March 30 – April 2, 2016 ANAHEIM, CALIFORNIA

SOCIETY OF TRAUMA NURSES

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SOCIETY OF TRAUMA NURSES

Indiana University Health

Leading the Charge in Anticoagulation Reversal: Benefits, Risks, and Key Factors in Application to the Traumatically Injured Patient

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IU Health Methodist Hospital

March 31st, 2016

The speaker has no actual or potential conflicts of interest with regards to this presentation

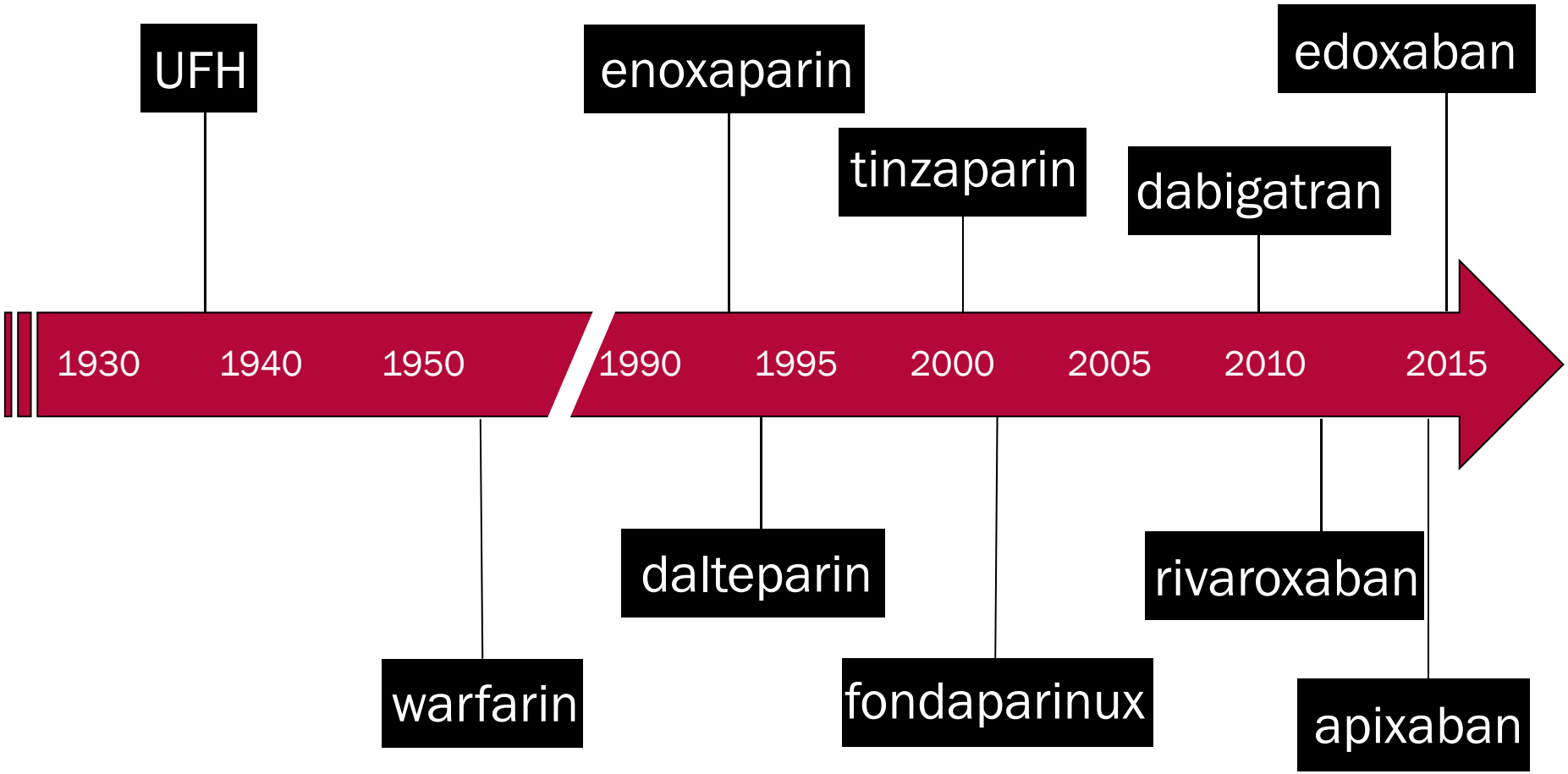
Successful Completion

- To successfully complete this course, participants must attend the entire event and complete/submit the evaluation at the end of the session.
- Society of Trauma Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Background of Evaluation

- Compare and contrast the new oral anticoagulant medications, including apixaban, dabigatran, edoxaban, and rivaroxaban.
- Evaluate therapeutic options for traumatically injured patients who require emergent reversal of a new oral anticoagulant.
- Review the budgetary impact of the various emergent reversal options for new oral anticoagulants.

Anticoagulation Timeline



New Oral Anticoagulants…..

Steps in Hemostasis

Primary Stage

- Injured blood vessel causes vasoconstriction, exposure of tissue factor on the endothelium
- Platelets adhere to injured endothelium → promote coagulation by exposing procoagulant binding site on membrane surface

Secondary Stage

- Traditional vs cell based model of coagulation cascade → fibrin + platelets form hemostatic plug

Tertiary Stage

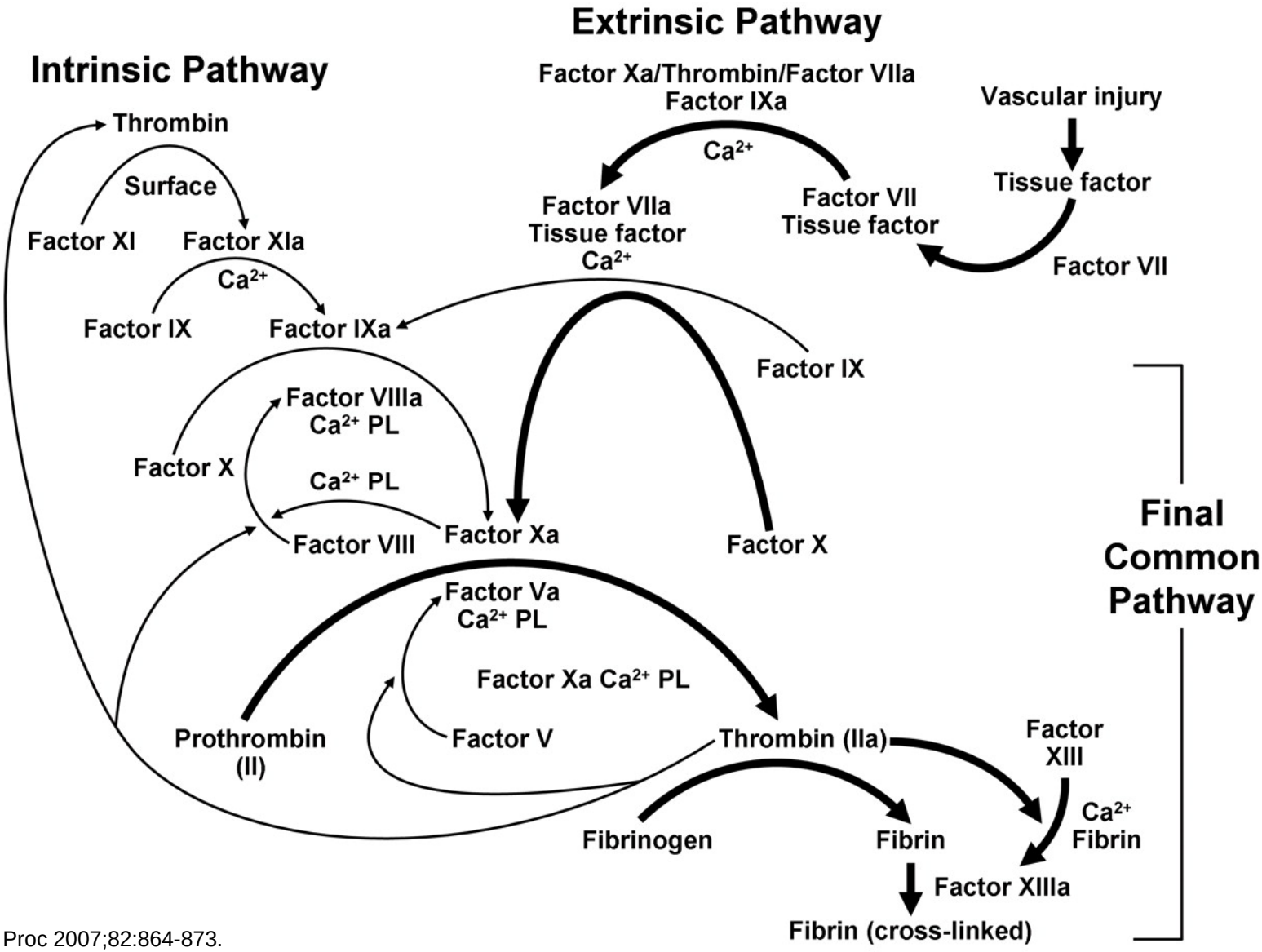
- Endogenous anticoagulants control progress of clot formation

Quaternary Stage

- Endogenous fibrinolytic proteins activated to dissolve clot and prevent expansion

Harvey RD. Hemophilias and thrombophilias. PSAP (5th ed). 17-35.

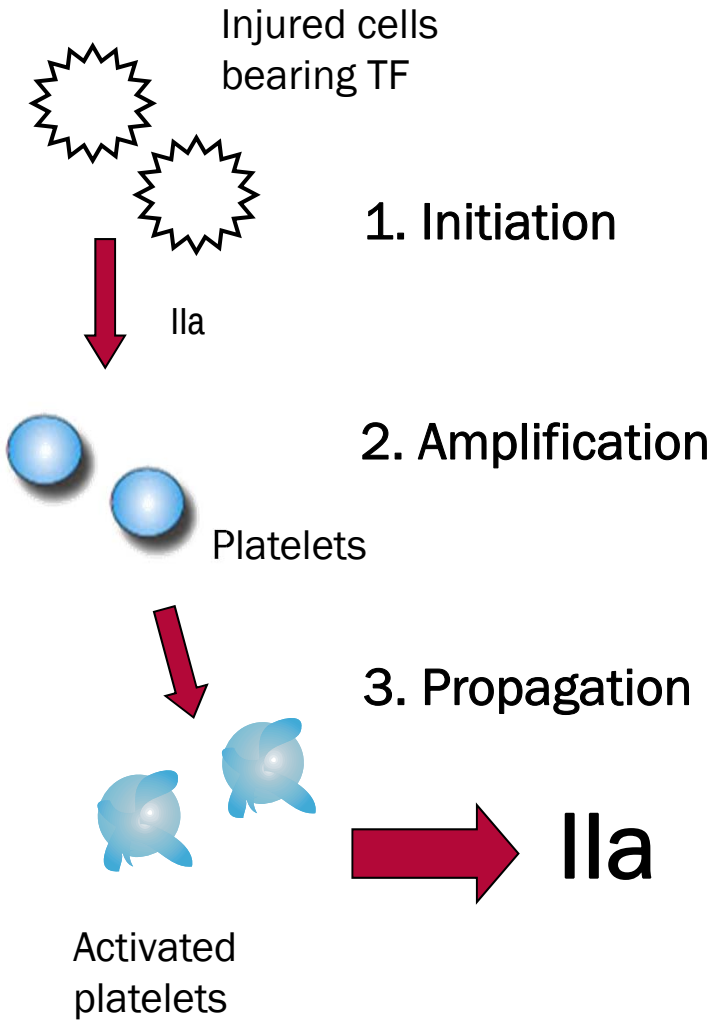
Traditional Coagulation Cascade



Kamal. Mayo Clin Proc 2007;82:864-873.

