Emergent Reversal of Antiplatelets and Anticoagulants

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August 2nd, 2022

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OBJECTIVES

- Understand why reversal of antiplatelets and anticoagulants is a growing concern in trauma
- Identify the strengths and limitations of available data for reversal agents
- Develop a management strategy for anticoagulant reversal

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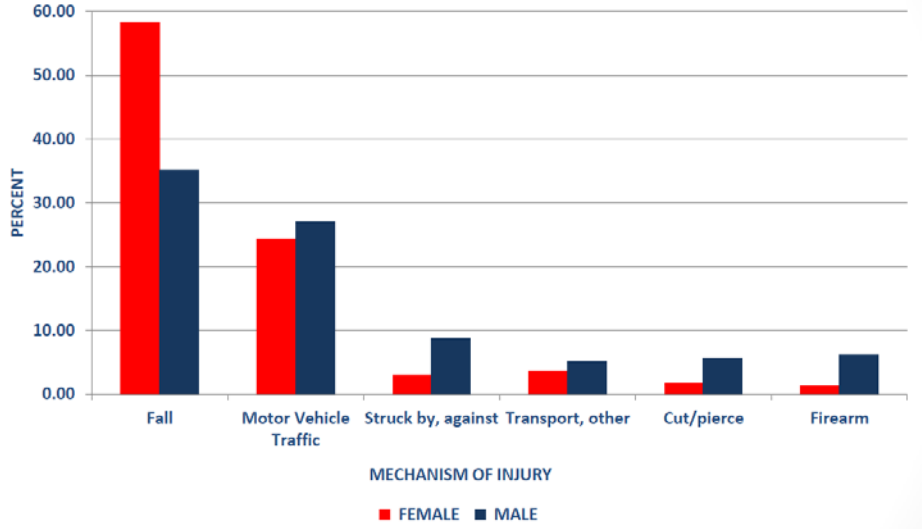
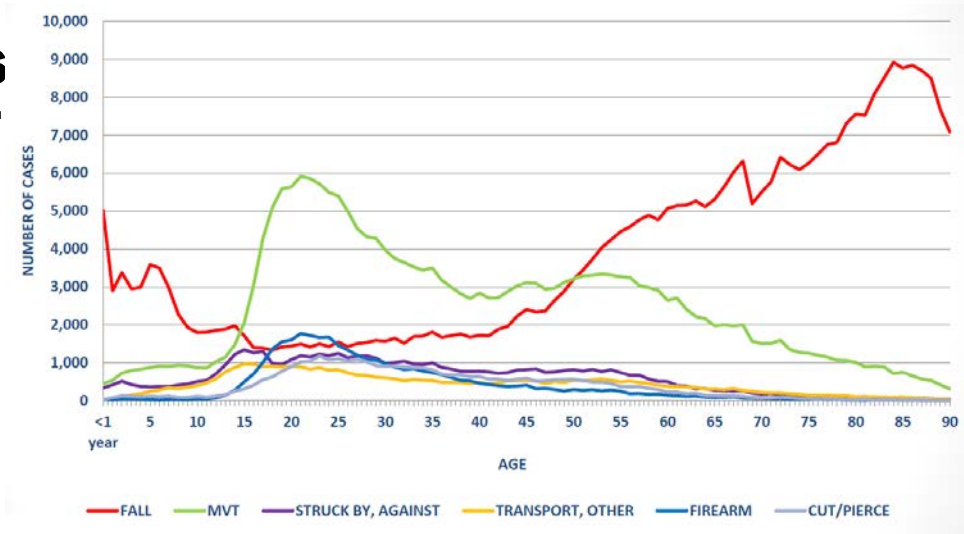
THE FACE OF TRAUMA IS CHANGING

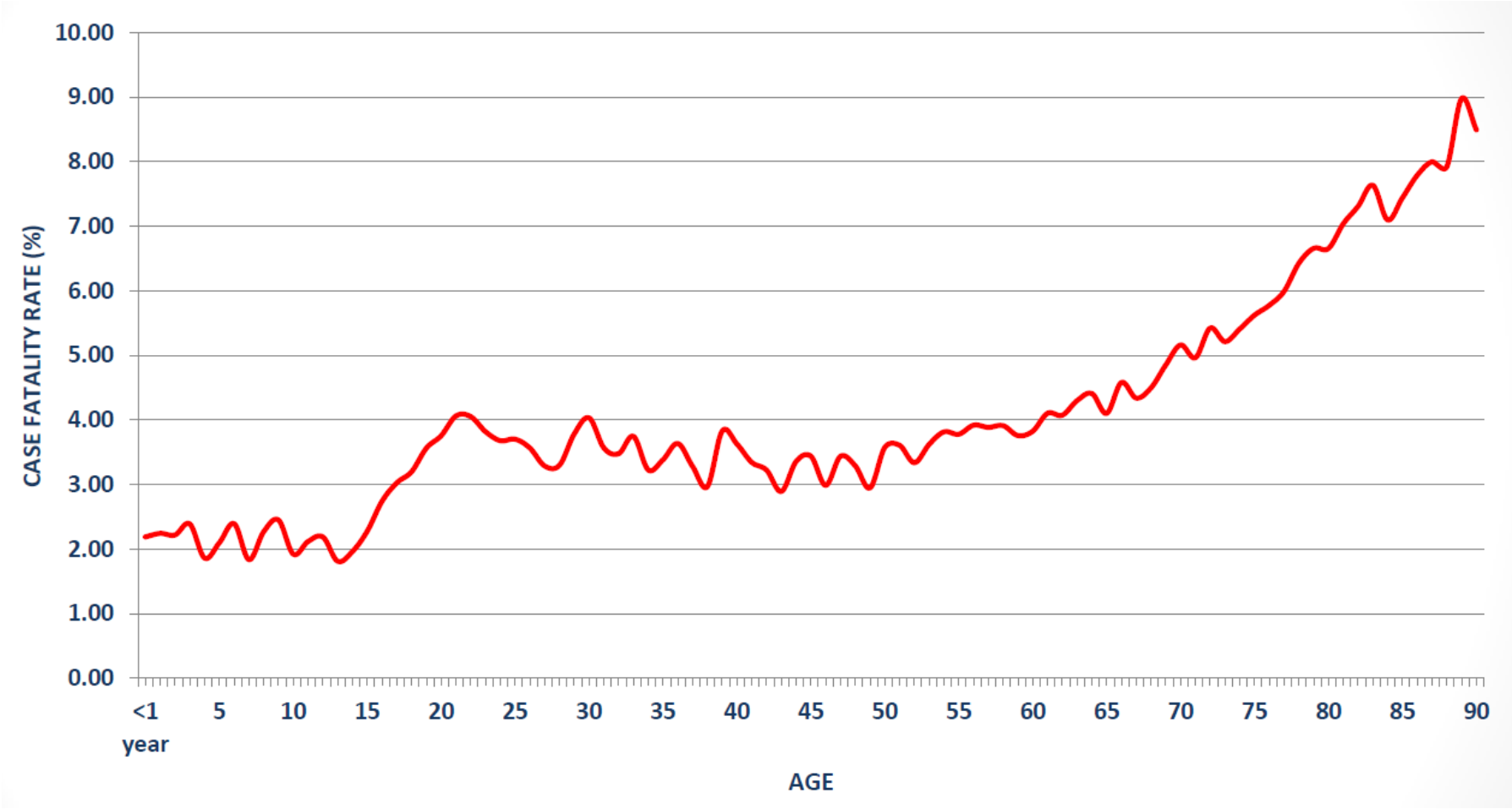
- The average age of trauma is increasing
- Older patients have more comorbities and more medications
- Medication evaluation is recommended as part of the primary survey for geriatric trauma
  - Antiplatelets
  - Anticoagulants





