Factor(s)	Outcome
Eerenberg 2011	12	Dabigatran 150 mg BID X 2.5 d	4-factor PCC 50 units/kg IV	No reversal of aPTT, ECT, or TT
Marlu 2012	10	Dabigatran 150 mg X 1	4-factor PCC, rFVIIa, aPCC	All corrected thrombin generation rFVIIa & aPCC corrected altered lag time
Arellano-Rodrigo 2015	10	Dabigatran 150 mg BID X 5 d	4-factor PCC, rFVIIa, aPCC	4-factor PCC no effect on aPTT rFVIIa & aPCC partially improved all parameters

14 aPCC cases

Which of the following therapies is probably most effective in reversing dabigatran?

Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**




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

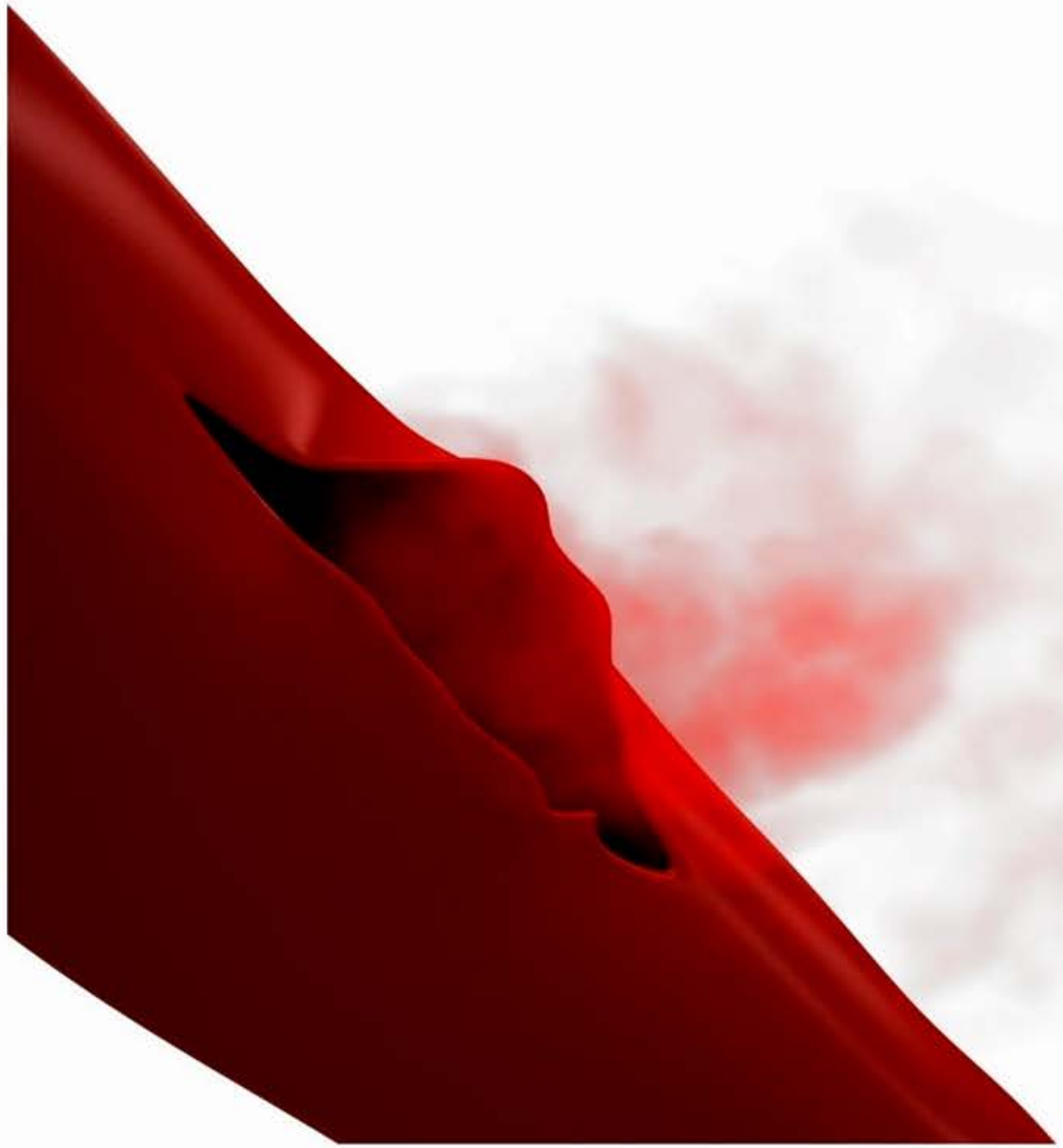
Activated Charcoal

Renal Replacement Therapy

65 y/o male

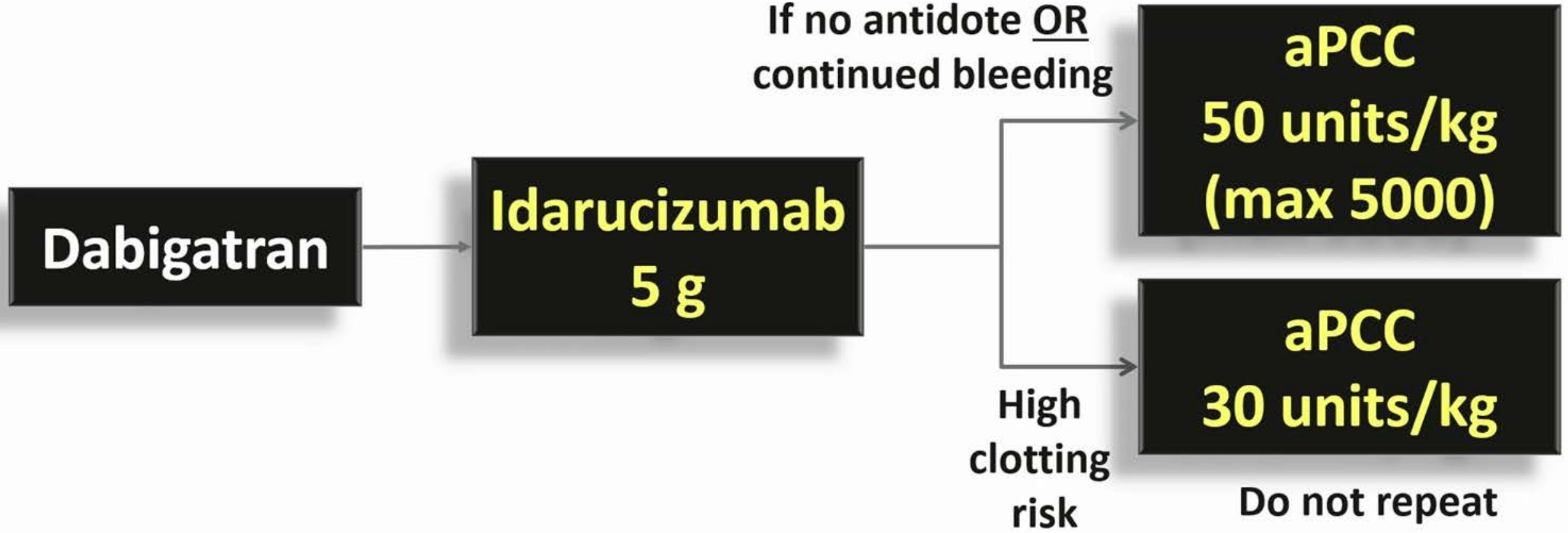
BP: 74/52 mm Hg

HR: 122 bpm

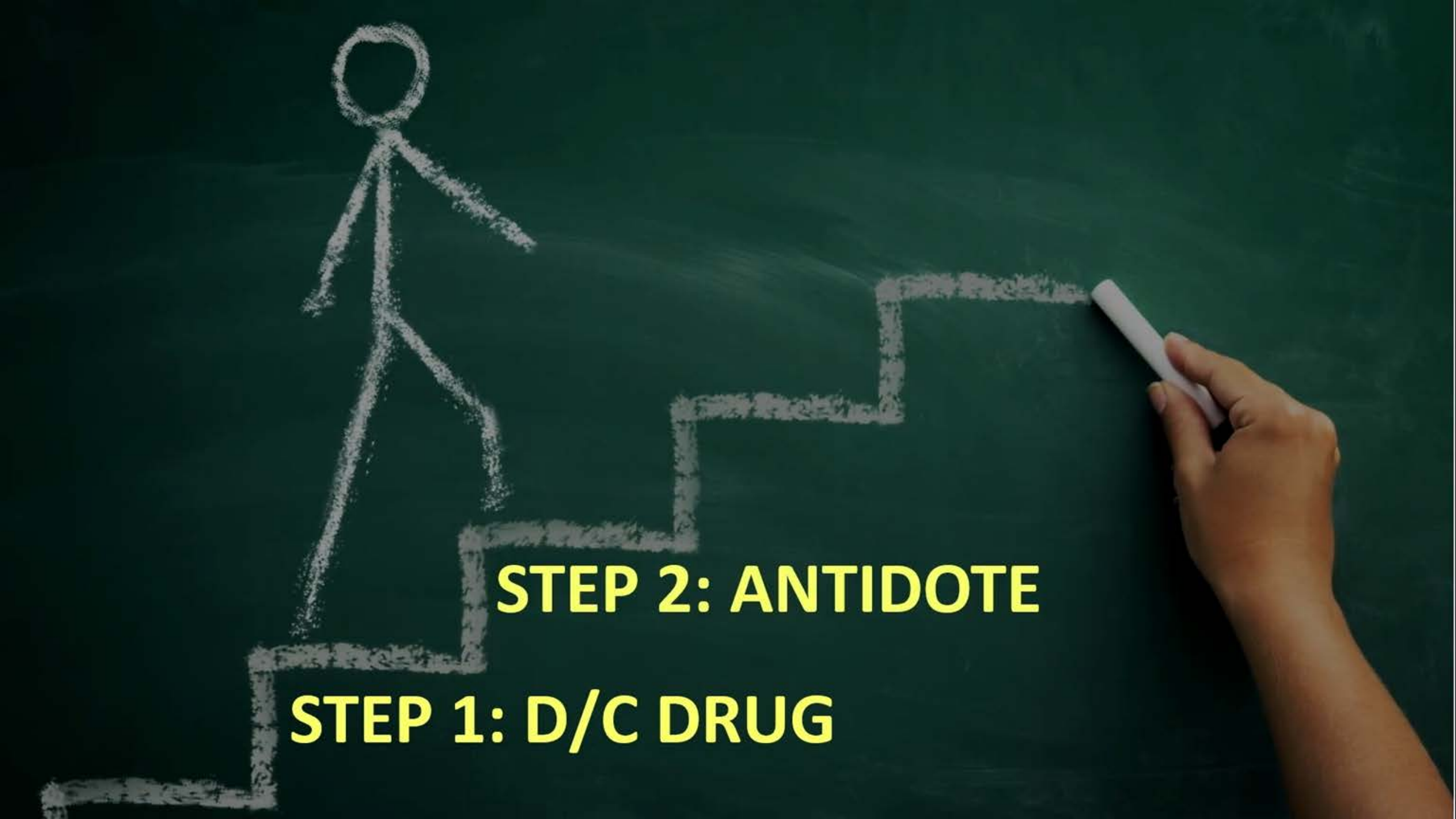


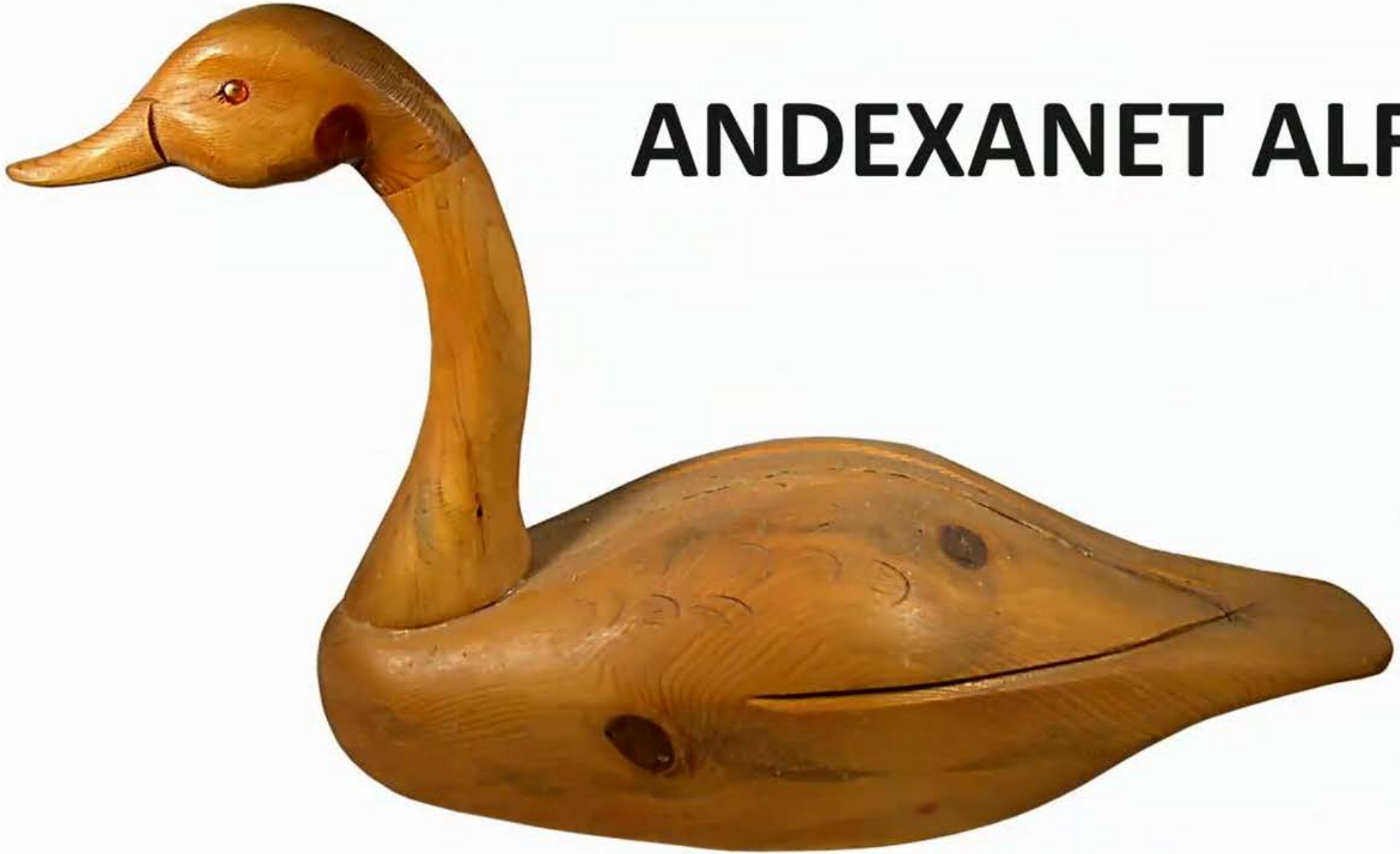
Plt	106	76
PT	23.4	13.3
INR	2.0	1.0
PTT	74	70
TT	120	24