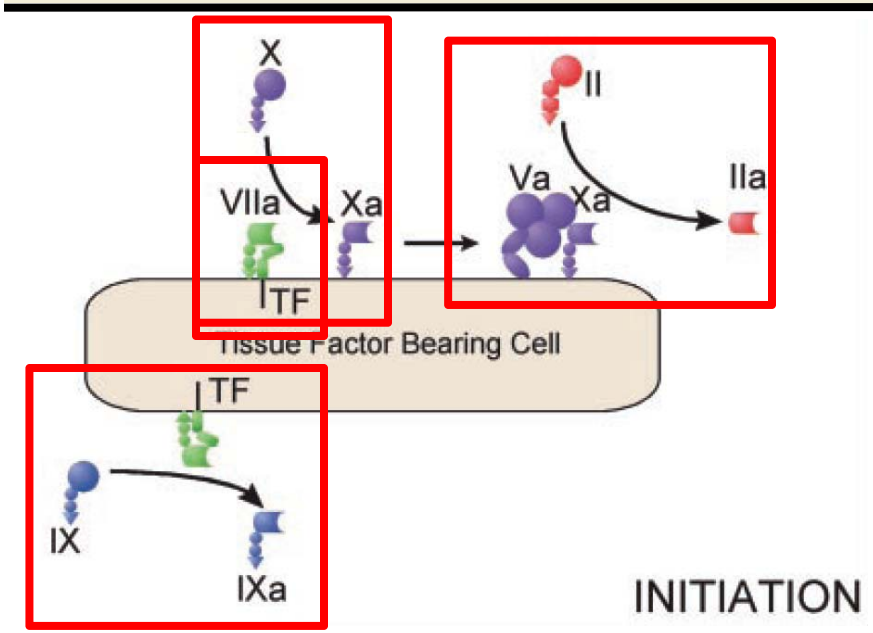
Cell Based Model for Coagulation

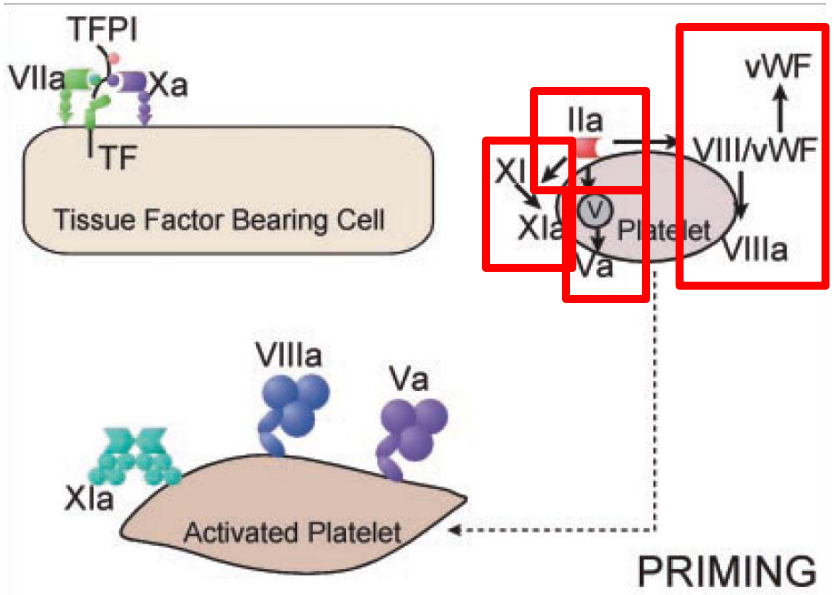
- Reflects *in vivo*
  - Occurring on cell surfaces
    - Tissue factor bearing cells
    - Platelets
  - Overlapping phases
    - Initiation (TF bearing cells)
    - Amplification (platelets)
    - Propagation (platelets)
- The coagulation cascades are still important, but are cell-based
  - **extrinsic pathway:** surface of tissue factor bearing cells
  - **intrinsic pathway:** surface of platelets

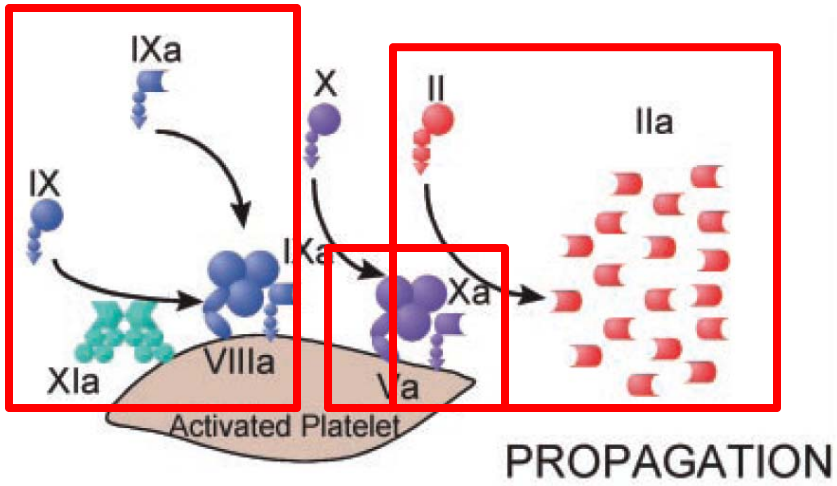


Monroe, DM. et al. *Arterioscler Thromb Vasc Biol* 2002;22:1381.
Hoffman M et al. *Thromb Haemost* 2001;85:958 –65.

Cell-Based Model





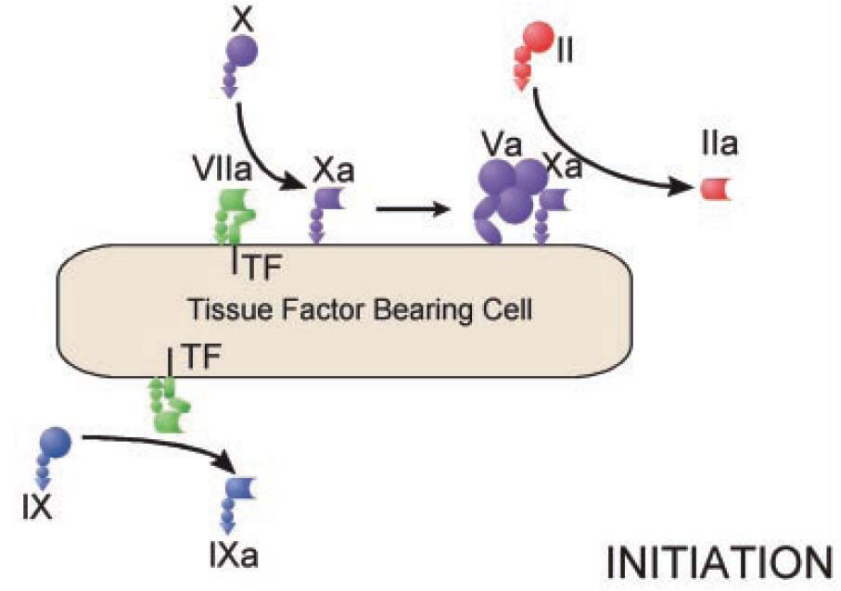


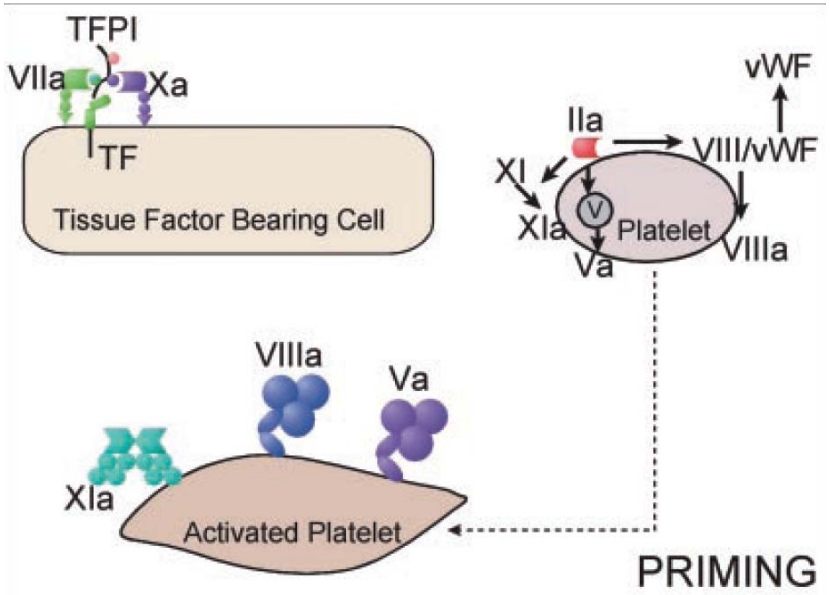
Adapted from Monroe DM. *Arterioscler Thromb Vasc Biol*. 2002;22:1381-89.

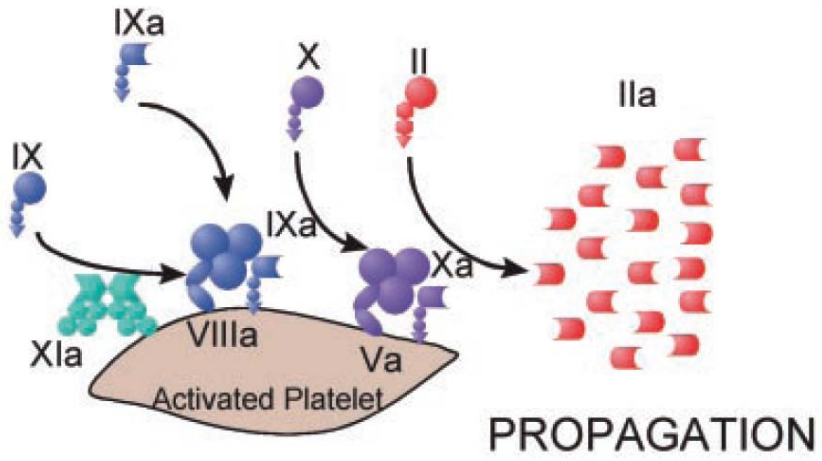
Current Antithrombotic Agents

- Unfractionated Heparin
- Low-molecular weight heparins
- Vitamin K antagonist (warfarin)
- Direct thrombin inhibitors
  - Argatroban
  - Lepirudin
  - Bivalirudin (Angiomax®)
  - Dabigatran (Pradaxa®)
- Factor Xa Inhibitor
  - Fondaparinux (Arixtra®)
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
  - Edoxaban (Savaysa®)

Dabigatran Effects

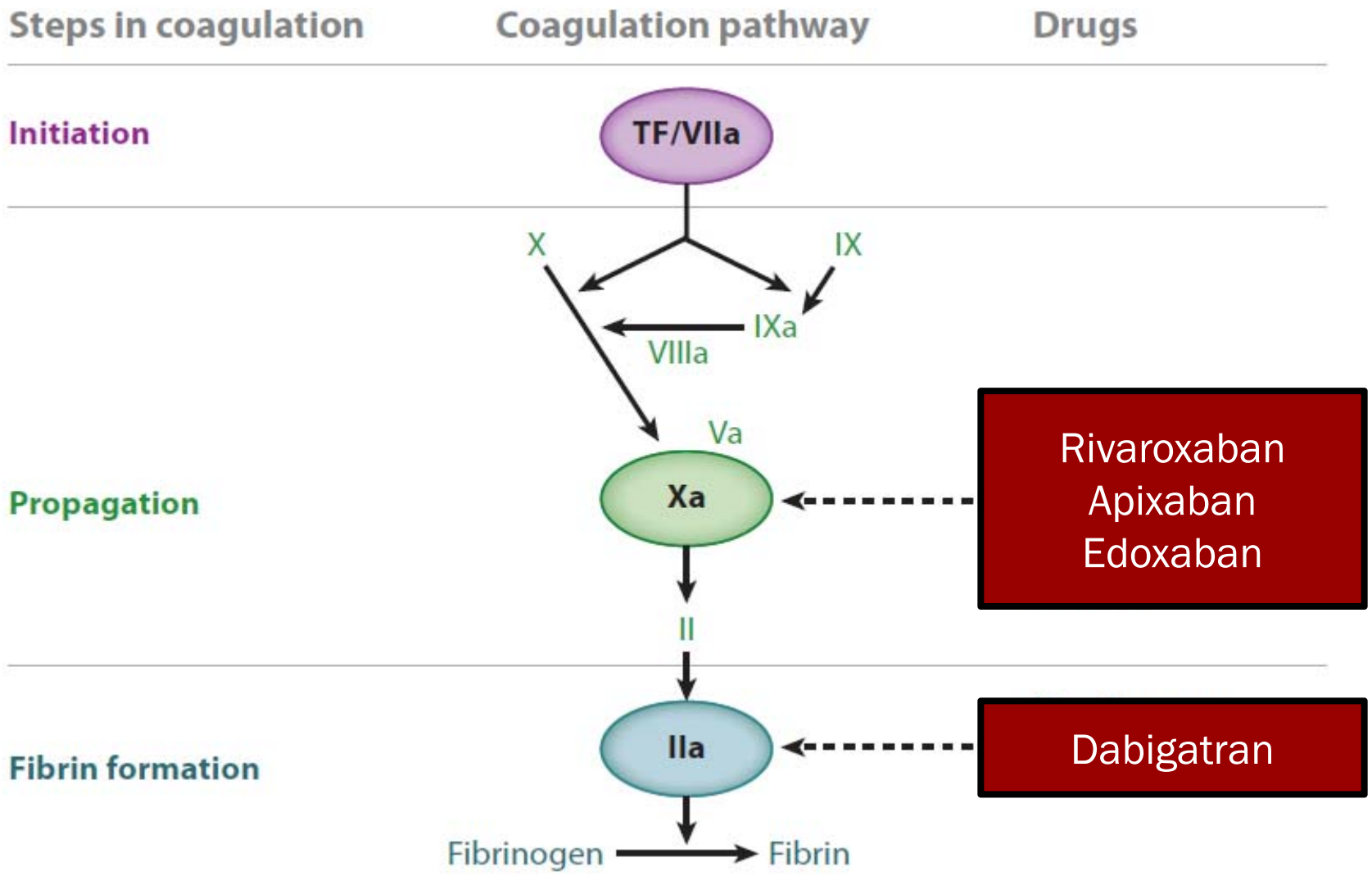






Adapted from Monroe DM. *Arterioscler Thromb Vasc Biol*. 2002;22:1381-89.