Adams AD, Holcomb JB. Curr Opin Crit Care 2015
ACS TQIP Geriatric Management Guidelines
National Trauma Data Bank 2016 Annual Report (American College of Surgeons)

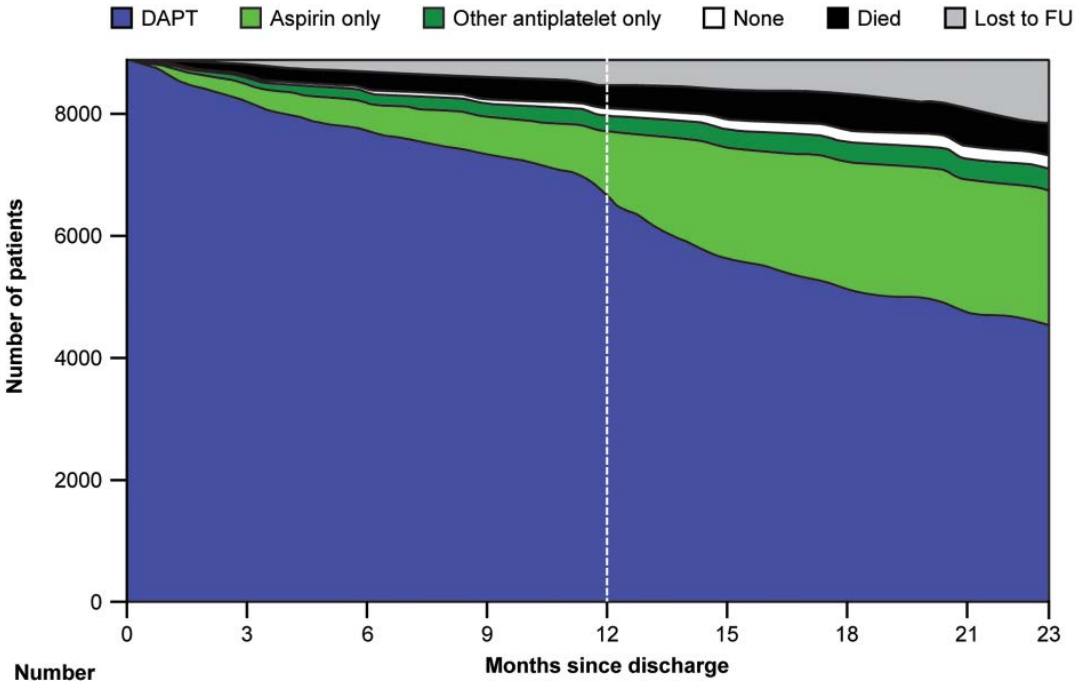
MORTALITY INCREASES WITH AGE



National Trauma Data Bank 2016 Annual Report (American College of Surgeons)

ANTIPLATELET PRESCRIBING

- **Aspirin remains the drug of choice for primary prevention of coronary heart disease events in patients with risk factors**
- **2016 AHA updated recommendations for dual antiplatelet therapy (DAPT) duration in CAD**



"Should be given" in most clinical settings for at least 6–12 months
"May be reasonable" to continue DAPT beyond the initial 6-12 months

"Necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk"

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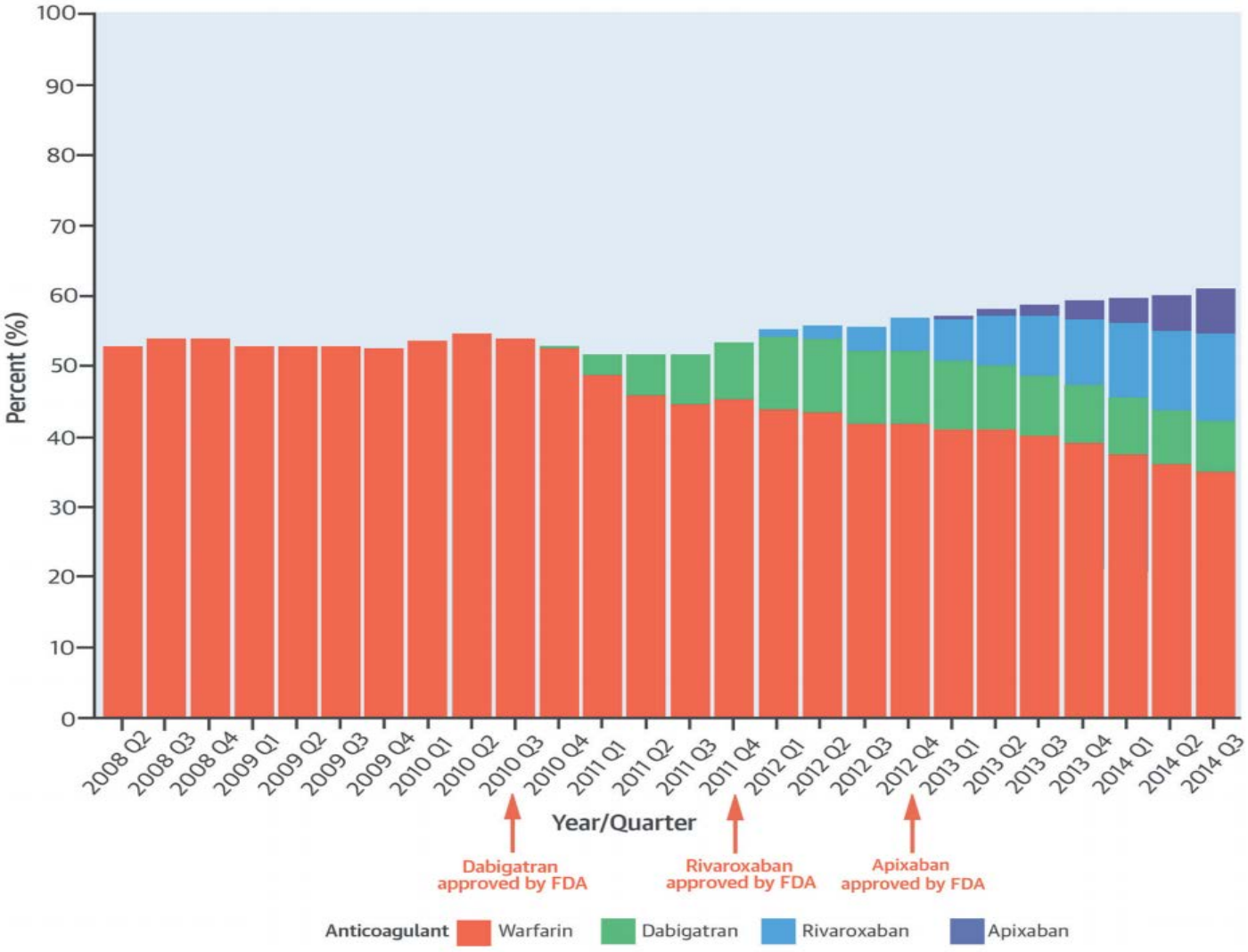
Levine, et al. JACC 2016
Bueno, et al. Heart 2017