Alhashem HM, et al. *Am J Emerg Med.* 2017;35(1):193.e3-193.e5.



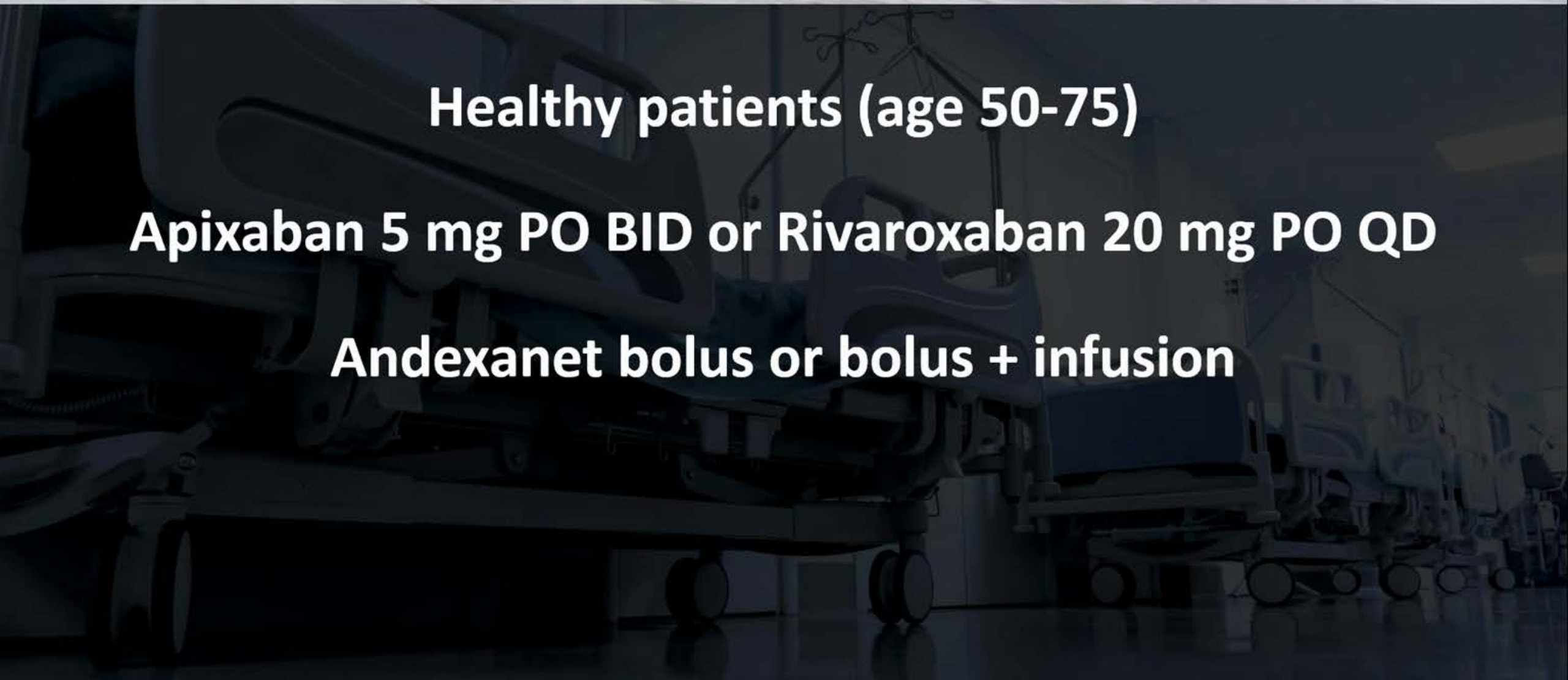
Proposed Institutional Treatment Algorithm