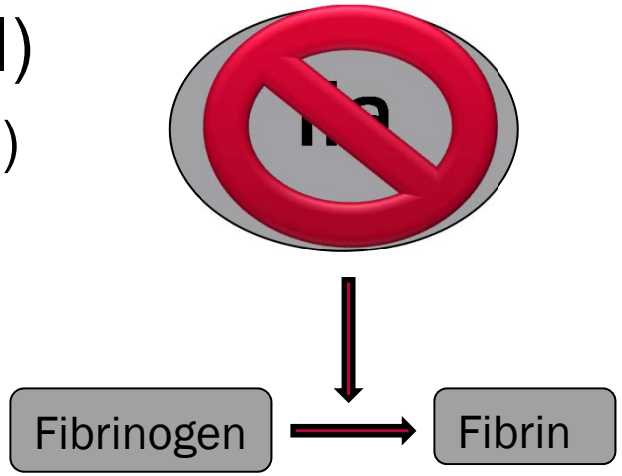
Anticoagulant Targets



Eriksson et al. *Ann Rev Med* 2011; 62:41-57.

Dabigatran etexilate (Pradaxa®)

- Oral direct thrombin inhibitor (DTI)
  - Selectively inhibits thrombin (factor IIa) from converting fibrinogen → fibrin
  - Prevents thrombus formation
- FDA Approved Indication:
  - Prevention of stroke or thrombosis in NON-VALVULAR afib
  - Treatment of pulmonary embolism (PE) & deep venous thrombosis (VTE)
  - Postoperative thromboprophylaxis
  - Reduction of Recurrence of DVT/PE



Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2011.

Dabigatran Properties

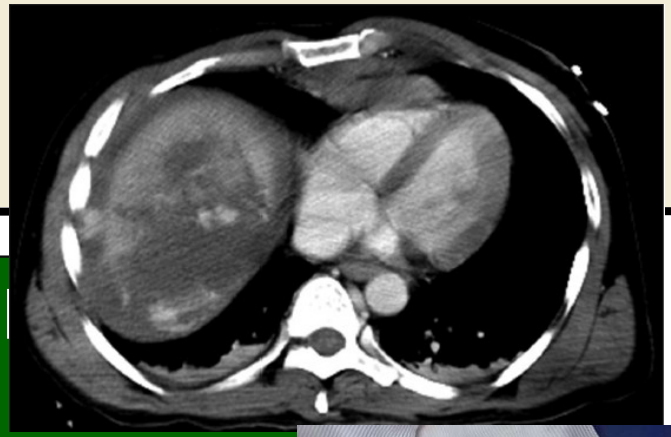
Medication	Mechanism of action	Elimination	Half-life	Hepatic/ Renal Adjustments	Dialyzable
Dabigatran	Direct inhibition of thrombin (Factor IIa), including platelet activation	>80% Renal	12-17 h (27.5 h in severe renal failure, 34.1 h in HD)	Renal	Yes (~57% over 4 h)

Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2011.

Management prior to surgery

Discontinuation (Days) prior to procedure		
	Major Surgery	Minor Surgery
CrCl ≥ 50 mL/min	2 days	1 day
CrCl 30-50 mL/min	4 days	2 days
CrCl < 30 mL/min	6 days	4 days

Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2011.



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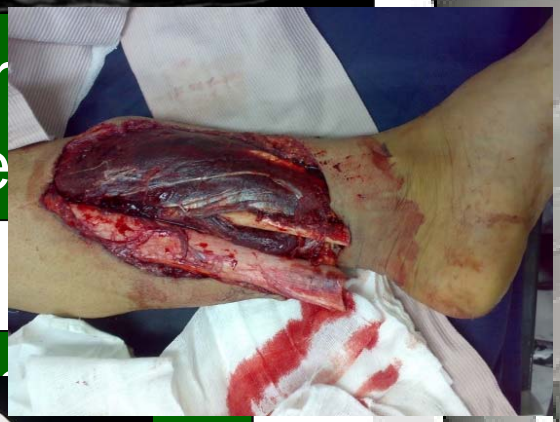
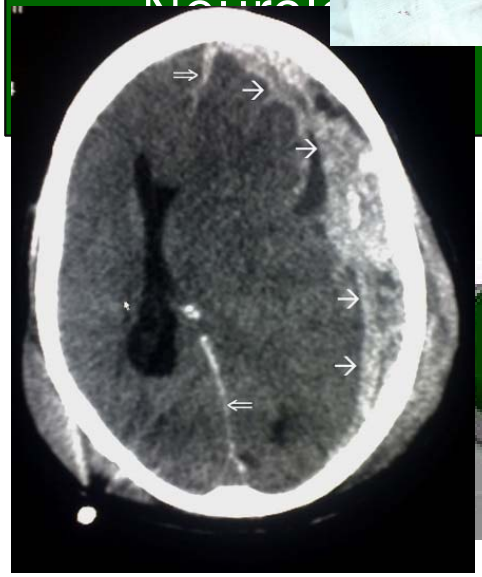


Challenge to detect and reverse

Neurosurgery/ Trauma



Dabigatran

Monitoring and Reversal

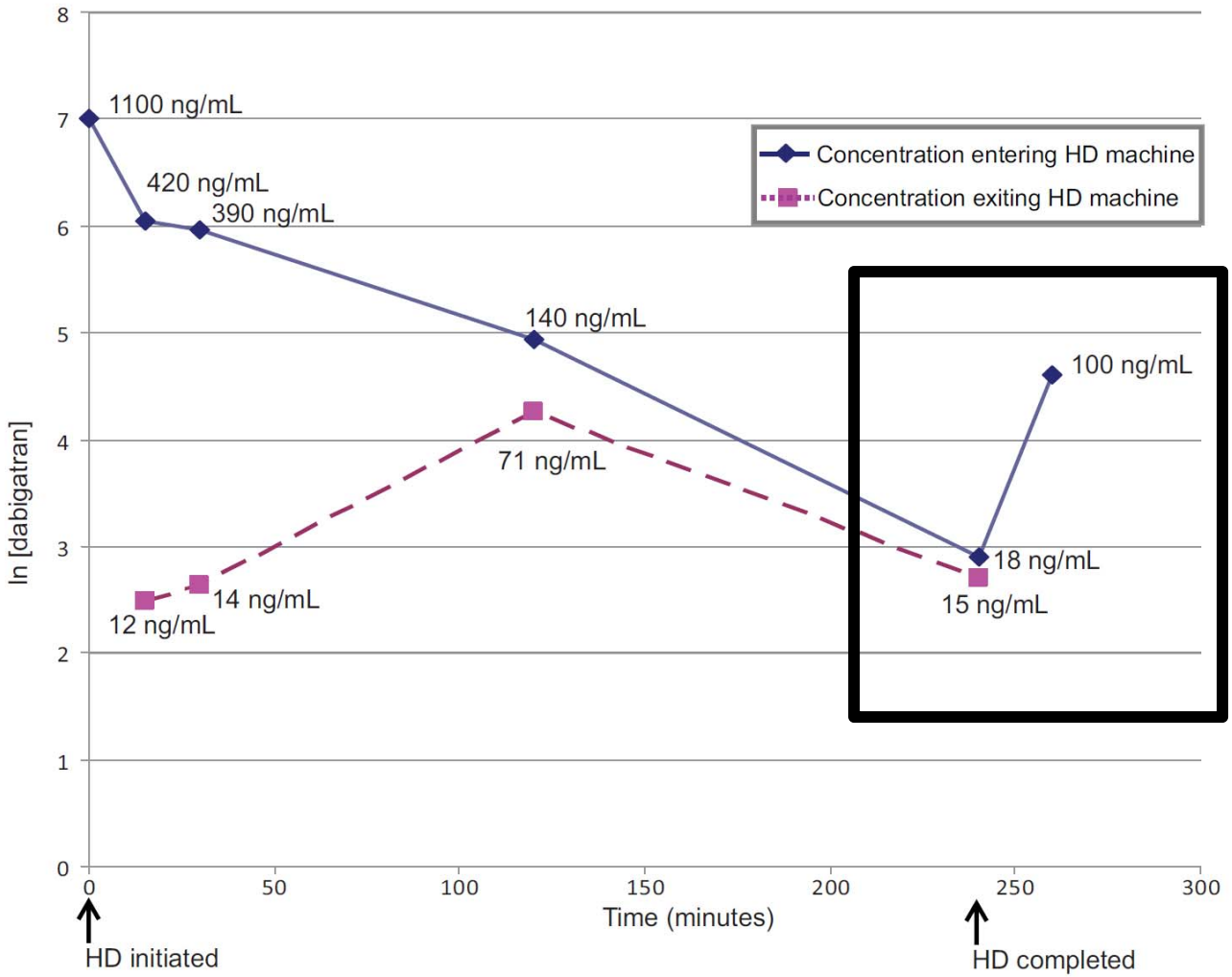
Dabigatran (Pradaxa®)

- Monitoring Parameters:
  - aPTT/INR: may be elevated, but no correlation
  - Thrombin Clotting Time (TCT)/Thrombin Time (TT): most accurate
  - Thromboelastometry/thromboelastography
- Reversal of Dabigatran:
  - Activated charcoal
  - Hemodialysis
  - Idarucizumab (Praxbind®)

Erenberg ES et al. *Circ.* 2011;124(14):1573-1579.
Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2012.
Praxbind® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2015.
Am J Kidney Dis 2013; 62(3):591-4.

Hemodialysis: Dabigatran Removal

- 49% removal over 4 hrs
- Redistribution



Am J Kidney Dis 2013; 62(3):591-4.
Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2012.

Dabigatran (Pradaxa®)

- Monitoring Parameters:
  - aPTT/INR: may be elevated, but no correlation
  - Thrombin Clotting Time (TCT)/Thrombin Time (TT): most accurate
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Erenberg ES et al. *Circ.* 2011;124(14):1573-1579.
Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2012.
Praxbind® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2015.
Am J Kidney Dis 2013; 62(3):591-4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

- Humanized mouse monoclonal antibody fragment
- Affinity for dabigatran 350 x that of thrombin
- Binds free and thrombin-bound dabigatran
- Idarucizumab-dabigatran complex renally cleared
- Ongoing, multicenter, prospective, single-arm, observational, phase-III cohort (n=90)
  - Group A: overt, uncontrollable/life-threatening bleed
  - Group B: required surgery/invasive procedure within 8 h

N Engl J Med 2015; 373:511-20.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Intervention

- Idarucizumab 2.5 g/50 mL IV bolus x2

Primary Endpoint

- Maximum percentage of anticoagulant effect of dabigatran (dilute TT and ECT)

Secondary Endpoints

- Proportion of patients with complete normalization of dTT/ECT and reduction in unbound dabigatran
- Mortality due to vascular/non-vascular causes
- Group A: extent of bleeding/hemodynamic instability
- Group B: classification of hemostasis during intervention

N Engl J Med 2015; 373:511-20.