ANTICOAGULANT PRESCRIBING PATTERNS



Marzek LN, et al. J Am Coll Cardiol 2017

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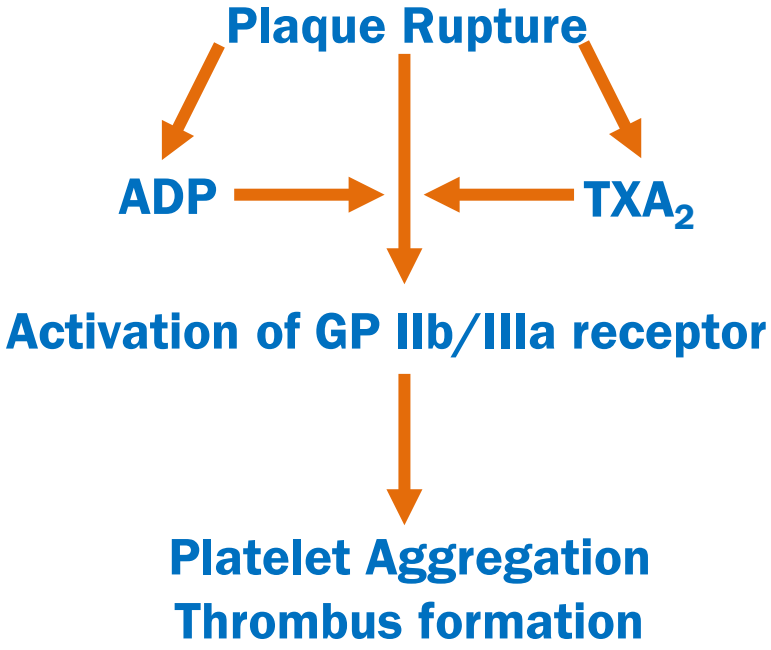

ANTIPLATELET AGENTS

Aspirin

$P2Y_{12}$ Inhibitors ***clopidogrel, ticagrelor, prasugrel***

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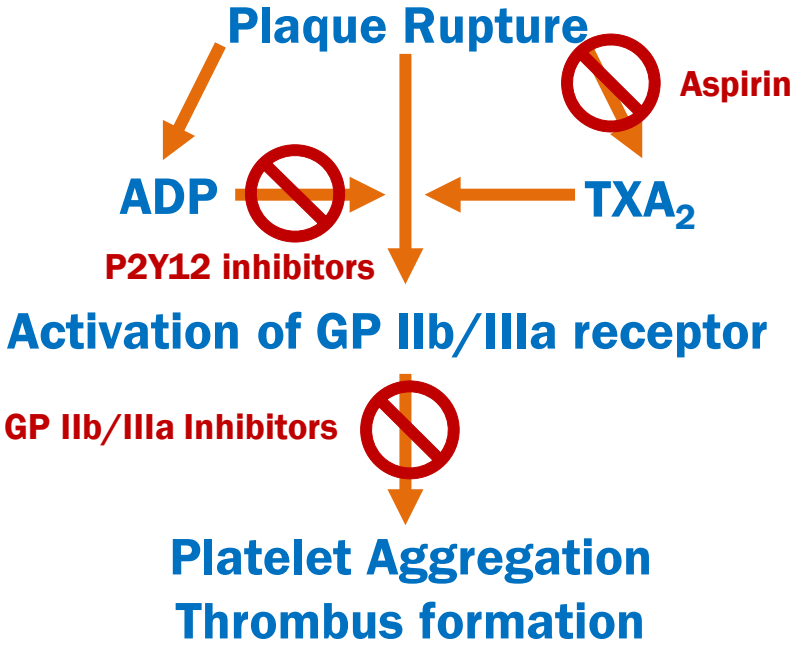

ANTIPLATELET AGENTS

Aspirin

$P2Y_{12}$ Inhibitors ***clopidogrel, ticagrelor, prasugrel***

MEASURING ANTIPLATELET EFFECT

- **Platelet count**
- **Maximum amplitude**

- **TEG-PM or ROTEM-PM (Platelet Mapping)**
- **VerifyNow – assays for aspirin or $P2Y_{12}$**

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Bachelani AM, et al. Surgery 2011
Lam, et al. Cureus 2018

ANTIPLATELET REVERSAL

- **Platelet Transfusion**
  - **May be over exposing patients to platelets**
  - **Significantly decreased platelet inhibition from ASA (76% to 52.7%, p<0.01), but not clopidogrel (64.5% to 48.4%, p=0.07)**
  - **Dose-response relationship**
  - **Risks vs. benefits of platelet administration**
  - **Not associated with change in clinical outcomes (CT score, length of stay, mortality)**

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Holzmacher JL, et al. Brain Inj 2018
Bachelani AM, et al. Surgery 2011
Choi, et al. Neurosurgery 2017

ANTIPLATELET REVERSAL

- Platelet Transfusion
  - May be over exposing patients to platelets
  - Significantly decreased platelet inhibition from
  - Not associated with change in clinical outcomes (CT score, length of stay, mortality)

Neurocritical Care/SCCM Guidelines –
"Suggest against platelet transfusion who will not undergo a neurosurgical intervention"
"Suggest platelet transfusion in those that will"
"Recommend platelet function testing"

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Frontera, et al. Crit Care Med 2016

ANTIPLATELET REVERSAL

- Desmopressin (DDAVP)
  - Promotes platelet adhesion by increasing von Willebrand Factor
  - Small, retrospective studies have shown improved platelet aggregation
  - Mixed results on effect on hemorrhage progression
  - Dose range 0.3 – 0.4 mcg/kg
  - Often given in combination with platelet transfusions

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Naidech, et al. Stroke 2014
Kapapa, et al. Neurol Res International 2014
Kim, et al. Journal of Neurotrauma 2015

ANTIPLATELET REVERSAL

- Desmopressin (DDAVP)
  - Promotes platelet adhesion by increasing von Willebrand Factor

Neurocritical Care/SCCM Guidelines –
"Suggest consideration of a single dose of desmopressin in ICH (0.4 µg/kg IV)"
"Can be used in addition to platelet transfusion in patient that will undergo a neurosurgical procedure"

transfusions

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Naidech, et al. Stroke 2014
Kapapa, et al. Neurol Res International 2014
Kim, et al. Journal of Neurotrauma 2015

ANTIPLATELET REVERSAL

- 200 patients with TBI and evidence of platelet dysfunction using VerifyNow
- 74 received desmopressin and 54 received platelets; compared to no intervention
  - Rates of ICH progression were similar
  - Lower discharge GCS and GOS

- Desmopressin and platelet transfusions were not protective against poor outcomes in logistic regression analysis