STEP 2: ANTIDOTE
STEP 1: D/C DRUG



ANDEXANET ALFA

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

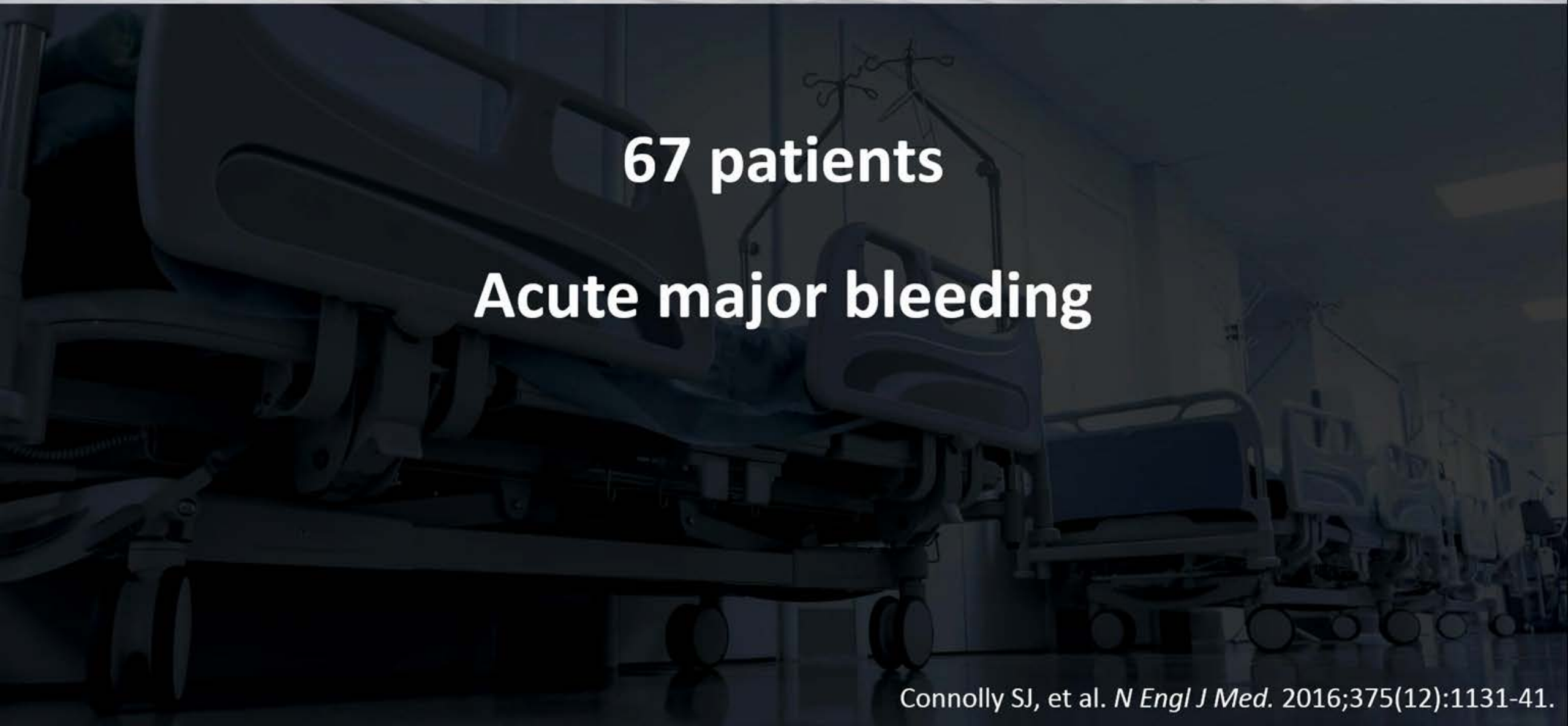


Healthy patients (age 50-75)

Apixaban 5 mg PO BID or Rivaroxaban 20 mg PO QD

Andexanet bolus or bolus + infusion

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors



67 patients

Acute major bleeding

Connolly SJ, et al. *N Engl J Med.* 2016;375(12):1131-41.