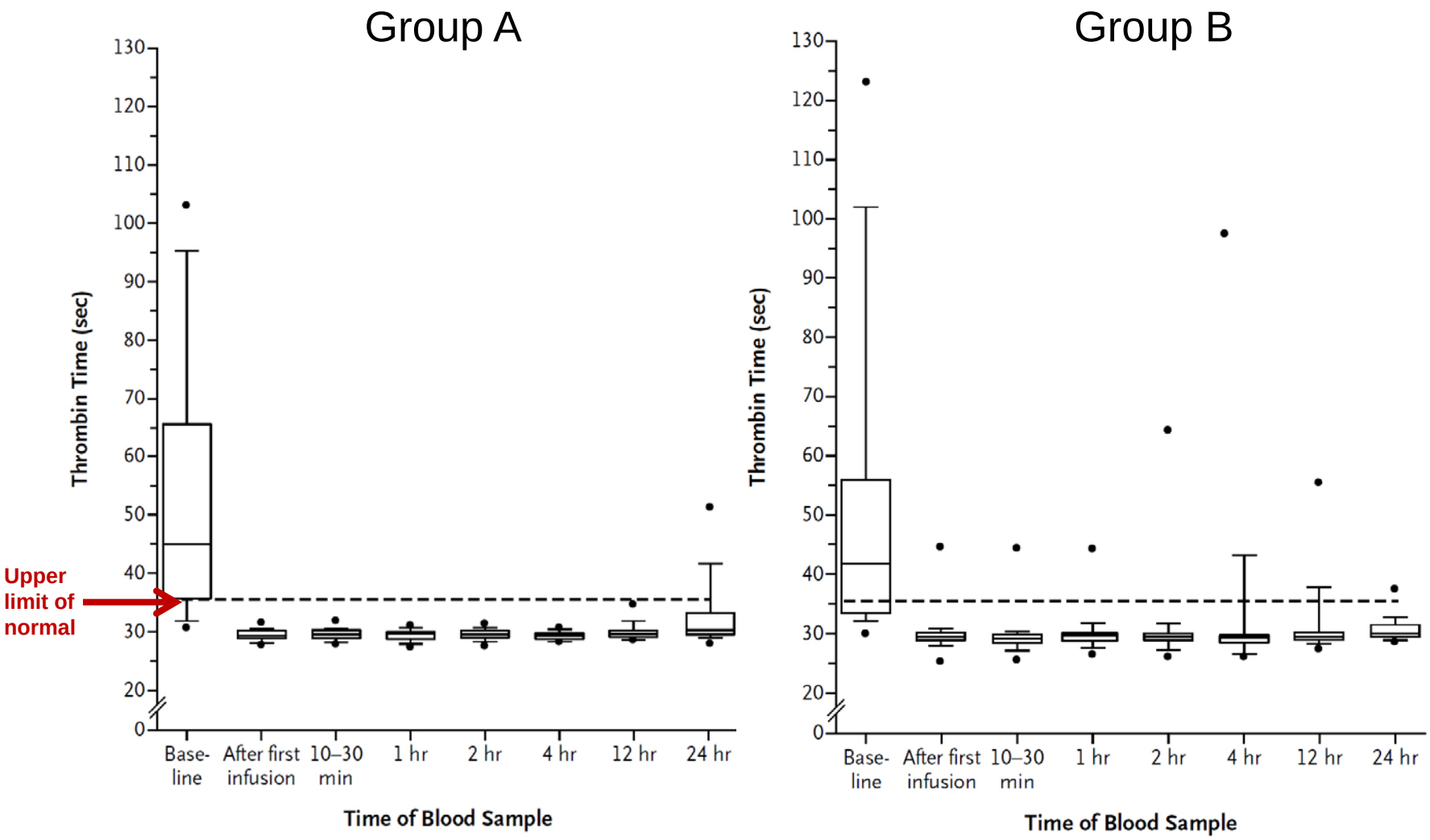
Baseline Characteristics

	Group A (n=51)	Group B (n=39)
Age (yr)*	77 (48-93)	76 (56-93)
Male#	32 (63)	18 (46)
Weight (kg)*	70.5 (42.4-127.5)	73 (49.5-116)
CrCl (mL/min)*	54 (16-187)	60 (11-171)
Indication for dabigatran# Atrial fibrillation VTE Other	 47 (92) 1 (2) 3 (6)	 39 (100) 0 0
Time since last dose (h)	15.2	16.6
Elevated dilute TT at baseline#	40 (78)	28 (72)
Elevated ECT at baseline#	47 (92)	34 (87)

* Median with or without (Range); # no. (%)

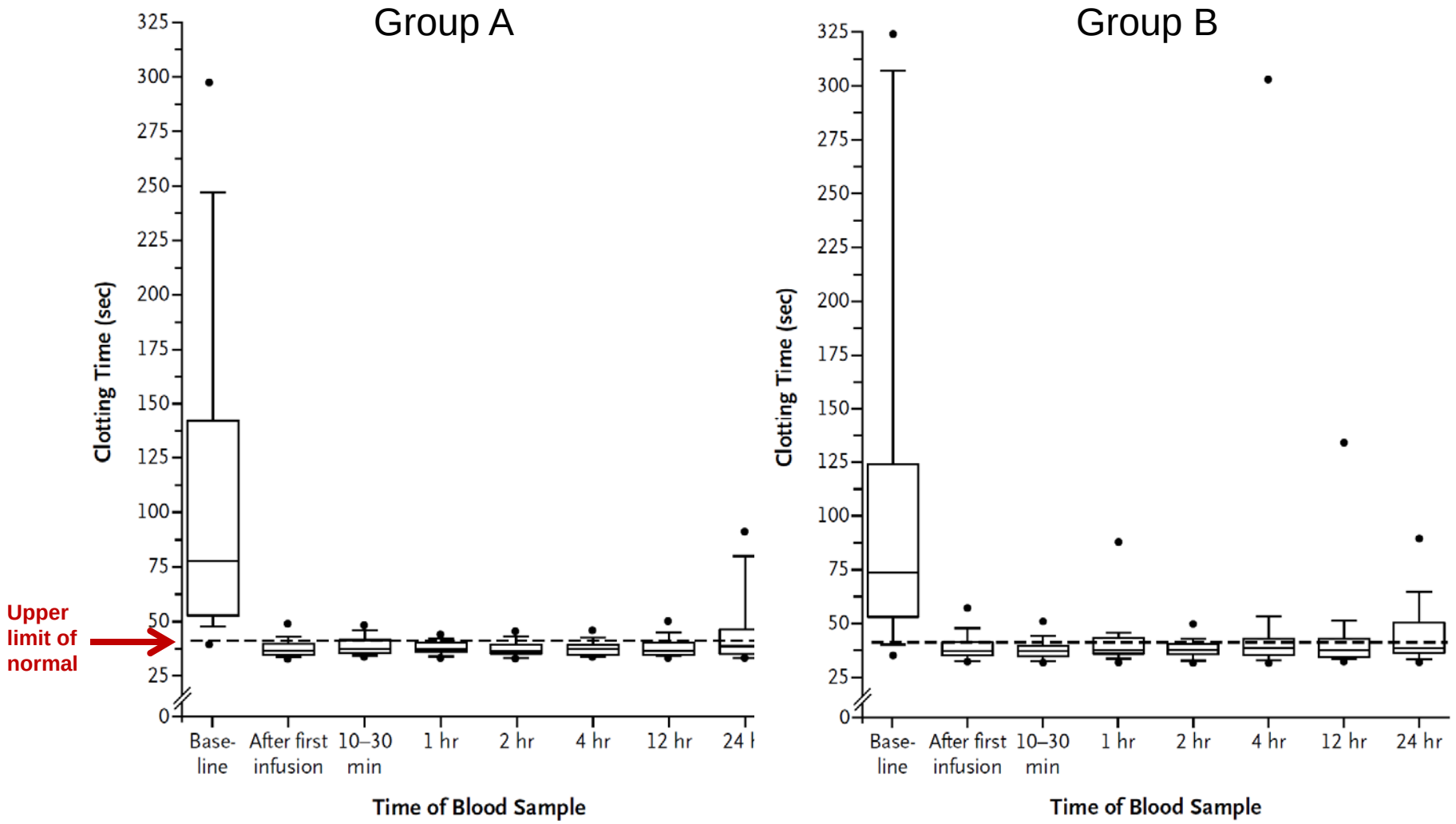
N Engl J Med 2015; 373:511-20.

Dilute TT after Idarucizumab



N Engl J Med 2015; 373:511-20.

ECT after Idarucizumab



N Engl J Med 2015; 373:511-20.

Summary of Results

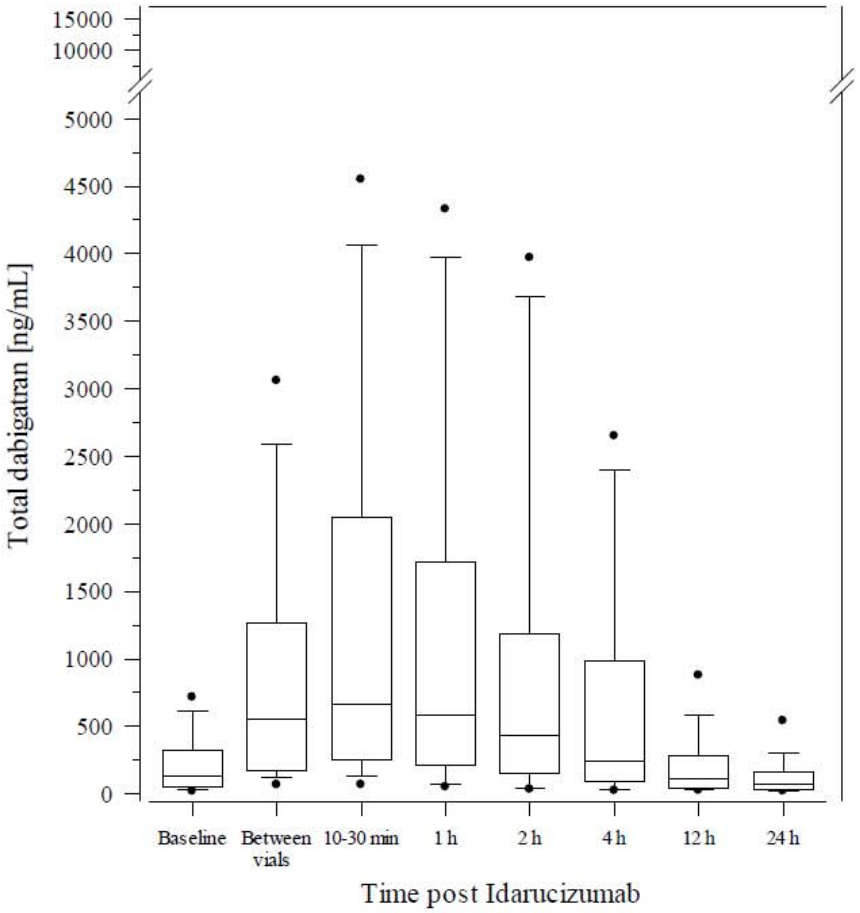
	Group A	Group B
Median maximum percentage of reversal, %	100	100
Patients with normalized dilute TT within 4 h, %	98	93
Patients with normalized ECT within 4 h, %	89	88
Patients with dilute TT below ULN at 12 and 24 h post-dose, %	90	81
Patients with ECT below ULN at 12 and 24 h post-dose, %	72	54

Dilute TT evaluated in 68 of 90 patients
ECT evaluated in 81 of 90 patients

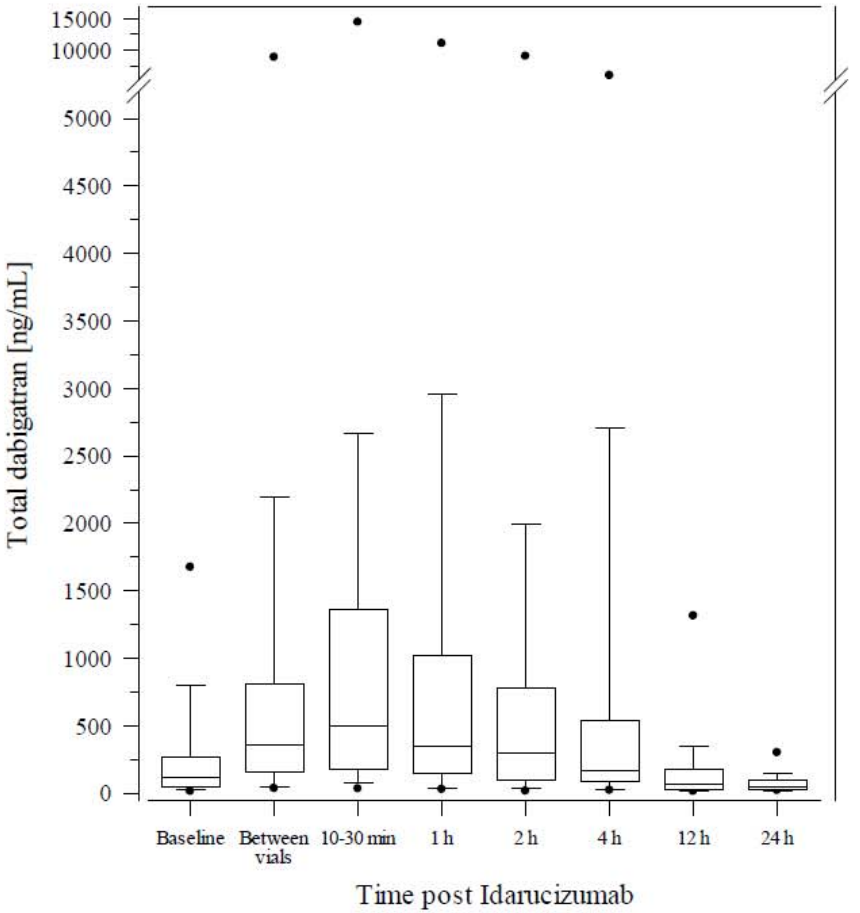
N Engl J Med 2015; 373:511-20.