Glass, et al. Am J Surg 2022

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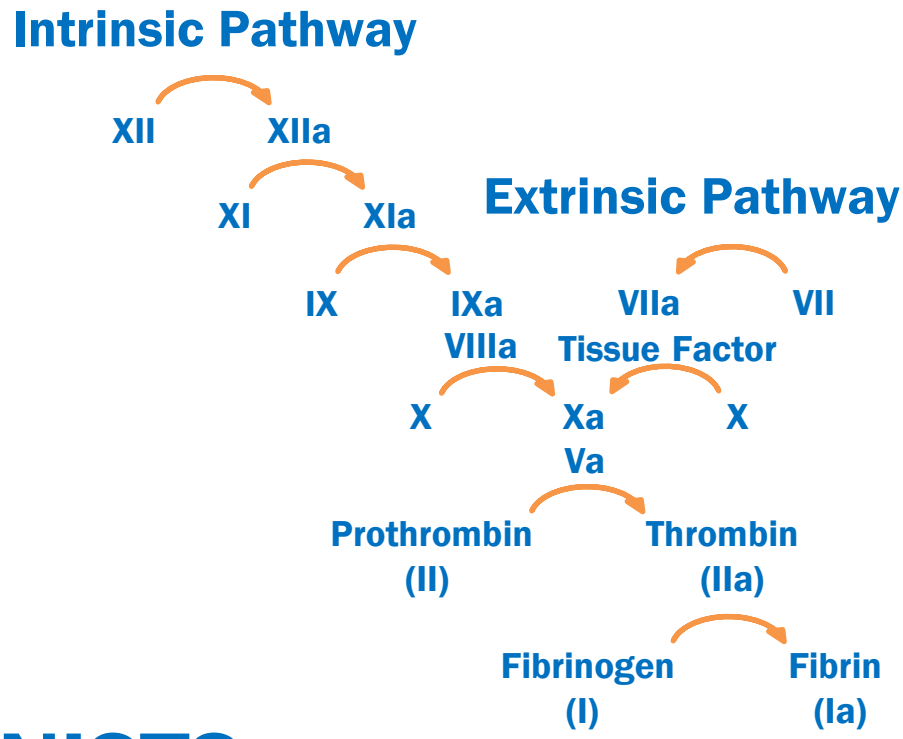

VITAMIN K ANTAGONISTS

Warfarin

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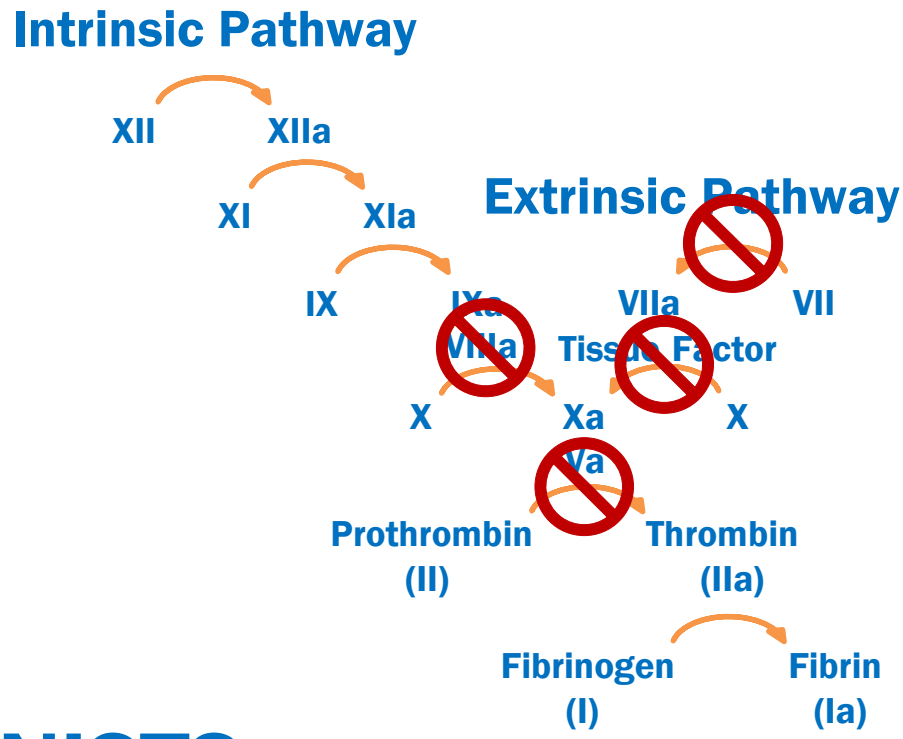

VITAMIN K ANTAGONISTS

Warfarin

WARFARIN MONITORING & REVERSAL

- **Warfarin monitoring – INR**

- **Vitamin K**
- **FFP**
- **Prothrombin complex concentrate**
- **Recombinant Factor VIIa**

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Tomaselli, et al. JACC 2020

WARFARIN MONITORING & REVERSAL

- Warfarin monitoring – INR
- Vitamin K

ACC/AHA Guidelines –
"Administer weight/INR based 4F-PCC OR fixed-dose (1000 units for non-ICH and 1500 units for ICH)"
"If 4F-PCC not available, use FFP 10-15 mL/kg"

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Tomaselli, et al. JACC 2020

PROTHROMBIN COMPLEX CONCENTRATE

- 3 vs. 4 Factor
- Activated (FEIBA) vs. non-activated (Kcentra)
- Why vitamin K is still necessary
- Fixed dose vs. weight/INR based

FDA DOSING RECOMMENDATIONS

INR	Weight-based dose	Max total dose
2 to < 4	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
> 6	50 units/kg	5000 units

FIXED DOSE PCC

- Strategy to improve time to administration
- Later recognized as effective and cost savings
- Doses range from 1000-2000 units with ability to re-dose if needed
- Most studies show acceptable reversal
  - INR goal < 1.5: ~65-75%
  - INR goal < 2: > 90%

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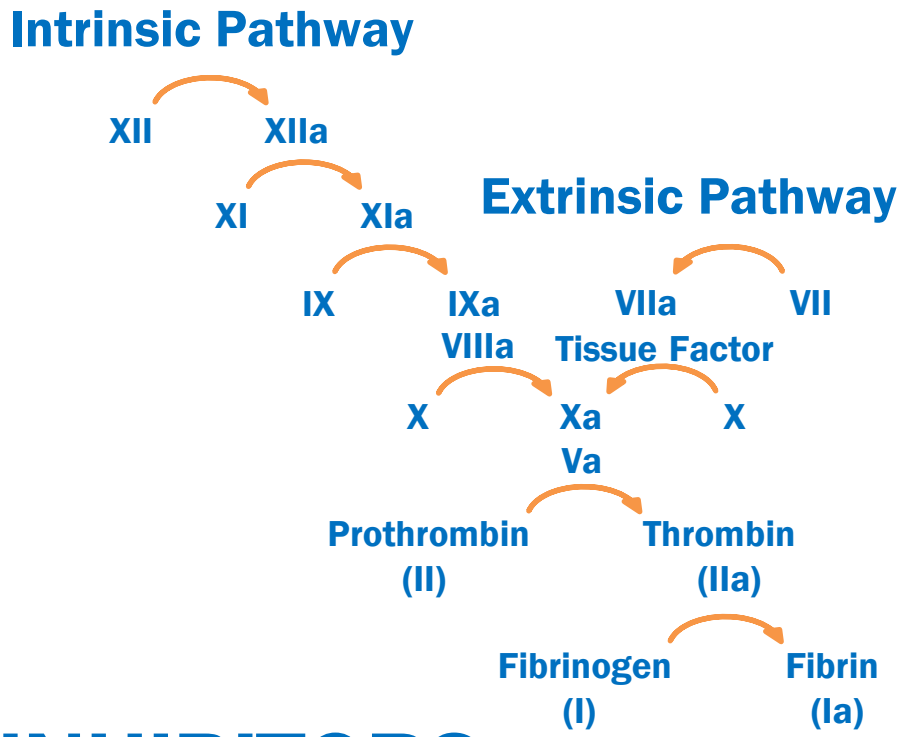