~90% reduction in anti-factor Xa activity

79% excellent/good hemostasis

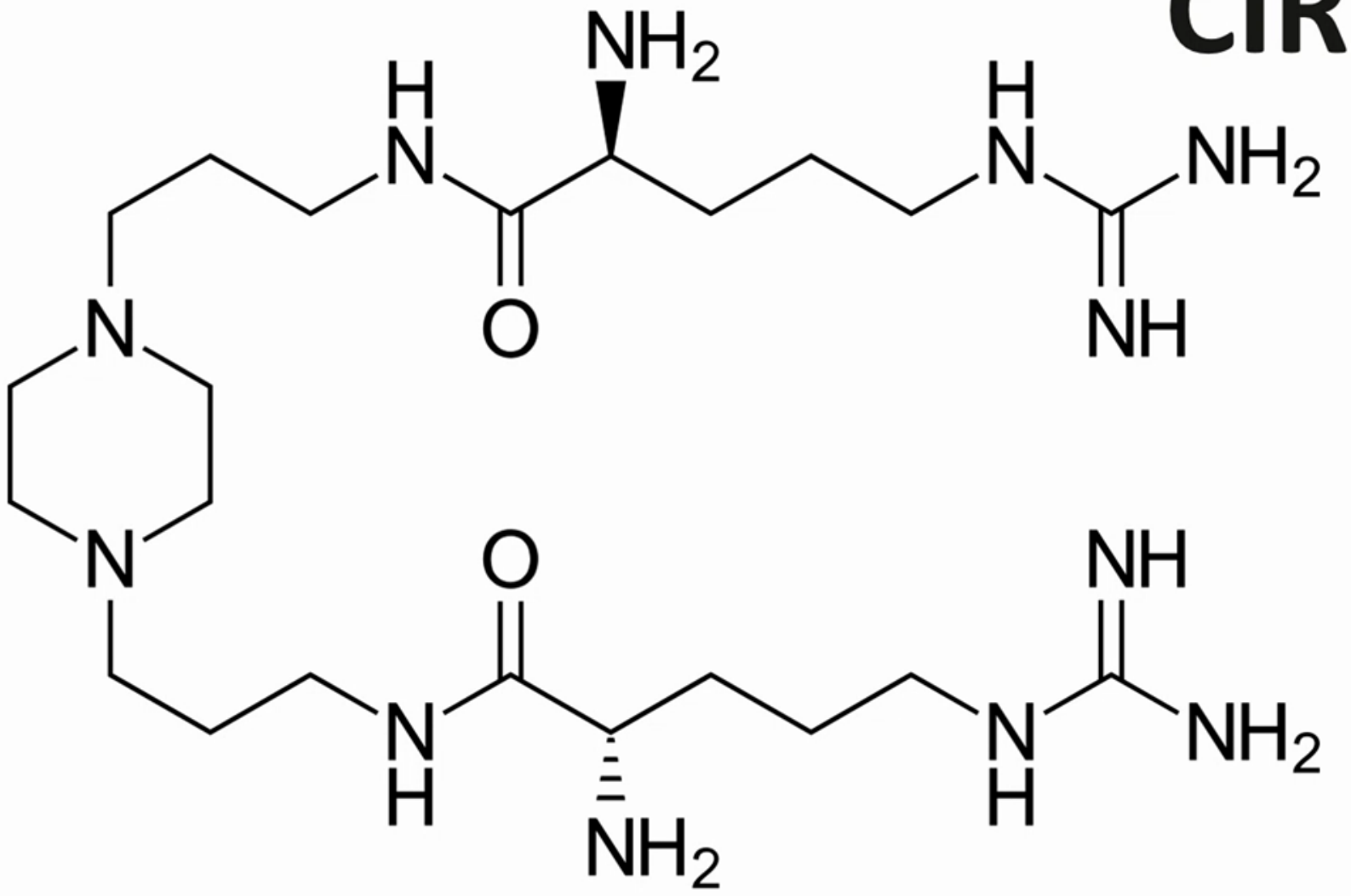
18% thrombotic events

No control group

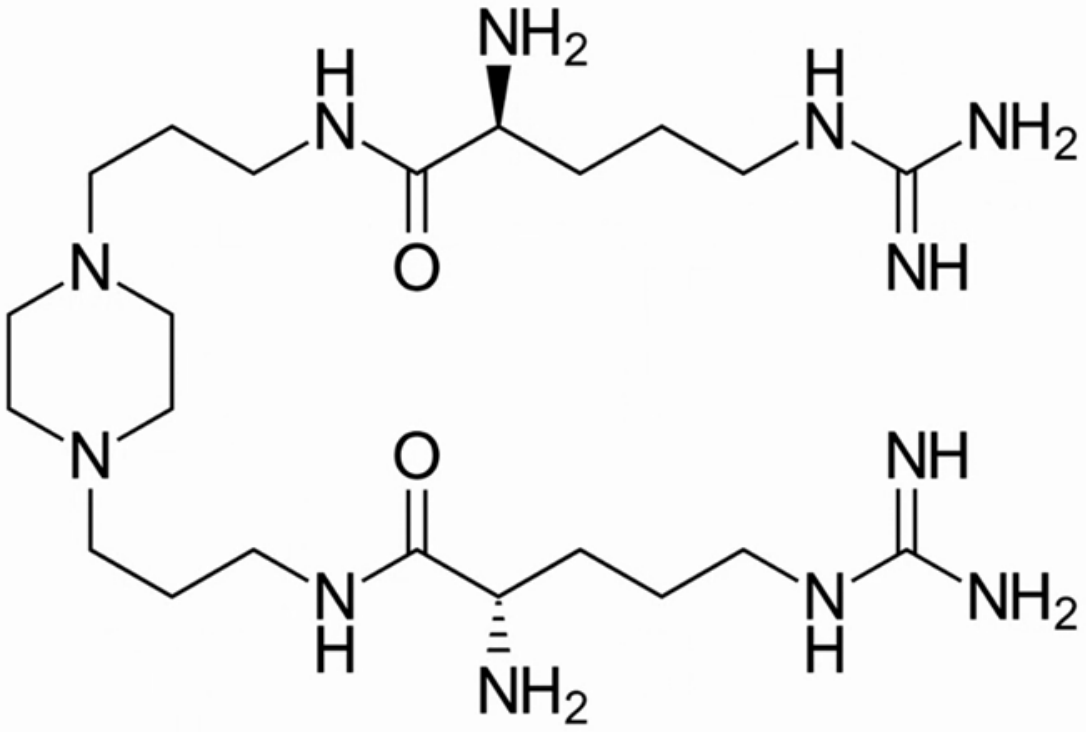
Not approved by FDA

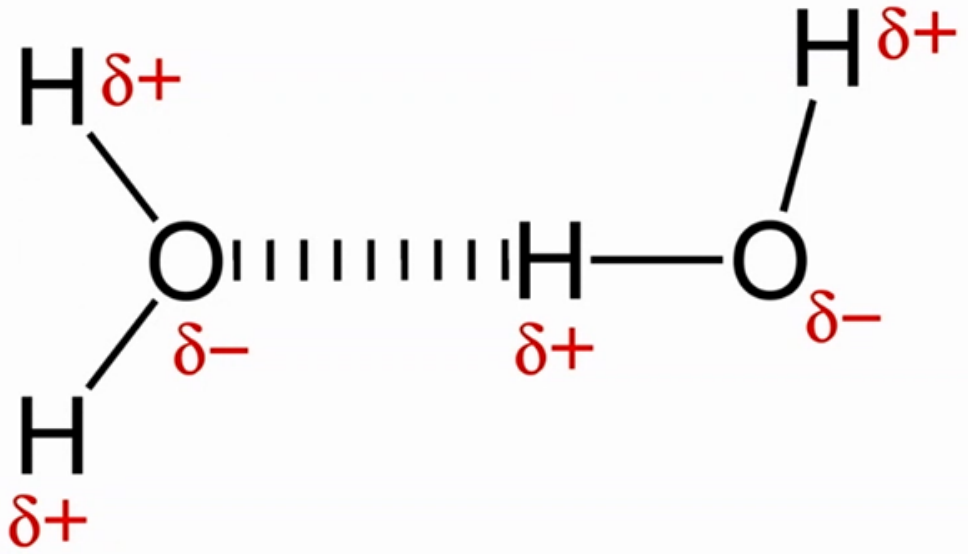
Connolly SJ, et al. *N Engl J Med.* 2016;375(12):1131-41.