Total Dabigatran Concentrations

Group A

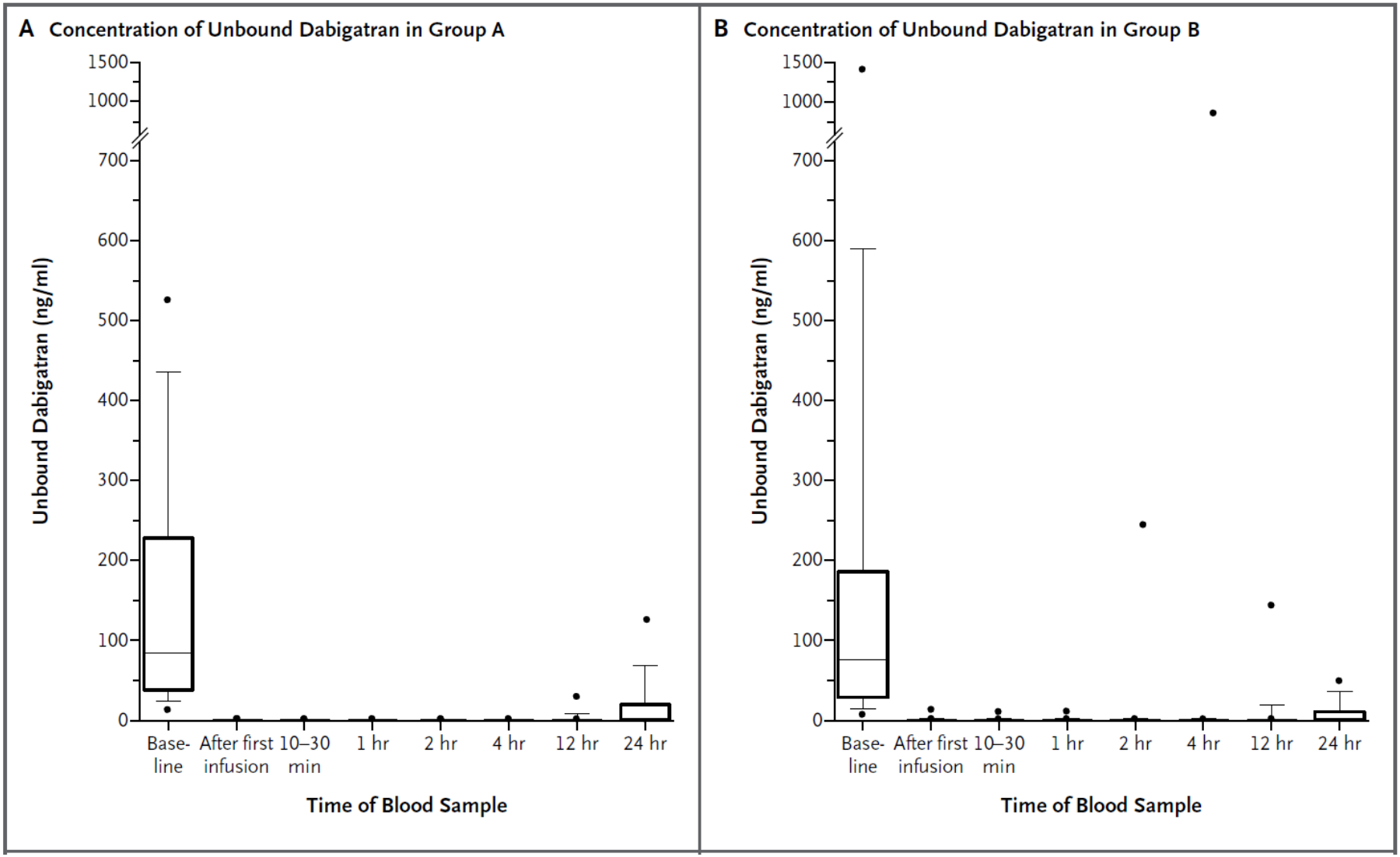


Group B



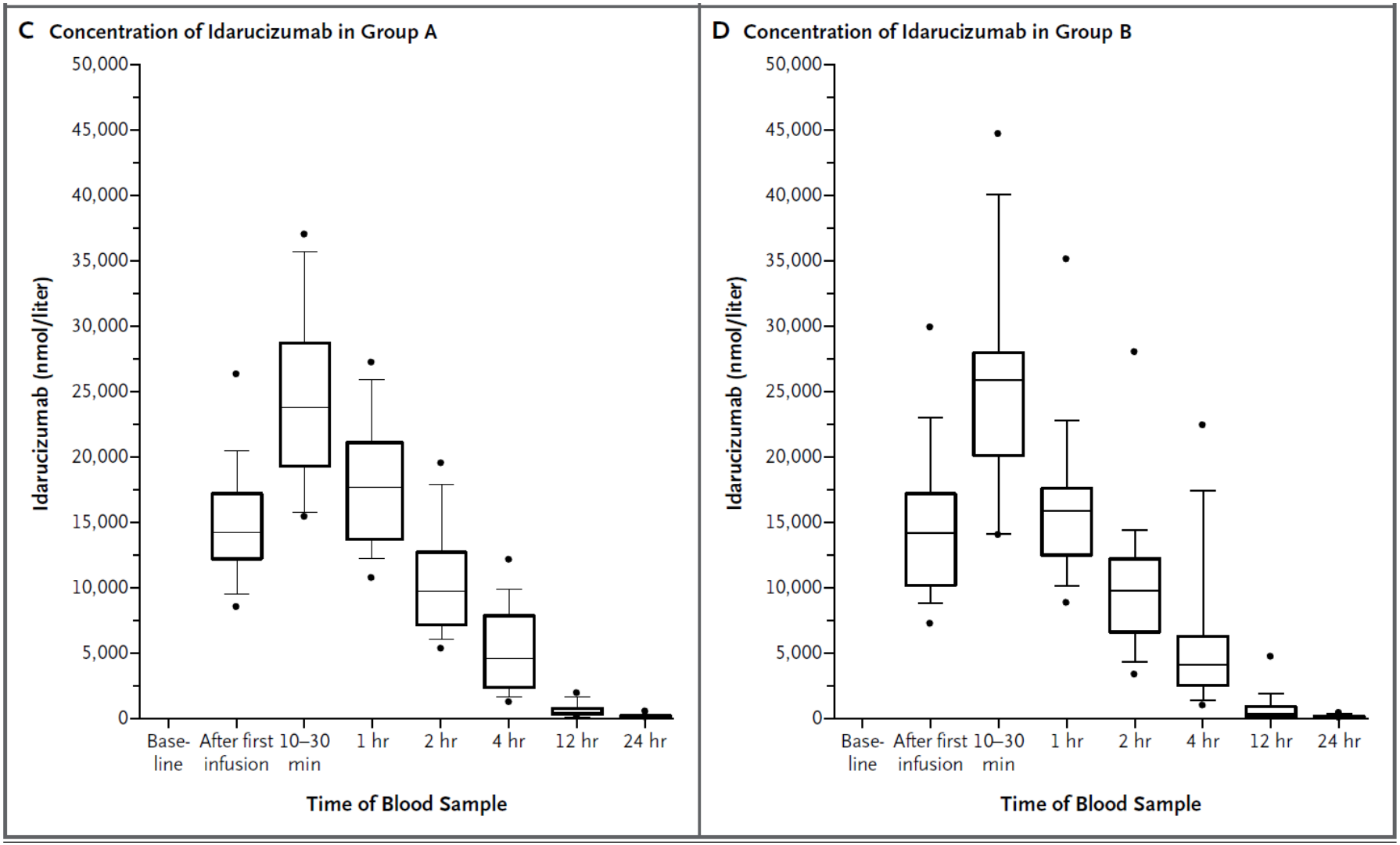
N Engl J Med 2015; 373:511-20.

Unbound Dabigatran Concentrations



N Engl J Med 2015; 373:511-20.

Idarucizumab Concentrations



N Engl J Med 2015; 373:511-20.

Safety Evaluation

Mortality (n=13)

- Vascular causes (n=10, fatal bleeding =5)

Thrombotic Events (n=5)

- VTE, PE
- VTE, PE, atrial thrombus
- DVT
- NSTEMI
- Ischemic stroke

Serious Adverse Events (n=21)

- Deaths/thrombotic events (n=18)
- Gastrointestinal hemorrhage (n=2)
- Postoperative wound infection (n=1)
- Delirium (n=1)
- Right ventricular failure (n=1)
- Pulmonary edema (n=1)

N Engl J Med 2015; 373:511-20.

Budget Impact of Idarucizumab

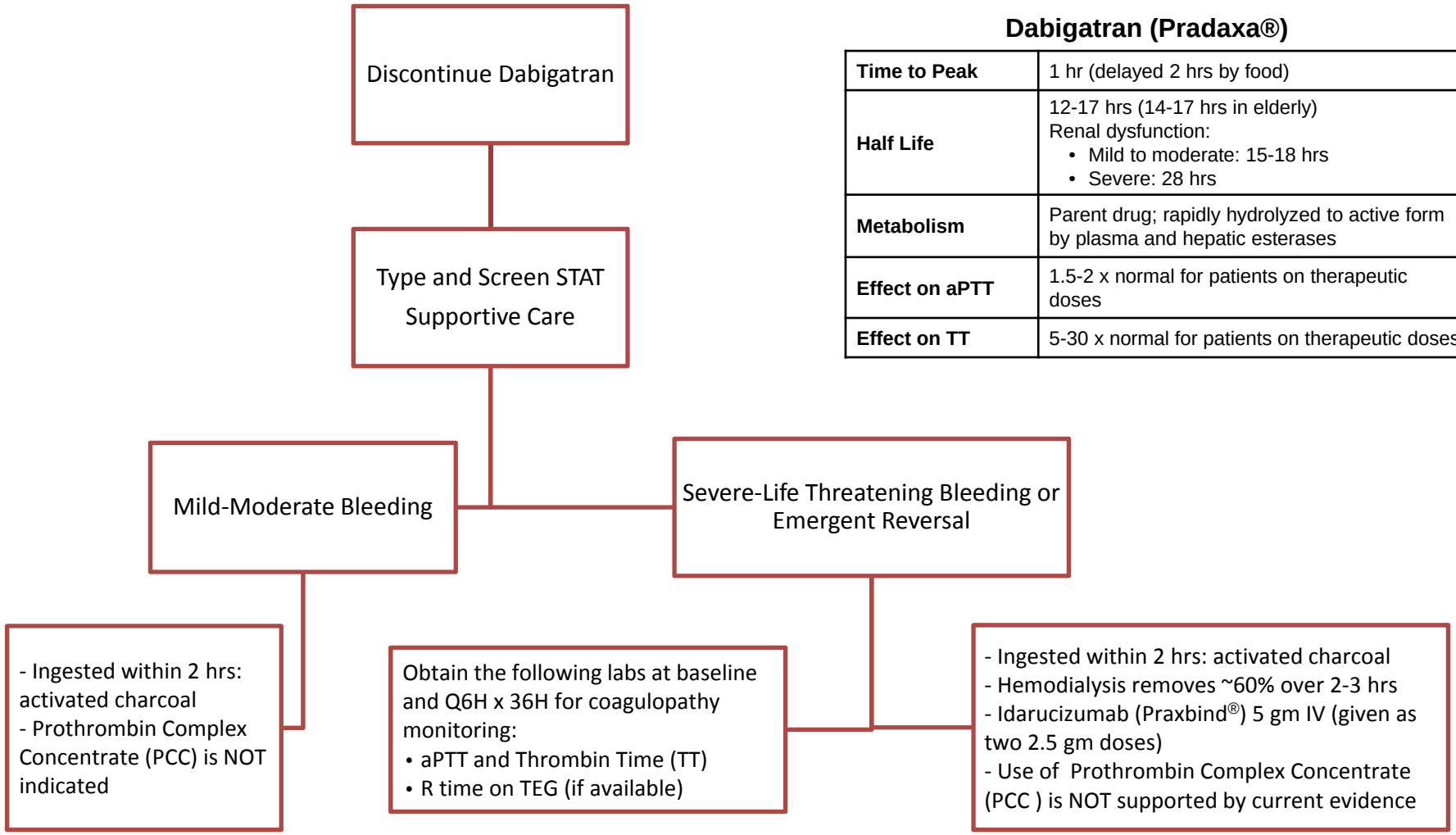
- 2.5 gm/50 mL: $2100

One patient requiring emergent dabigatran reversal: 2 x $2100

- $4,200

- Trauma center who sees 50 patients needing emergent reversal: $210,000/yr
- Reimbursement requirements