DIRECT THROMBIN INHIBITORS

Dabigatran

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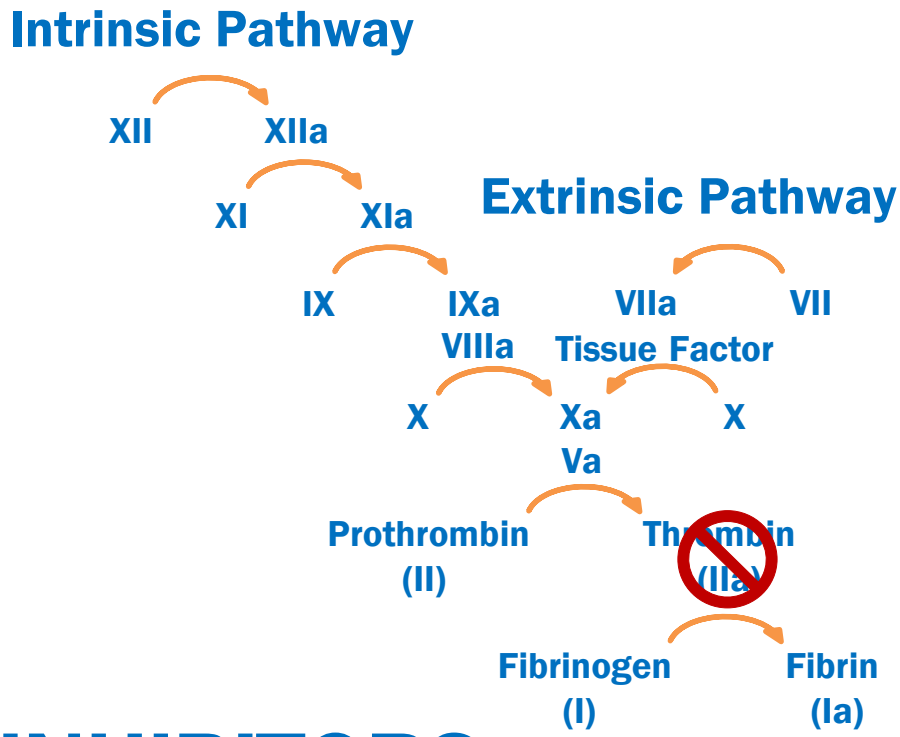

DIRECT THROMBIN INHIBITORS

Dabigatran

DTI MONITORING

- **Qualitative Tests**
  - **Thrombin time (TT)***
  - **aPTT**

- **Quantitative Tests**
  - **Dilute thrombin time (dTT)**
  - **Ecarin clotting time (ECT)**

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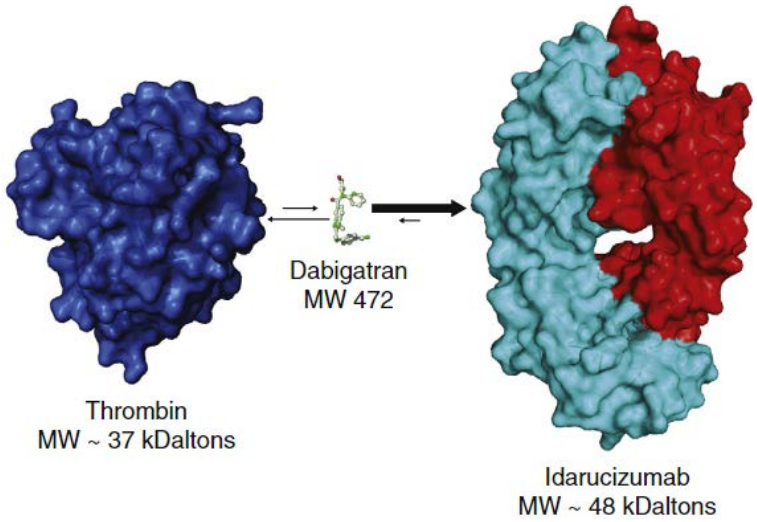
Tomaselli, et al. JACC 2020

DTI REVERSAL

- **Idarucizumab (Praxbind®)**
  - **Monoclonal antibody specific for dabigatran**
  - **350x affinity for dabigatran than thrombin**

- **PCC or aPCC**



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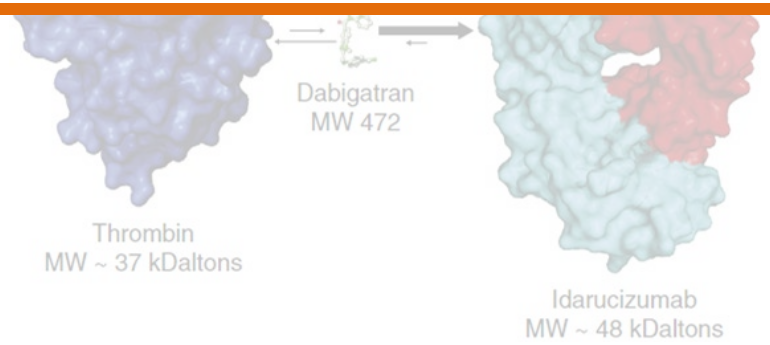
Reilly, et al. Am J Med 2016
Tomaselli, et al. JACC 2020

DTI REVERSAL

- Idarucizumab (Praxbind®)
  - Monoclonal antibody specific for dabigatran

ASH AC Forum Guidelines –
"Suggest idarucizumab"
"If idarucizumab not available, suggest aPCC"



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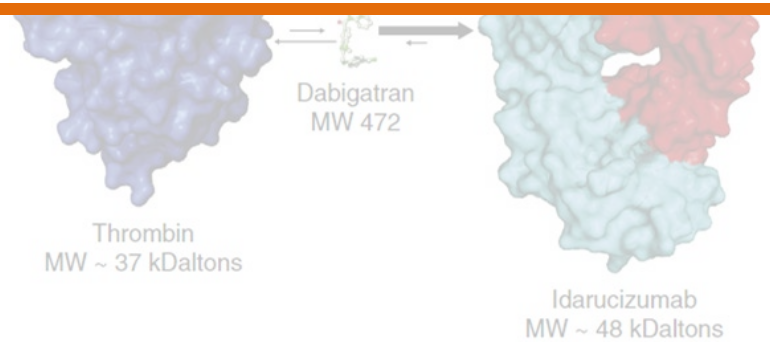
Reilly, et al. Am J Med 2016
Cucker, et al. AJH 2019
Tomaselli, et al. JACC 2020

DTI REVERSAL

- Idarucizumab (Praxbind®)
  - Monoclonal antibody specific for dabigatran

ACC/AHA Guidelines –
"Administer 5g idarucizumab"
"If idarucizumab not available, use PCC or aPCC"



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Reilly, et al. Am J Med 2016
Cucker, et al. AJH 2019
Tomaselli, et al. JACC 2020

REVERSE-AD

- 503 patients
  - 301 uncontrolled bleeding, 202 urgent procedure
  - 45.5% GI bleed, 32.6% intracranial hemorrhage
- Median time to bleeding cessation 2.5 hours
- Median time to initiation of procedure 1.6 hours
- Thrombotic events 6.3% in bleeding group, 7.4% in urgent procedure group
- Overall mortality 18.8%