CIRAPARANTAG

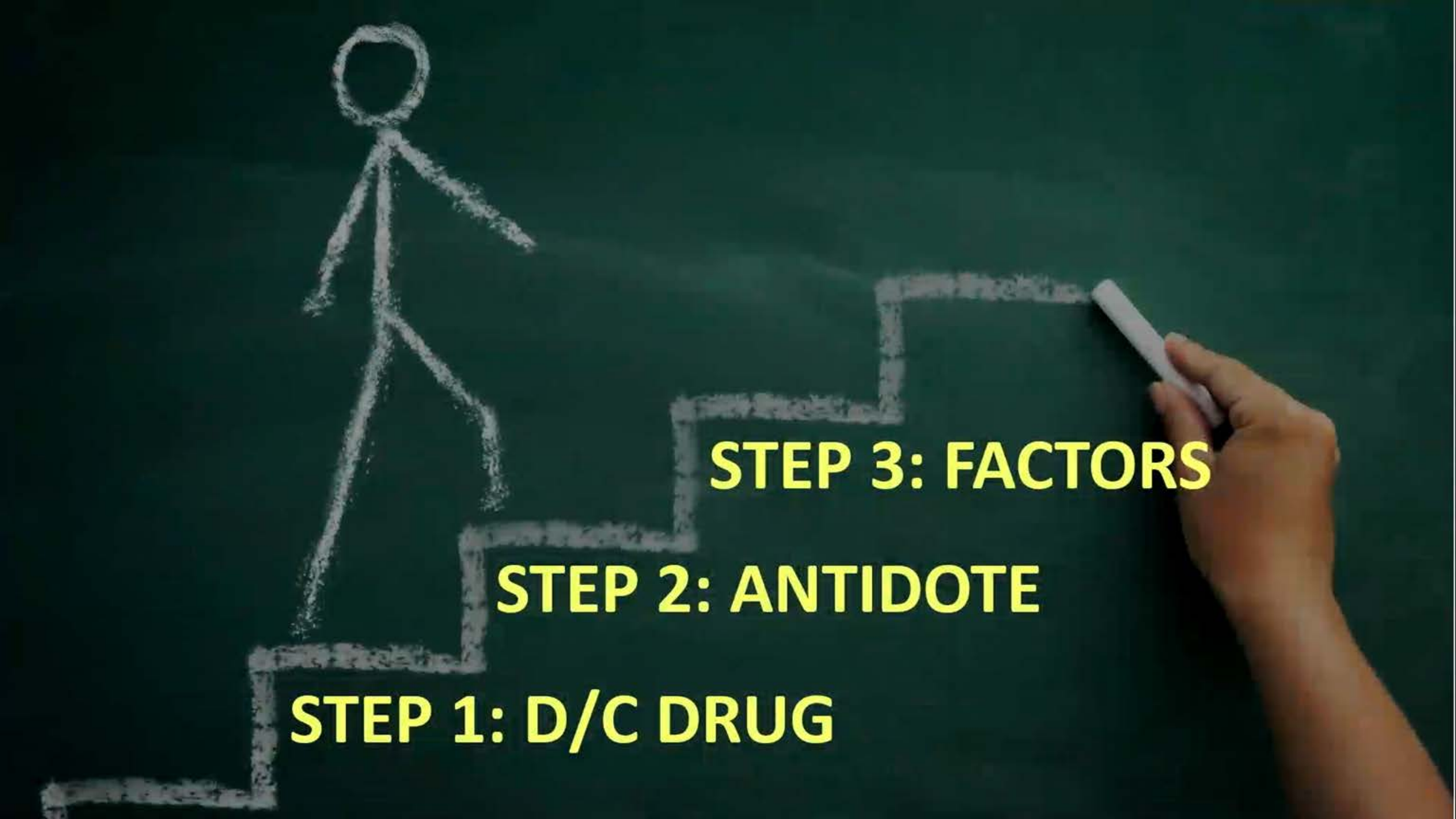


Hydrogen Bonds





Lu G, et al. *Circulation.* 2014;130:A18218. [abstract]
Ansell JE, et al. *Thromb Haemost.* 2017;117(2):238-45.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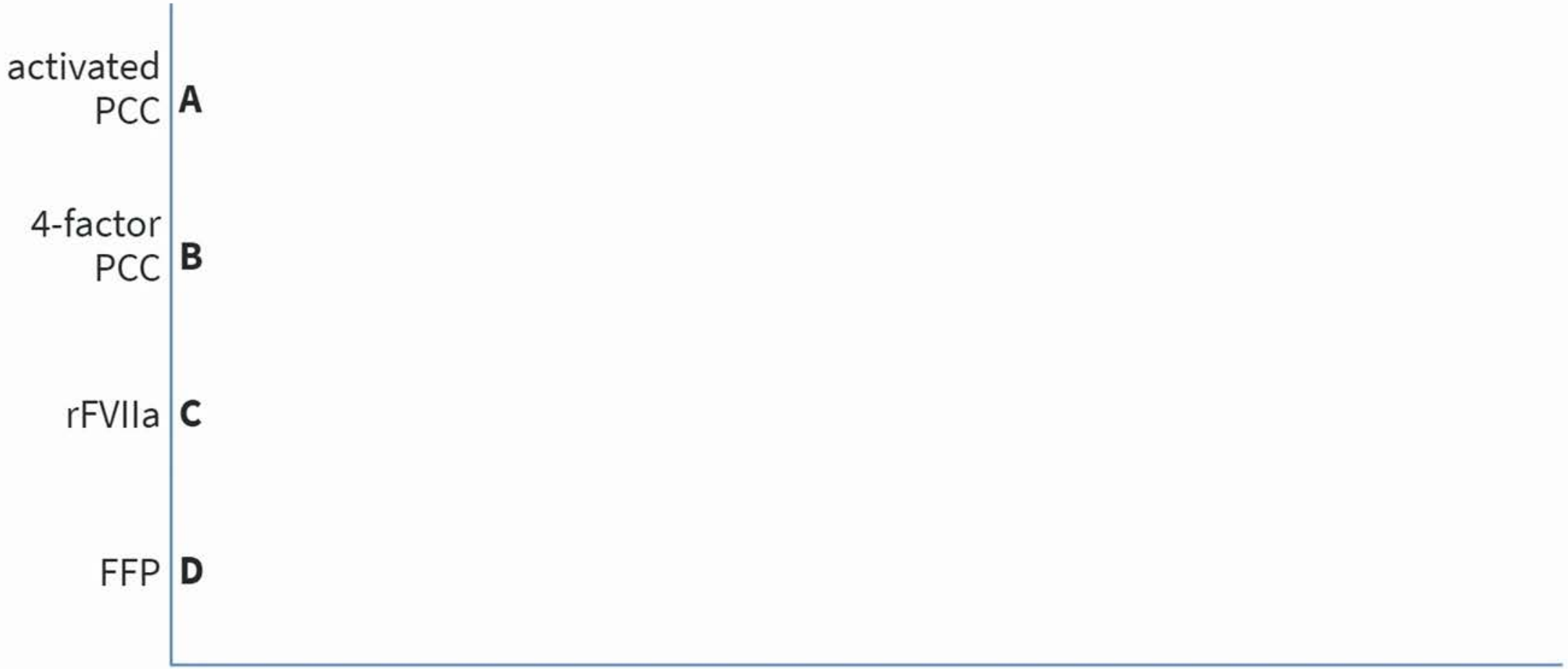
STEP 1: D/C DRUG

Citation	N	Drug	Factor(s)	Outcome
Eerenberg 2011	12	Rivaroxaban 20 mg BID X 2.5 d	4-factor PCC 50 units/kg IV	Complete reversal of PT & ETP
Marlu 2012	10	Rivaroxaban 20 mg X 1	4-factor PCC, rFVIIa, aPCC	4-factor PCC corrected ETP-AUC rFVIIa corrected lag time/time to peak aPCC corrected all parameters
Cheung 2015	6	Apixaban 10 mg BID X 7 d	4-factor PCC 37.5 units/kg, 25 units/kg, or placebo	Both partial reversal of PT & ETP
Halim 2014	6	Edoxaban ex-vivo	aPCC or rVFIIa	Both normalized aPTT, PT, & extrinsic anti-FXa

Which of the following factor replacements is probably most effective in reversing factor Xa inhibitors?

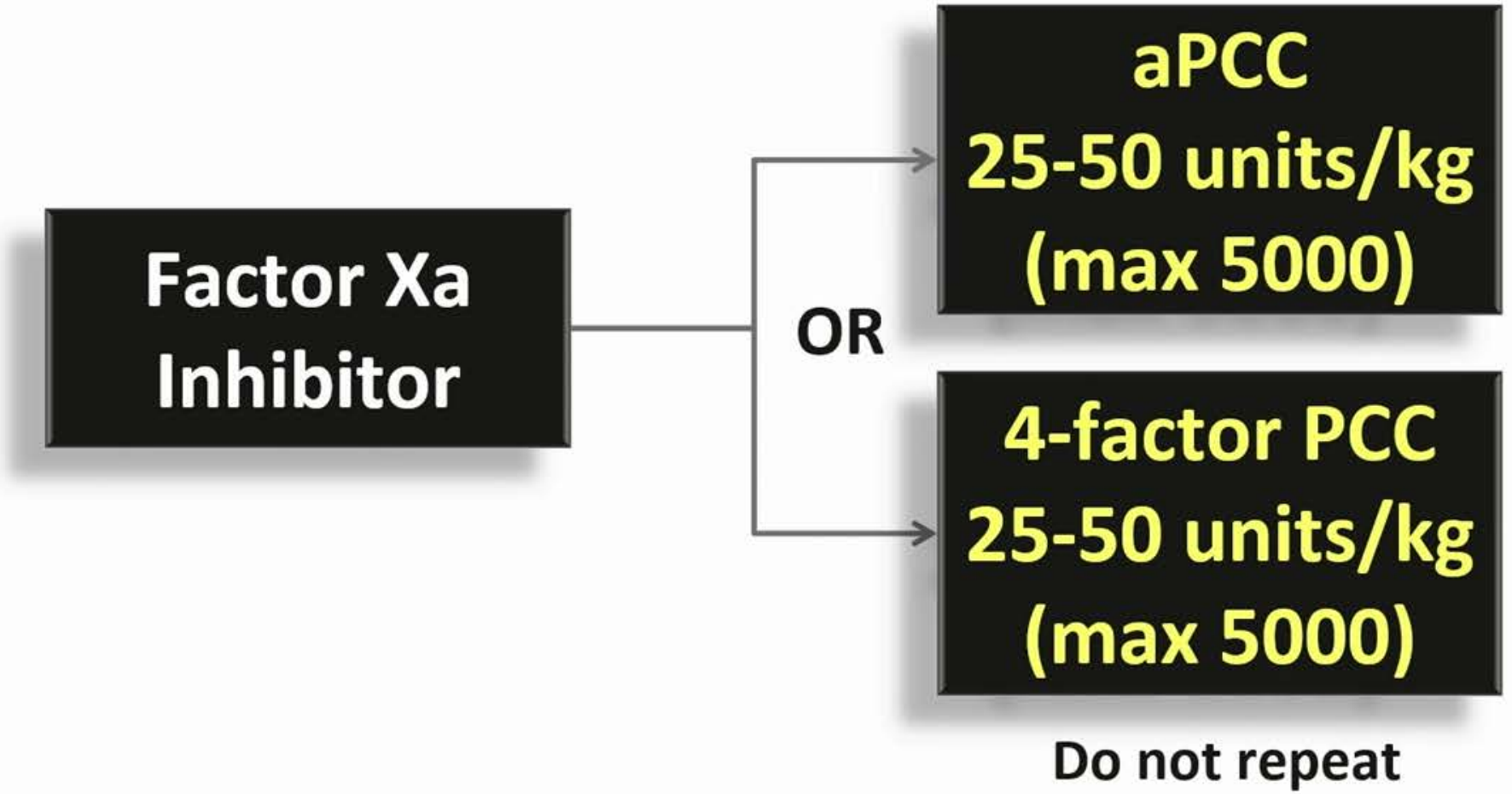
Respond at **PollEv.com/ashp2** Text **ASHP2** to **22333** once to join, then **A, B, C, or D**