Dabigatran Reversal



Dabigatran (Pradaxa®)

Time to Peak	1 hr (delayed 2 hrs by food)
Half Life	12-17 hrs (14-17 hrs in elderly) Renal dysfunction: • Mild to moderate: 15-18 hrs • Severe: 28 hrs
Metabolism	Parent drug; rapidly hydrolyzed to active form by plasma and hepatic esterases
Effect on aPTT	1.5-2 x normal for patients on therapeutic doses
Effect on TT	5-30 x normal for patients on therapeutic doses

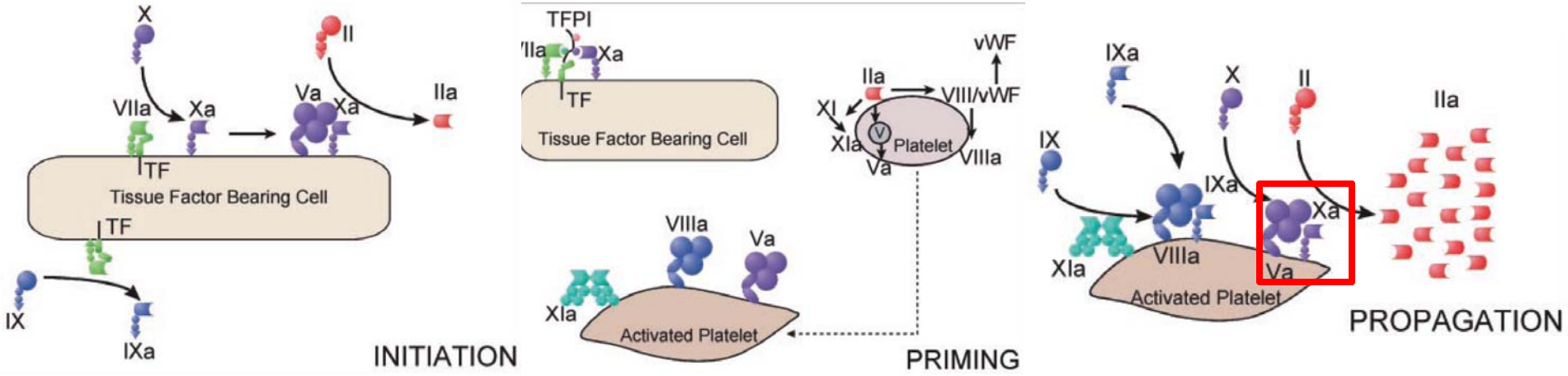
Erenberg ES et al. *Circulation.* 2011;124(14):1573-1579.
Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2012.

Apixaban, Edoxaban, Rivaroxaban

Monitoring and Reversal

Apixaban (Eloquis®), Edoxaban (Savaysa™), and Rivaroxaban (Xarelto®)

- Oral factor Xa inhibitor
  - Inhibits prothrombinase complex from converting prothrombin → thrombin
  - Indirectly ┤ platelet activation and fibrin clot formation



Xarelto® [package insert]. Leverkusen, Germany. Janssen Pharmaceuticals, Inc. 2011.
Eliquis® [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. 2015.
Savaysa™ [package insert]. Parsippany, NJ. Daiichi Sankyo Co., LTD. 2015.
Circ 2012;125:e244-46.

Oral Factor Xa Indications

	Treatment of DVT and/or PE	Prevention of thrombosis in NON-VALVULAR atrial fibrillation	Postoperative thrombo-prophylaxis	Reduction in the risk of recurrence of DVT or PE (from 6 -12 mo)
Apixaban	X	X	X	X
Edoxaban	X	X		
Rivaroxaban	X	X	X	x

NONE of the new oral anticoagulants are approved for any of the following:

- Anticoagulation with prosthetic heart valves
- Treatment of heparin-induced thrombocytopenia (HIT)
- Treatment of hypercoagulable states

Xarelto® [package insert]. Leverkusen, Germany. Janssen Pharmaceuticals, Inc. 2011.
Eliquis® [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. 2015.
Savaysa™ [package insert]. Parsippany, NJ. Daiichi Sankyo Co., LTD. 2015.

Comparison of New Anticoagulants

Medication	Mechanism of action	Elimination	Half-life	Hepatic/ Renal Adjustments	Dialyzable
Dabigatran	Direct inhibition of thrombin (Factor IIa), including platelet activation	>80% Renal	12-17 h (27.5 h in severe renal failure, 34.1 h in HD)	Renal	Yes (~57% over 4 h)
Apixaban	Inhibits Xa-mediated conversion of prothrombin to thrombin	Fecal	12 h	Both	Minimal
Edoxaban		50% Renal	10-14 h	Both	No
Rivaroxaban		66% Renal, 28% Fecal	5 h	Both	No

Pradaxa® [package insert]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2011.
Xarelto® [package insert]. Leverkusen, Germany. Janssen Pharmaceuticals, Inc. 2011.
Eliquis® [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. 2015.
Savaysa™ [package insert]. Parsippany, NJ. Daiichi Sankyo Co., LTD. 2015.

Oral Factor Xa Inhibitors

- Monitoring Parameters:
  - aPTT/INR: may be elevated, but no correlation
  - Thromboelastometry/thromboelastography
  - Utility of Factor Xa activity
- Reversal of FXa Inhibitors:
  - Activated charcoal
  - Not dialyzable
  - Idarucizumab *ineffective*
  - Prothrombin Complex Concentrates (PCC), activated PCC (aPCC)
  - Recombinant modified human Factor Xa decoy

Xarelto® [package insert]. Leverkusen, Germany. Janssen Pharmaceuticals, Inc. 2011.
Eliquis® [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. 2015.
Savaysa™ [package insert]. Parsippany, NJ. Daiichi Sankyo Co., LTD. 2015.

PCC/aPCC Description

- Concentrated from human plasma
- Coagulation factors II, IX, X, ± VII
- Variable factor concentrations
  - 3 Factor PCC: Profilnine®
  - 4 Factor PCC: Kcentra®
  - Activated PCC (aPCC): FEIBA
- Duration of action
- Approved indications

Kamal. *Mayo Clin Proc* 2007;82:864-873.
CHEST. February 2012;141(2_suppl):e44S-e88S.
Bershad. *Neurocrit Care* 2010;12(3):401-13.
Leissinger. *Am J Hematol* 2008;83:137-43.

PCC/aPCC for rivaroxaban reversal

Study	Study Design	Study Population	Intervention	Outcome
Eerenberg *et al.* *Circulation* 2011	Randomized, double-blind, placebo controlled cross-over study	12 healthy male volunteers	50 units/kg PCC vs placebo	PCC immediately and completely reversed PT and endogenous thrombin potential (ETP) lag time of rivaroxaban
Marlu *et al.* *Thromb Haemost* 2013	Randomized, cross-over, ex vivo study	10 healthy male volunteers	Addition of PCC, rFVIIa, or FEIBA at various concentrations in patient who got 1 dose of rivaroxaban	-PCC strongly corrected ETP AUC -FEIBA corrected all measured parameters

Published ahead of print. *Circulation*. 2011:124.
Thromb Haemost 2012; 108(2):217-24.

Oral Factor Xa Inhibitors

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Savaysa™ [package insert]. Parsippany, NJ. Daiichi Sankyo Co., LTD. 2015.
Thromb Haemost 2010; 103:815-25.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Deborah M. Siegal, M.D., John T. Curnutte, M.D., Ph.D., Stuart J. Connolly, M.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Brian L. Wiens, Ph.D., Vandana S. Mathur, M.D., Janice Castillo, B.S., Michele D. Bronson, Ph.D., Janet M. Leeds, Ph.D., Florie A. Mar, Ph.D., Alex Gold, M.D., and Mark A. Crowther, M.D.

- Recombinant, modified human factor Xa decoy protein
- Sequesters factor Xa inhibitors into vascular space
- Double-blind, randomized, placebo controlled, phase III study

N Engl J Med 2015; 373:2413-24.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

Population

- Healthy adult volunteers (50-75 years old)

Objectives

- Evaluate the ability of andexanet alfa to reverse apixaban and rivaroxaban
- Evaluate the safety of andexanet alfa in healthy adults

N Engl J Med 2015; 373:2413-24.

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Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity

2 Clinical Trials

- ANNEXA-A: evaluate reversal of apixaban
- ANNEXA-R: evaluate reversal of rivaroxaban

Intervention

- Part 1: Andexanet alfa IV bolus x1 (or placebo)
- Part 2: Andexanet alfa IV bolus x1 then 120 min infusion (or placebo)

Primary Endpoint

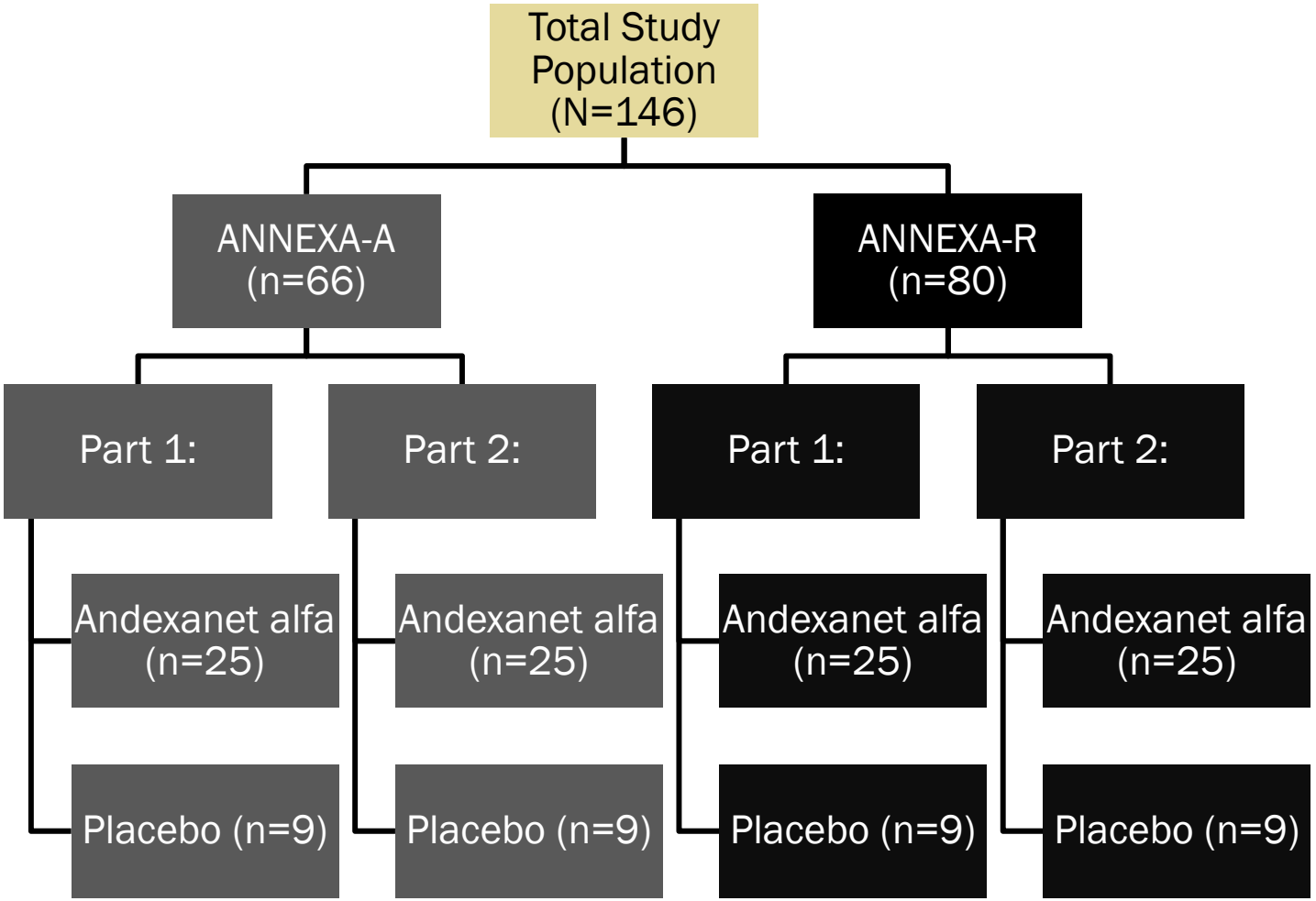
- Change in Anti-factor Xa activity (%) from baseline to post-andexanet alfa

Secondary Endpoints

- Proportion of patients with ≥80% reduction in anti-factor Xa activity
- Change in unbound inhibitor concentration, thrombin generation
- Bleeding and thrombosis

N Engl J Med 2015; 373:2413-24.