- No comparator group

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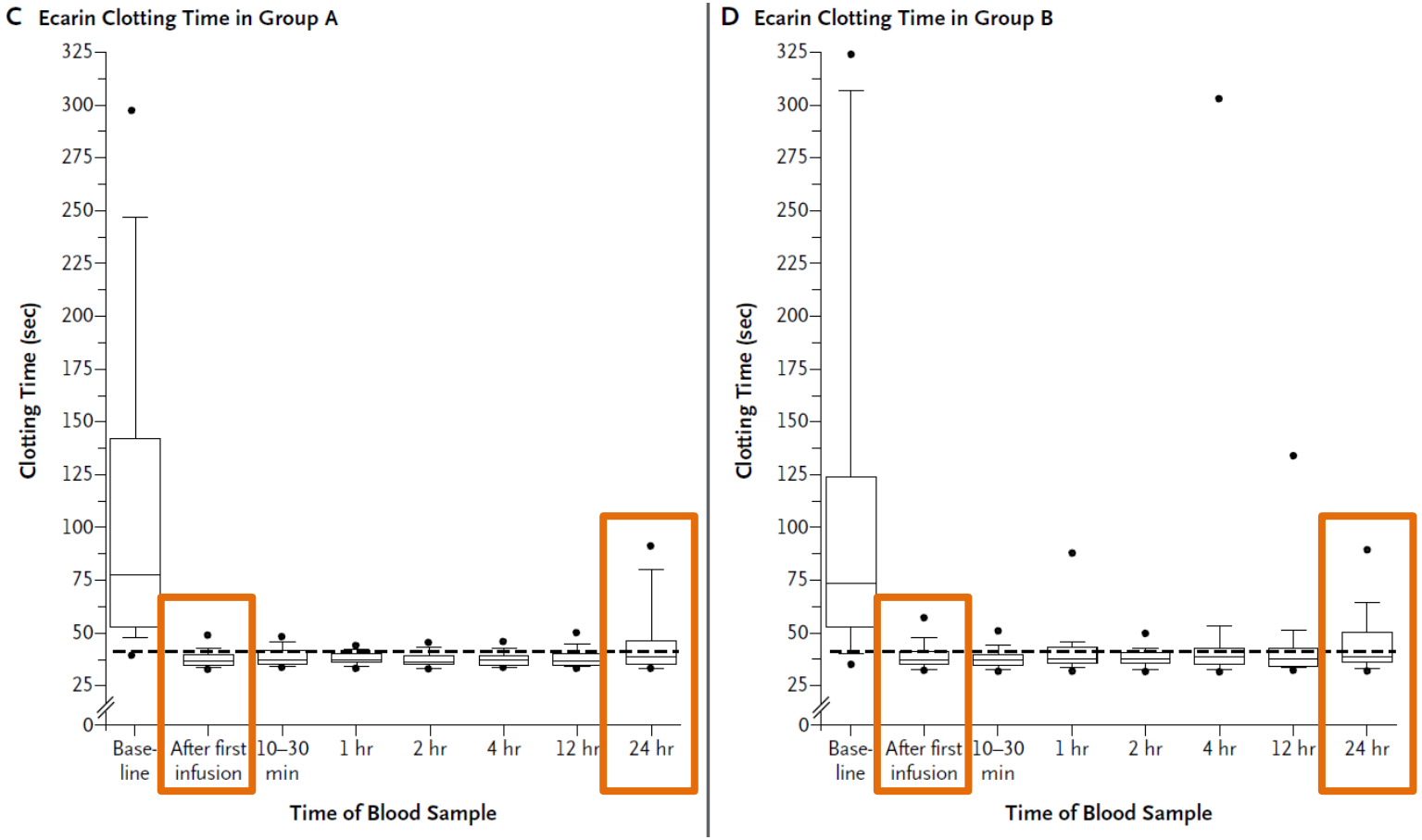
Pollack, et al. N Engl J Med 2017

REVERSE-AD



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Pollack, et al. N Engl J Med 2017

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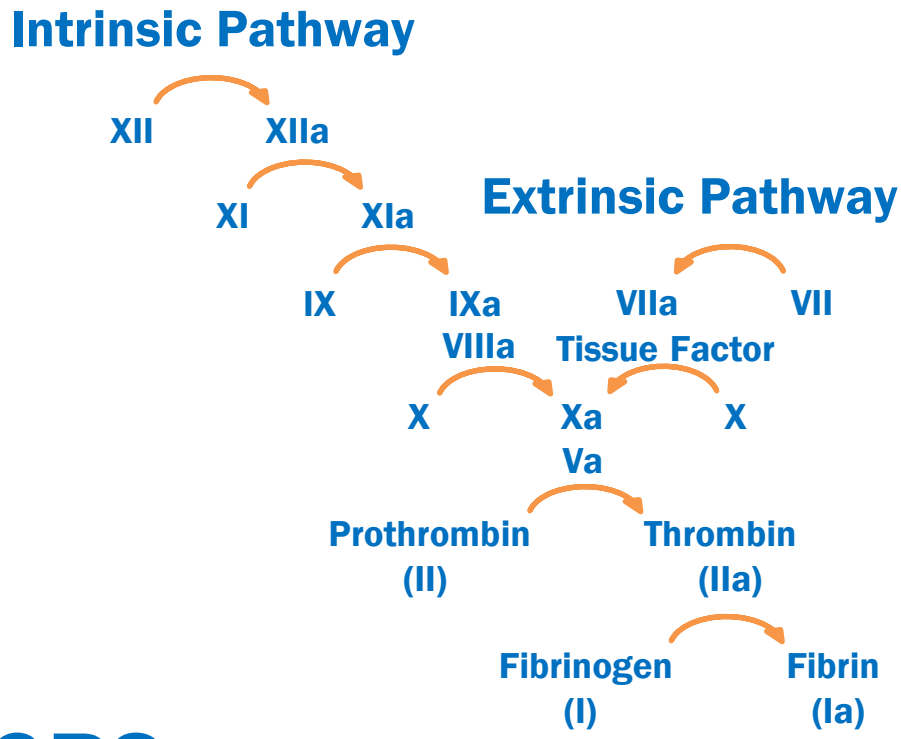