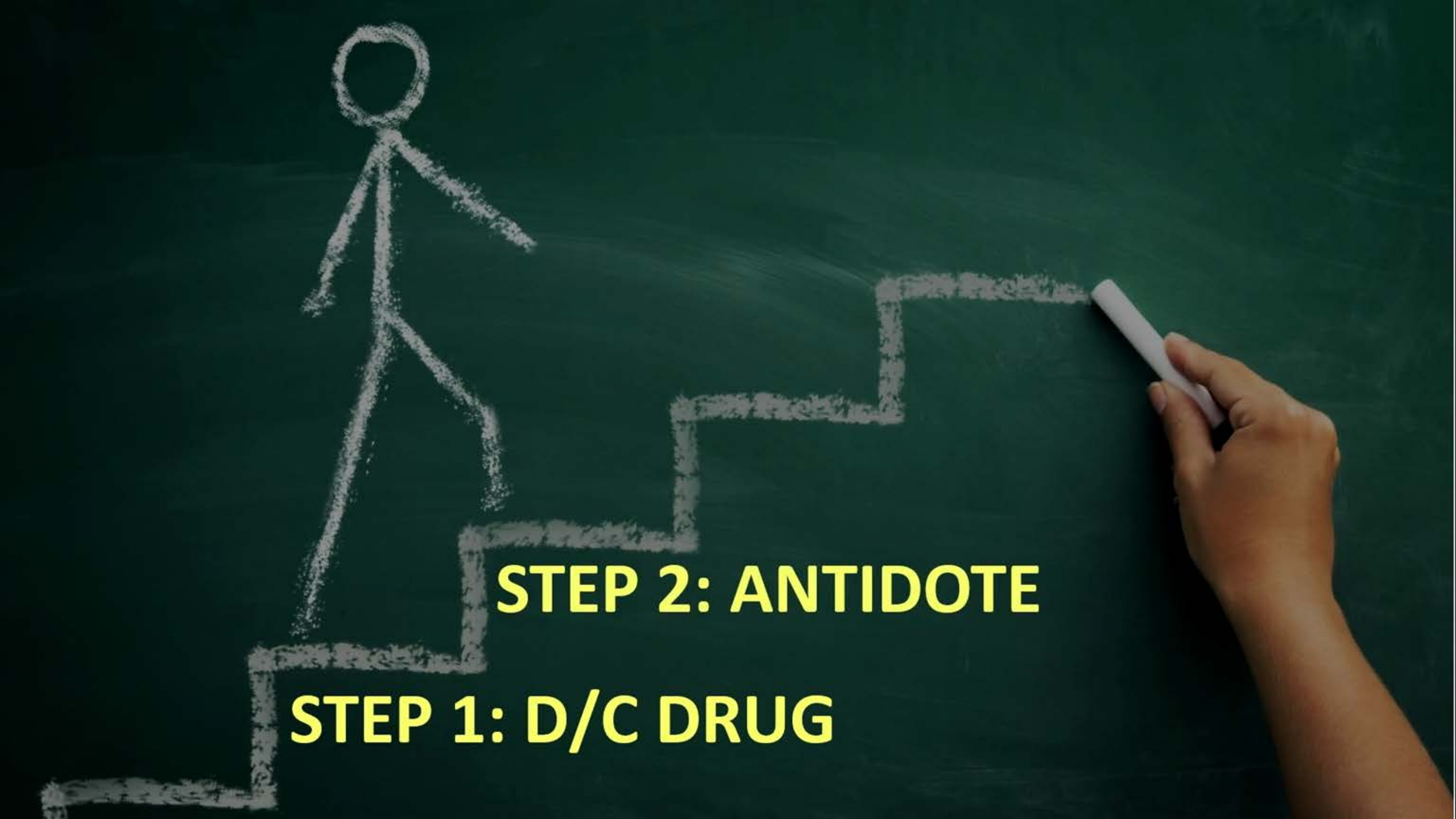
Activated Charcoal

Ollier E, et al. *Clin Pharmacokinet.* 2017;56(7):793-801.