Patient Enrollment



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Baseline Characteristics

	Apixaban				Rivaroxaban			
	Part 1 bolus only		Part 2 bolus + infusion		Part 1 bolus only		Part 2 bolus + infusion	
	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo
N	24	9	24	8	27	14	26	13
Age - Yr								
Median	60.0	58.0	56.0	58.5	56.0	53.5	56.0	57.0
Female sex, N (%)	11 (45.8)	3 (33.3)	7 (29.2)	3 (37.5)	9 (33.3)	6 (42.9)	11 (42.3)	6 (46.2)
BMI, Mean (SD)	26.7 (2.5)	27.4 (2.5)	27.5 (2.1)	27.8 (2.4)	27.0 (3.4)	25.9 (3.4)	27.8 (3.0)	27.6 (2.6)
Creatinine, Mean (SD) (mg/dL)	0.8 (0.2)	0.8 (0.1)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)
Race, N (%) White	24 (100)	9 (100)	21 (87.5)	8 (100)	22 (81.5)	10 (71.4)	20 (76.9)	8 (61.5)
Ethnicity, N (%) Hispanic or Latino	10 (41.7)	4 (44.4)	11 (45.8)	2 (25)	9 (33.3)	4 (28.6)	4 (30.8)	10 (38.5)

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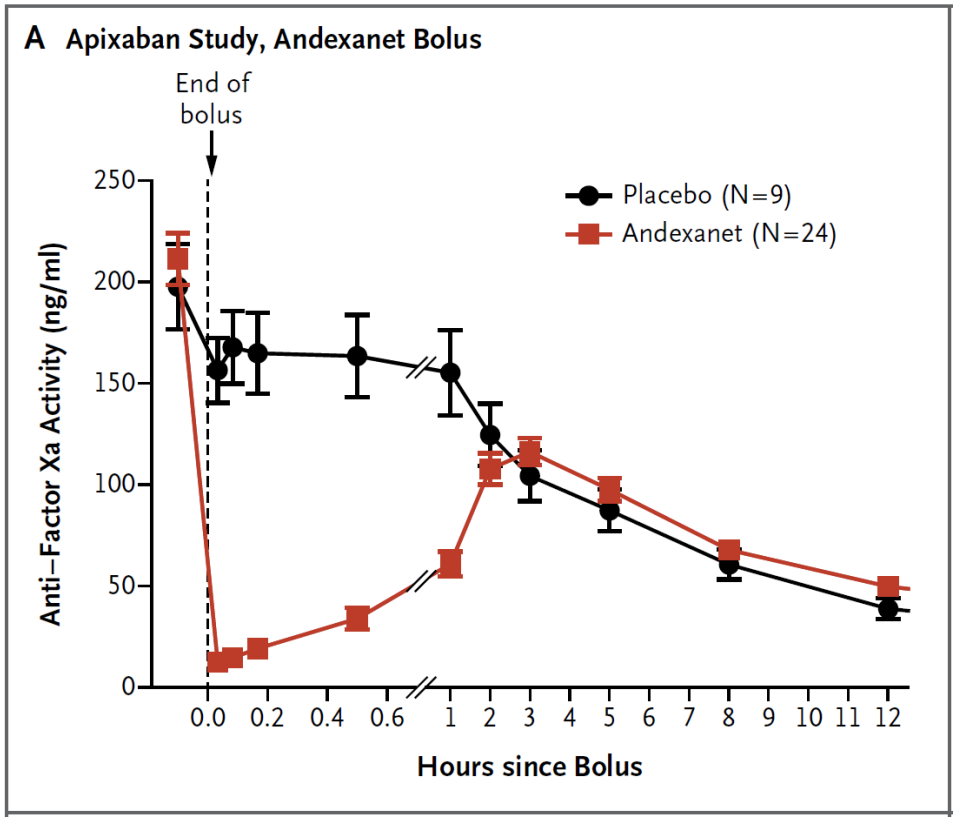
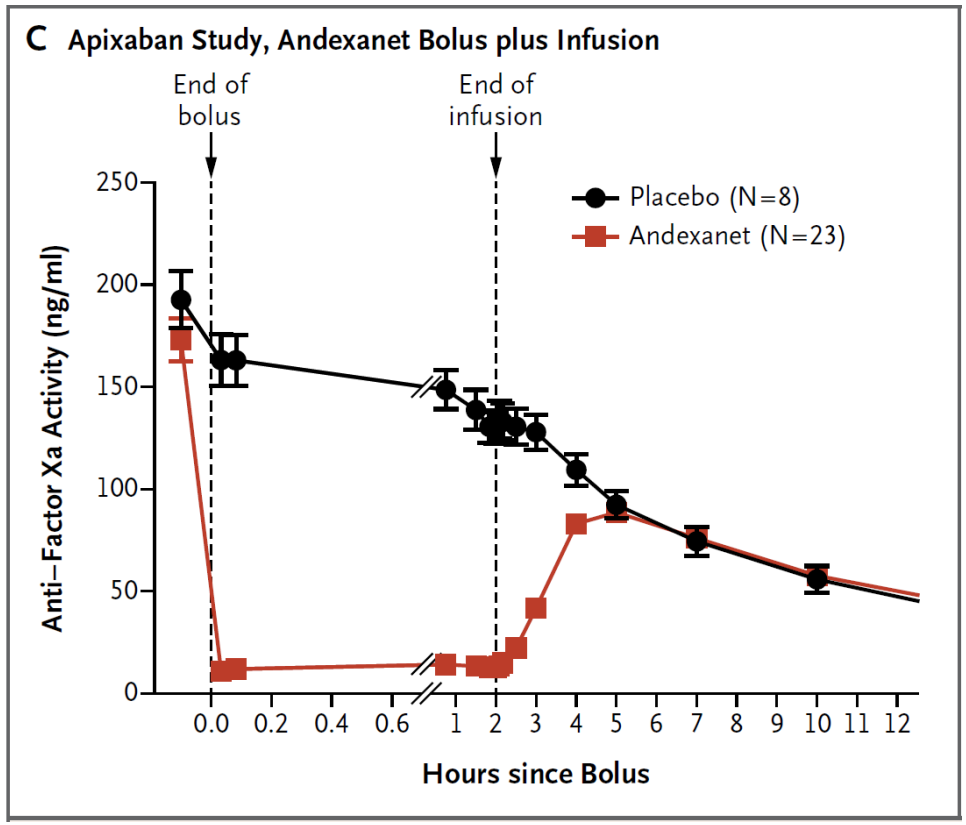
ANNEXA-A





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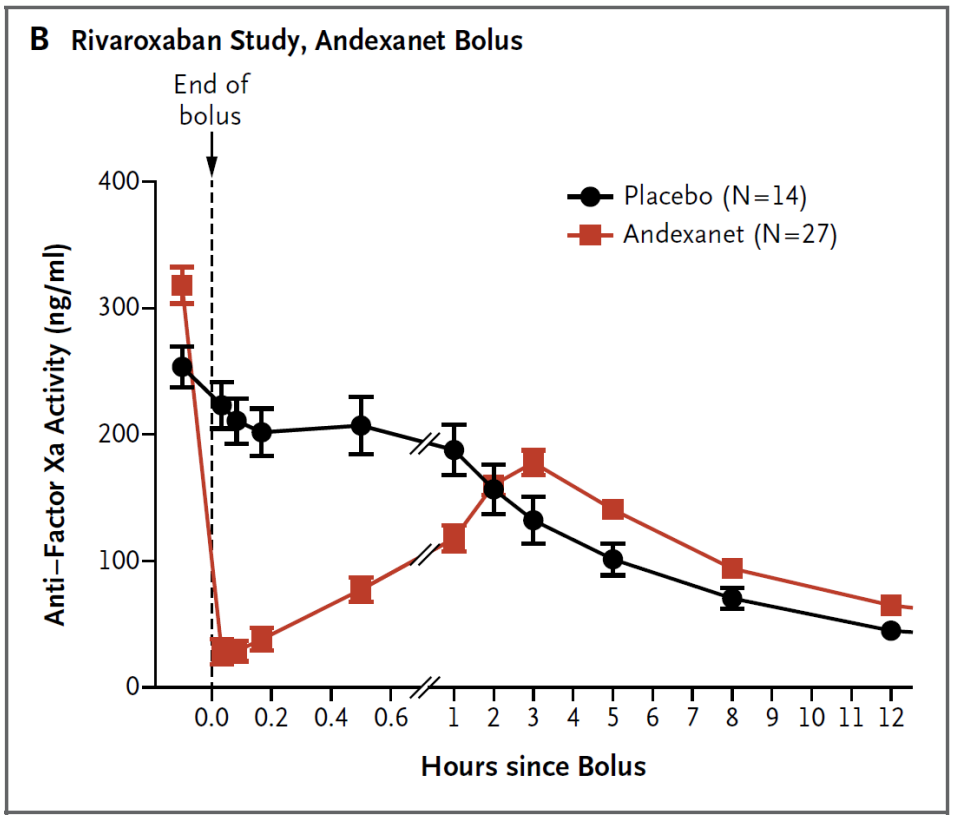
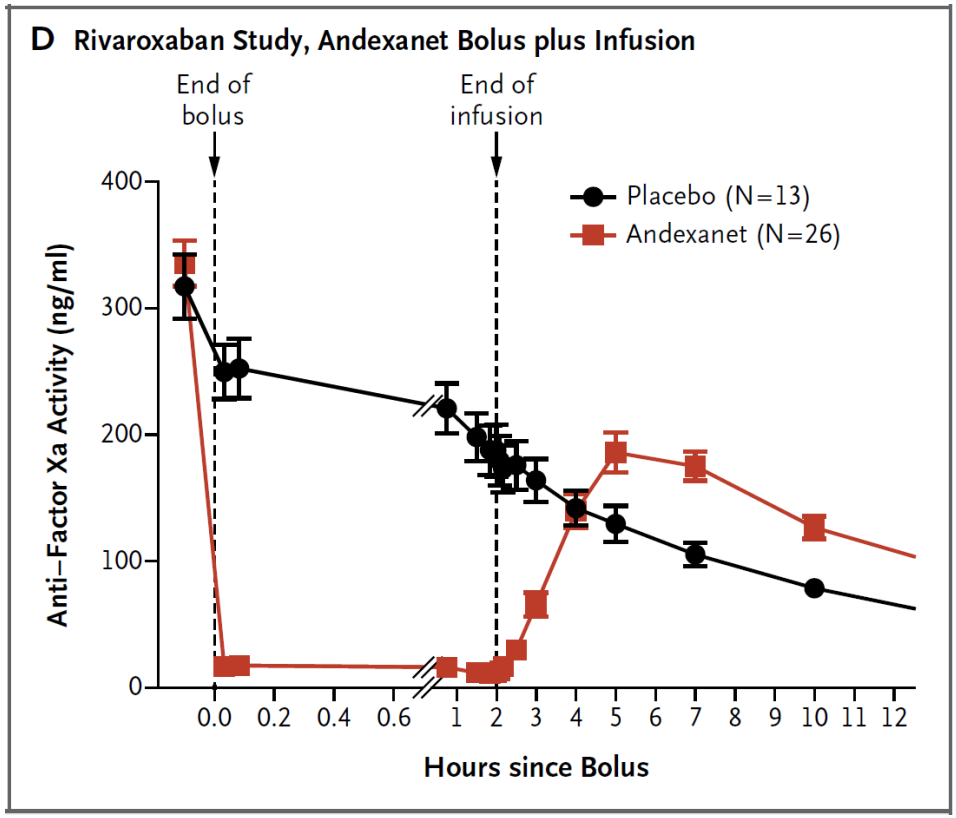
ANNEXA-R





N Engl J Med 2015; 373:2413-24.

Secondary Endpoints

- All patients except 1 had at least 80% reduction in anti-factor Xa activity
- Safety Outcomes
  - No serious events
  - Flushing
  - Urticaria
- No thrombotic events

N Engl J Med 2015; 373:2413-24.