FACTOR Xa INHIBITORS

Rivaroxaban, Apixiban, Edoxaban

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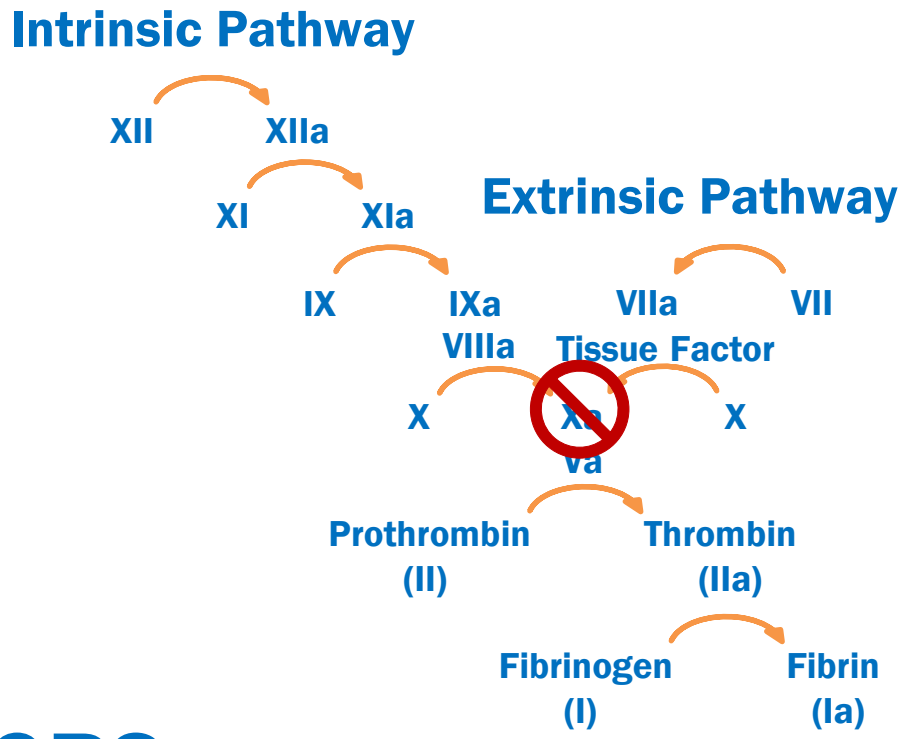

FACTOR Xa INHIBITORS

Rivaroxaban, Apixiban, Edoxaban

Xa INHIBITOR MONITORING

- **Qualitative Tests**
  - **INR**
  - **UFH or LMWH Anti-FXa***
- **Quantitative Tests**
  - **Anti-FXa calibrated to specific agent**

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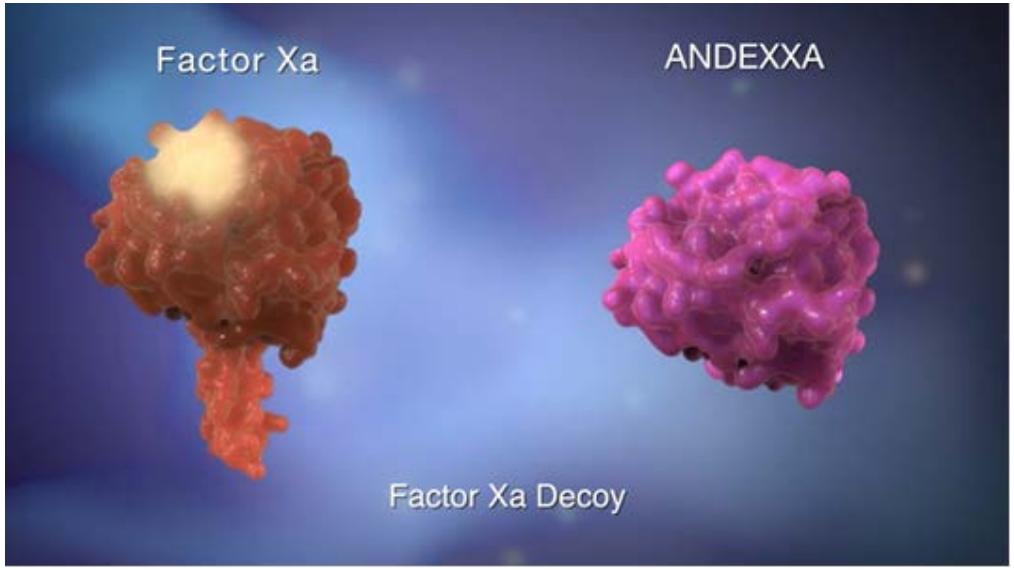
Tomaselli, et al. JACC 2020

Xa INHIBITOR REVERSAL

- FFP
- PCC



- Andexanet alfa (Andexxa®)
  - Decoy for Xa inhibitors
  - Irreversibly binding

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www.andexxa.com, accessed 5/28/19

ANEXXA-4

- Prospective, open-label, single-group
- Multicenter (63 hospitals in North America and Europe)
- 352 patients with acute major bleeding on Xa inhibitors within 18 hours of presentation
  - 64% ICH, 26% GIB
- Excellent hemostasis achieved in 82%
- Thrombotic events 10%, mortality 14%

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Connolly, et al. N Engl J Med 2019

ANEXXA-4

- Prospective, open-label, single-group
- Multicenter (63 hospitals in North America and Europe)
- Excellent hemostasis achieved in 82%
- Thrombotic events 10%, mortality 14%

ASH AC Forum Guidelines –
"We suggest treatment with andexanet alfa. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units"

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Connolly, et al. N Engl J Med 2019
Cucker, et al. AJH 2019

ANEXXA-4

- Prospective, open-label, single-group
- Multicenter (63 hospitals in North America and Europe)
-
- Excellent hemostasis achieved in 82%
- Thrombotic events 10%, mortality 14%

ACC/AHA Guidelines –
"Administer andexanet alfa
If andexanet alfa is not available,
administer PCC or aPCC"

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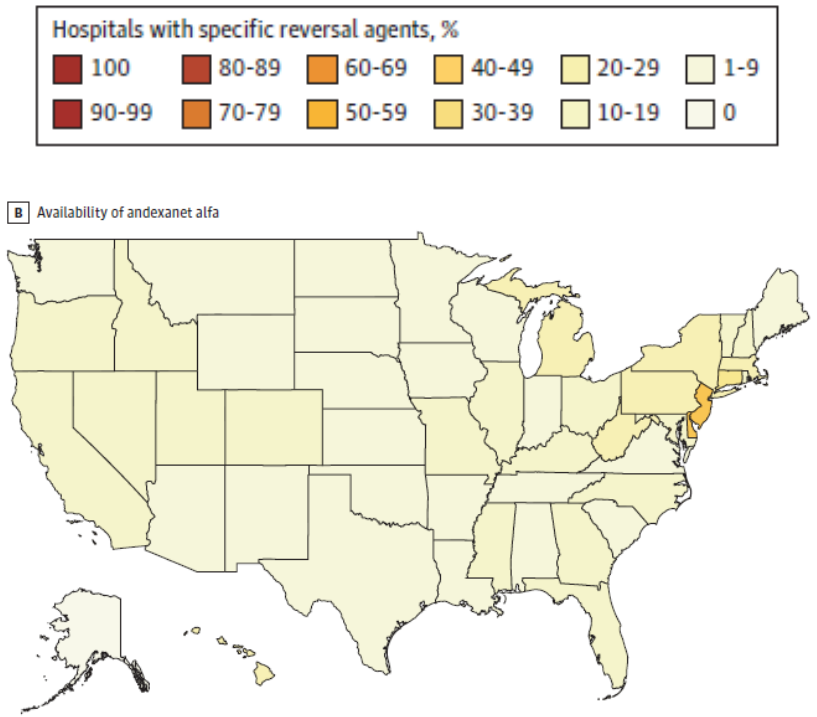
Connolly, et al. N Engl J Med 2019
Cucker, et al. AJH 2019
Tomaselli, et al. JACC 2020

WHY DOESN'T MY HOSPITAL HAVE ANDEXANET ALFA?