Proposed Institutional Treatment Algorithm



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


STEP 2: ANTIDOTE
STEP 1: D/C DRUG

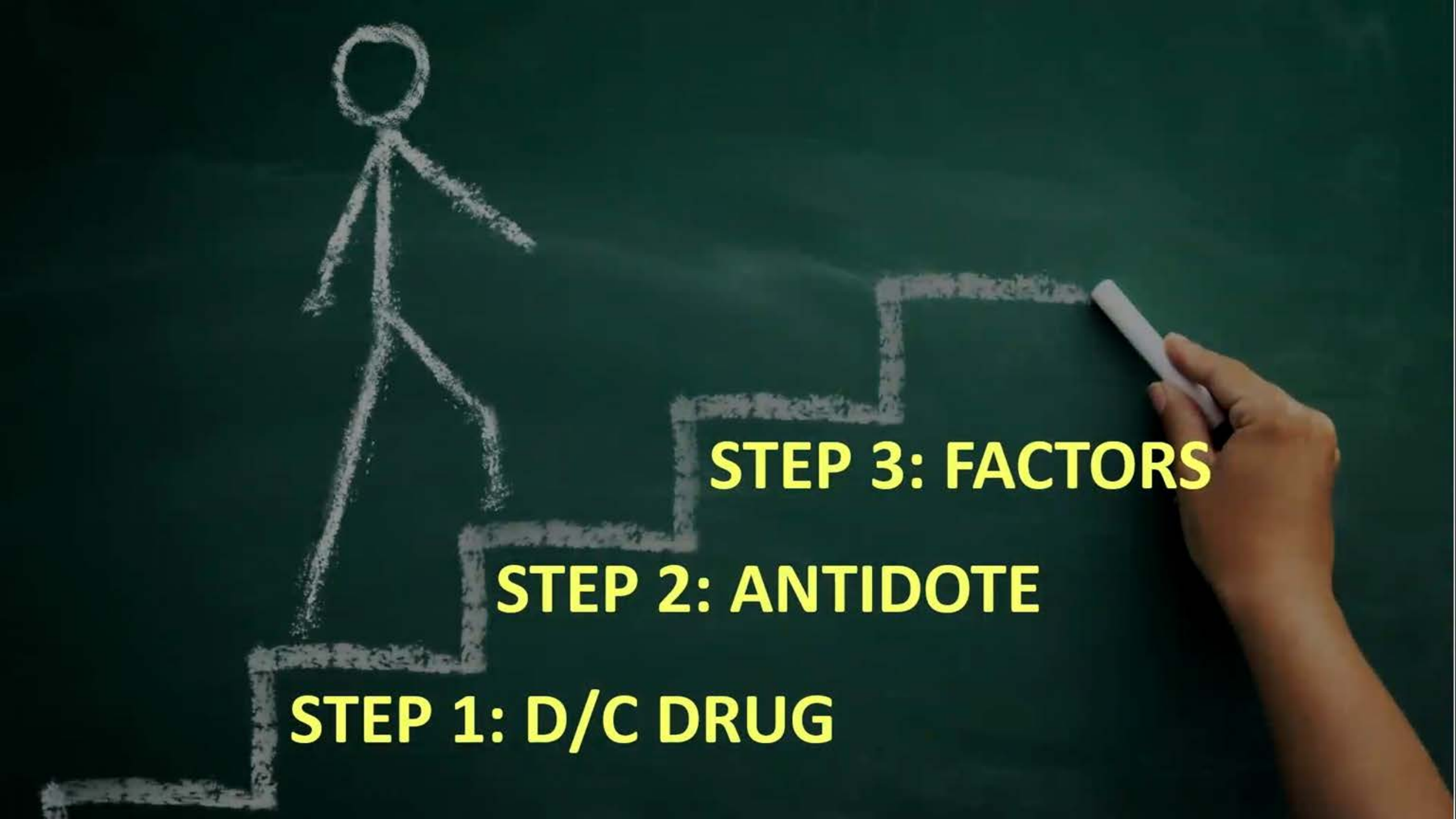
Vitamin K onset 6-8 hr

Vit K IV

5-10 mg

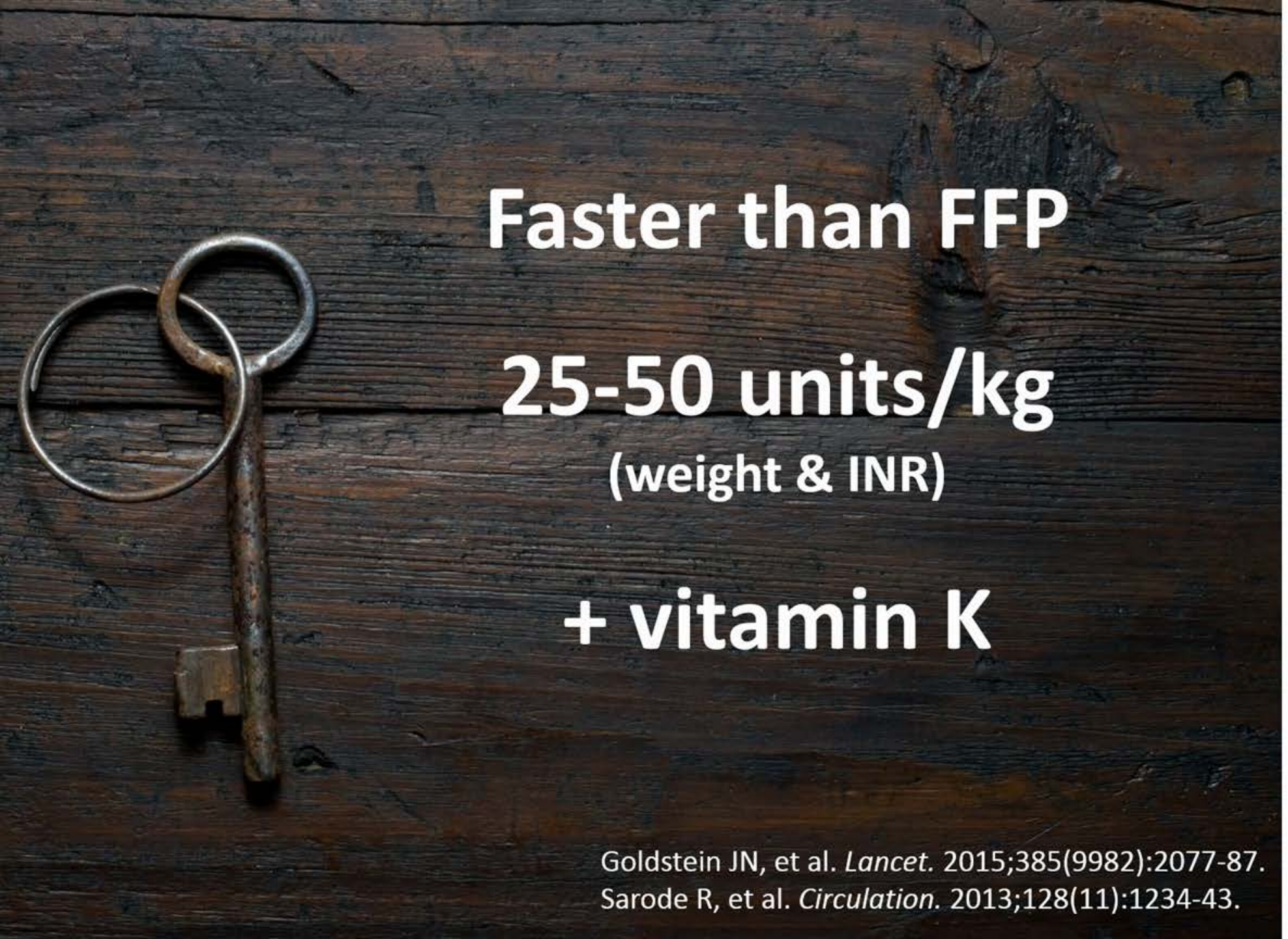
Dilute

Hemphill JC 3rd, et al. *Stroke.* 2015;46(7):2032-60.
Holbrook A, et al. *Chest.* 2012;141(2 Suppl);e152S-e184S.


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

Risks INR ~1.6 Time

Pandey S



Goldstein JN, et al. *Lancet.* 2015;385(9982):2077-87.
Sarode R, et al. *Circulation.* 2013;128(11):1234-43.

4-factor PCC

4-factor PCC vs. FFP in ICH

INR ≤ 1.2 (67% vs. 9%)

Hematoma (10 mL vs. 24 mL)

Steiner T, et al. *Lancet Neurol.* 2016;15(6):566-73.


Fixed 4-factor PCC dosing?
1,000/1,500/2,000 units
25 or 30 units/kg
Not validated

Intubated

4-factor PCC + Levetiracetam

Key Takeaways

- For dabigatran-associated bleeding, idarucizumab and aPCC have the best supporting data
- For oral factor Xa inhibitor-associated bleeding, aPCC or 4-factor PCC have the best supporting data
- For warfarin-associated bleeding, IV vitamin K + 4-factor PCC provide the most rapid reversal of laboratory parameters and bleeding

Questions?

ashp Certification Resources

ashp MIDYEAR 2017
Clinical Meeting & Exhibition