Andexanet alfa available	
Yes	No
499 (11.7)	3777 (88.3)
459 (15.6)	2491 (84.4)
40 (3.0)	1286 (97.0)
348 (9.3)	3400 (90.7)
151 (28.6)	377 (71.4)
79 (36.4)	138 (63.6)
72 (23.2)	239 (76.8)



Kanjee, et al. JAMA Network Open 2021

WHY DOESN'T MY HOSPITAL HAVE ANDEXANET ALFA?

- Product availability and cost
- Criticisms of the trial
- Viable alternative = 4 Factor PCC
  - Meta-analysis (n=340)
    - 69-77% achieved successful bleeding management
    - Crude mortality 16%
    - Thromboembolism 4%
  - On-going trial (estimated completion 2024)
    - Andexanet alfa vs. usual care

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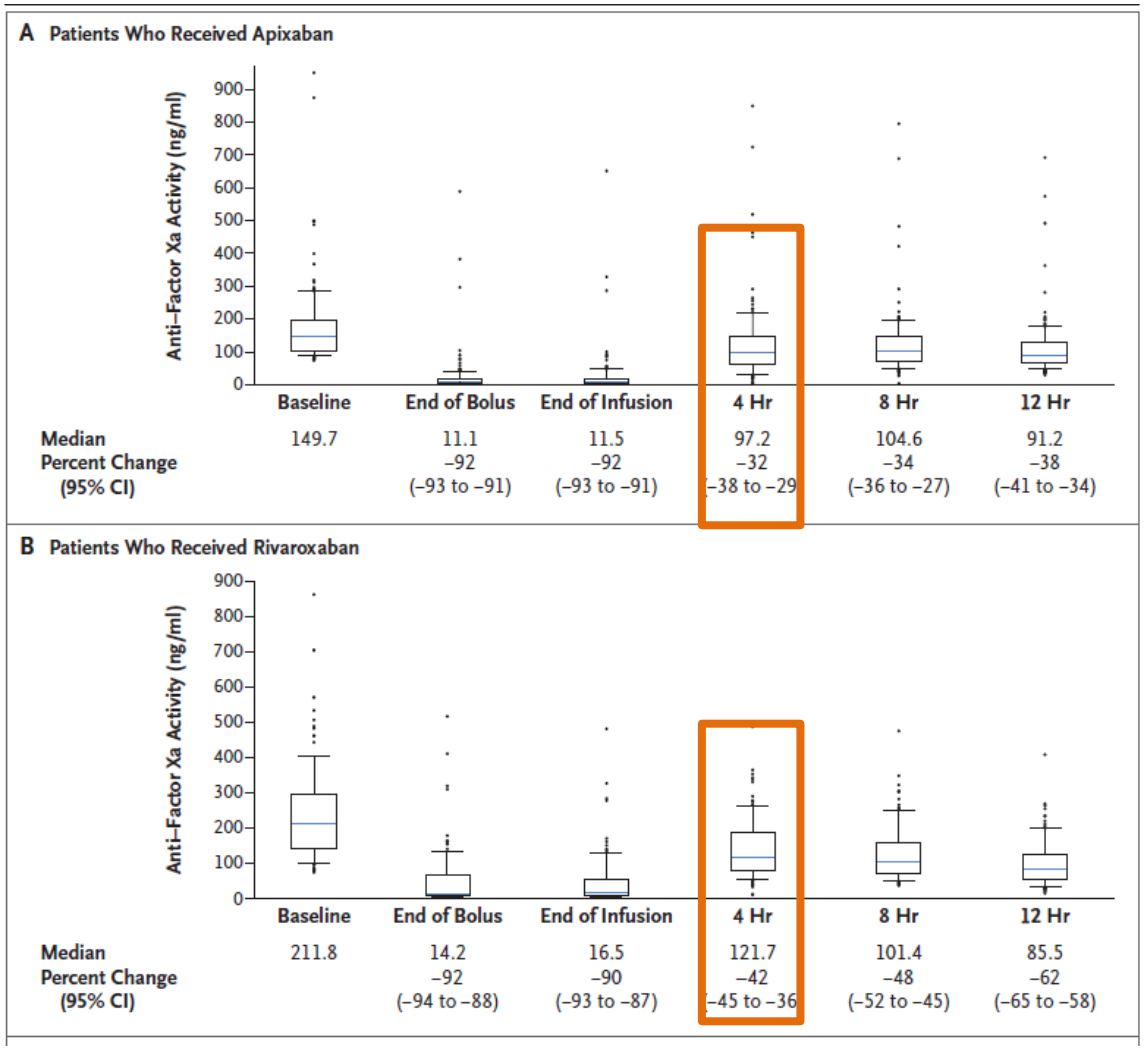
Smith, et al. Am J Hematol 2019
Piran, et al. Blood Advances 2019

ANDEXANET ALFA DURATION OF EFFECT



Connolly, et al. N Engl J Med 2019

A WORD OF CAUTION…

- **Little is known about the safety of administering andexanet alfa and PCC**

- **Case series have been published (n=28)**
  - **10 patients (36%) had a thromboembolic event**
  - **Venous and arterial events are reported**

Liu, et al. Am J Health-Syst Pharm 2022
Garber Bradshaw, et al. J Thromb Thrombolysis 2022

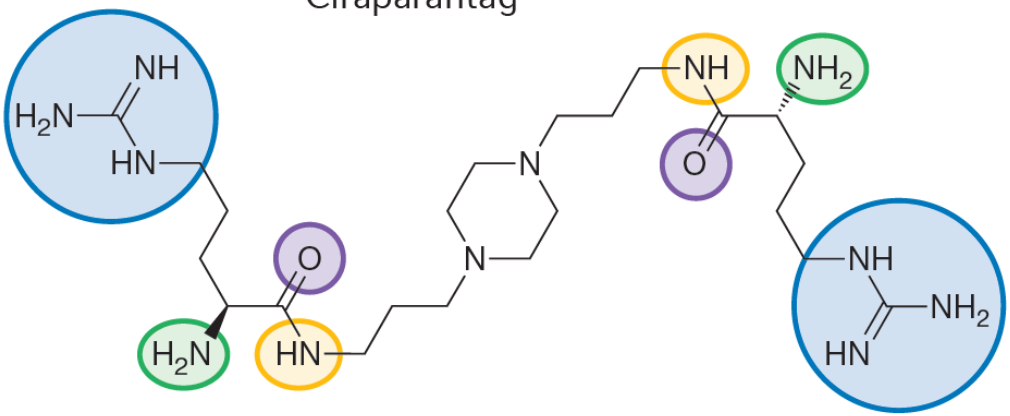
THE NEXT BIG THING?

Ciraparantag (originally PER977)

- **Small, synthetic, water-soluble**
- **Able to bind heparins, Xa inhibitors, and oral DTIs**
- **Currently planning for Phase III studies**

Drug	Binding sites
Apixaban	● ●
Dabigatran	● ● ●
Edoxaban	● ●
Fondaparinux	● ● ●
Rivaroxaban	● ● ●
UFH or LMWH	● ● ●

Ciraparantag



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Levy, et al. Nature Reviews Cardiology 2018

CONCLUSIONS

- Geriatric trauma is increasing in incidence and therefore the need for anticoagulant reversal is as well
- Anticoagulant reversal is a rapidly evolving area with new drug development
- Initial studies of new reversal agents have significant limitations and high drug cost
- Pharmacologic reversal should be guided by bleeding severity

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QUESTIONS?

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