Limitations

- Hea
- Onl
- Rev
- No
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- No evaluation of hemostasis

Moving Forward

Currently not FDA approved or available

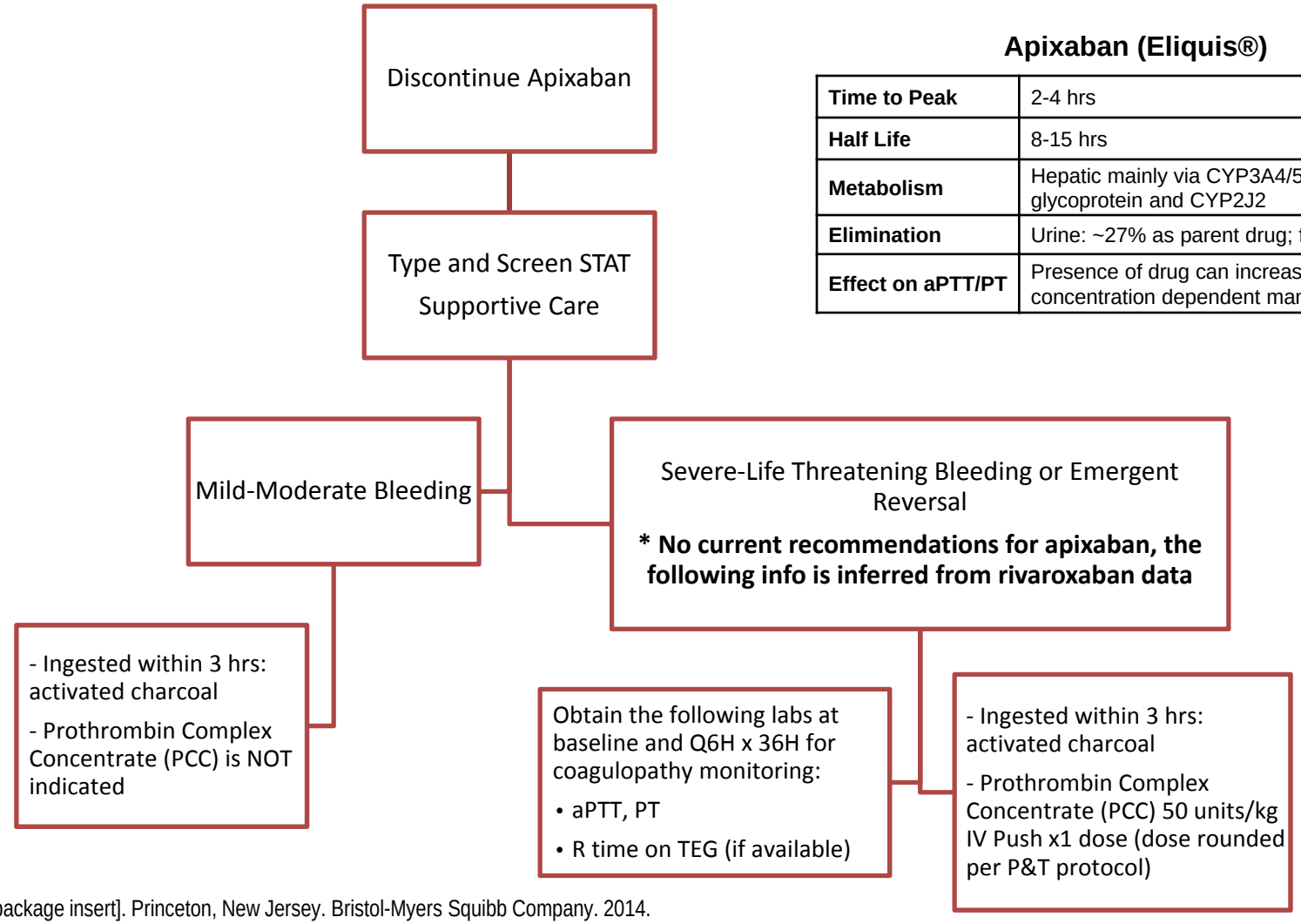
Ongoing, prospective, open label phase III trial evaluating andexanet alfa in patients with an acute bleed on apixaban, edoxaban, rivaroxaban, or enoxaparin. No information on dosing

N Engl J Med 2015; 373:2413-24.

Budget Impact

- No pricing information
- Unsure of final dosing regimen
- Possibly similar to dabigatran
- Possibly more frequent use

Apixaban Reversal

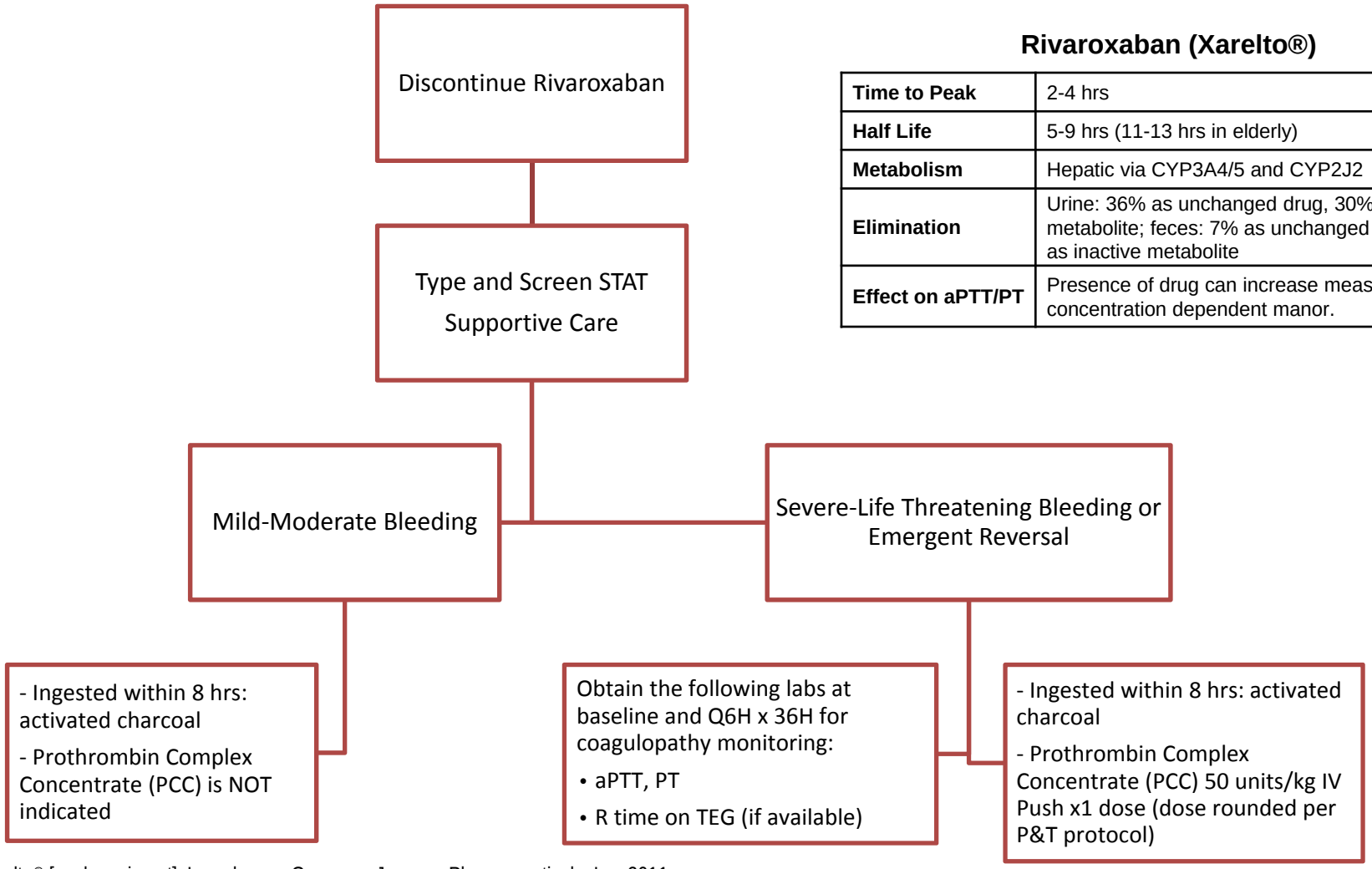


Apixaban (Eliquis®)

Time to Peak	2-4 hrs
Half Life	8-15 hrs
Metabolism	Hepatic mainly via CYP3A4/5, substrate of P-glycoprotein and CYP2J2
Elimination	Urine: ~27% as parent drug; feces: majority
Effect on aPTT/PT	Presence of drug can increase measurement in a concentration dependent manor.

Eliquis® [package insert]. Princeton, New Jersey. Bristol-Myers Squibb Company. 2014.
Miyares MA and Davis K. *Am J Health-Syst Pharm.* 2012;69:1473-84.
Erenberg ES et al. *Circulation.* 2011;124(14):1573-1579.

Rivaroxaban Reversal



Rivaroxaban (Xarelto®)

Time to Peak	2-4 hrs
Half Life	5-9 hrs (11-13 hrs in elderly)
Metabolism	Hepatic via CYP3A4/5 and CYP2J2
Elimination	Urine: 36% as unchanged drug, 30% as inactive metabolite; feces: 7% as unchanged drug, 21% as inactive metabolite
Effect on aPTT/PT	Presence of drug can increase measurement in a concentration dependent manor.

Xarelto® [package insert]. Leverkusen, Germany. Janssen Pharmaceuticals, Inc. 2011.
Miyares MA and Davis K. *Am J Health-Syst Pharm.* 2012;69:1473-84.
Erenberg ES et al. *Circulation.* 2011;124(14):1573-1579.

Future Directions

- Standardize reversal protocols
  - Patient selection
  - Laboratory monitoring
  - Medication options
- Monitor compliance of protocols
- Evaluate safety of reversal medications

Indiana University Health

Leading the Charge in Anticoagulation Reversal: Benefits, Risks, and Key Factors in Application to the Traumatically Injured Patient

Emily Hutchison, PharmD BCPS

Clinical Pharmacy Specialist, Trauma/Adult Critical Care

IU Health Methodist Hospital

March 31st, 2016

The speaker has no actual or potential conflicts of interest with regards to this presentation

PCC Properties

Onset	• Rapid (within 15 min)
Duration	• Approx 24 hrs
Administration	• Slow IVPush vs IVPB
Cost	• $800-2000 per dose
Major Adverse Effects	• Thrombosis, DIC

J Thromb Haemost 2006;4:967-70
ProfilNine® (Factor IX Complex Concentrate) package insert. Los Angeles, CA; 2004

Safety of PCC

- Meta-analysis evaluating safety of PCC for VKA reversal
- 27 studies
  - 15 prospective studies
  - 7 studies used 3-factor PCC
- Total patients: 1,032
  - 631 for major bleeding event
  - 319 for emergency surgery

Dentali F. *Thromb Haemost* 2011;106:429-438.

Results of Meta-analysis

Event	Rate (95% CI)
Total TE events	1.4% (0.8-2.1)
TE events with	% (1.0-3.0)
TE events with	% (0.0-2.4)
TE in patients t	% (1.0-3.1)
TE in patients t	% (0.1-2.0)
Viral transmission	1.9% (0.3-4.9)

"PCC is associated with a low but quantifiable risk of thromboembolic complications."

TE: Thromboembolic

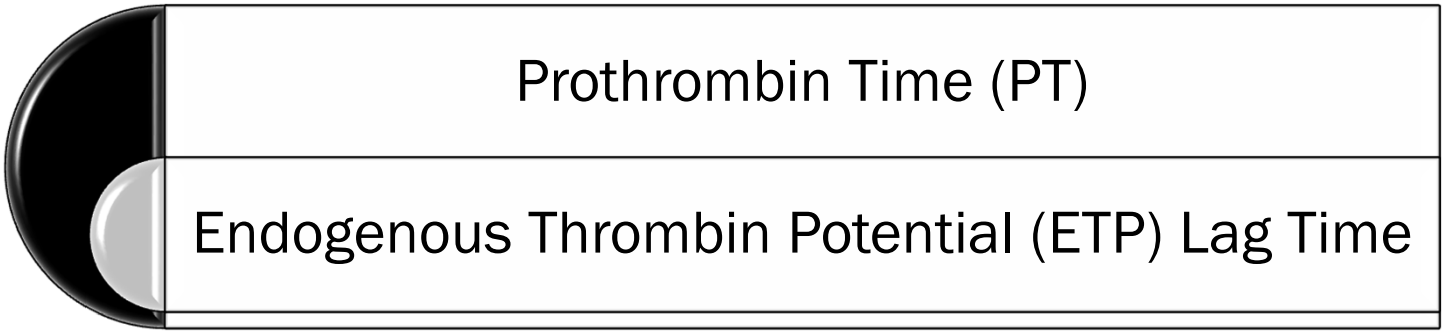
Dentali F. *Thromb Haemost* 2011;106:429-438.

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

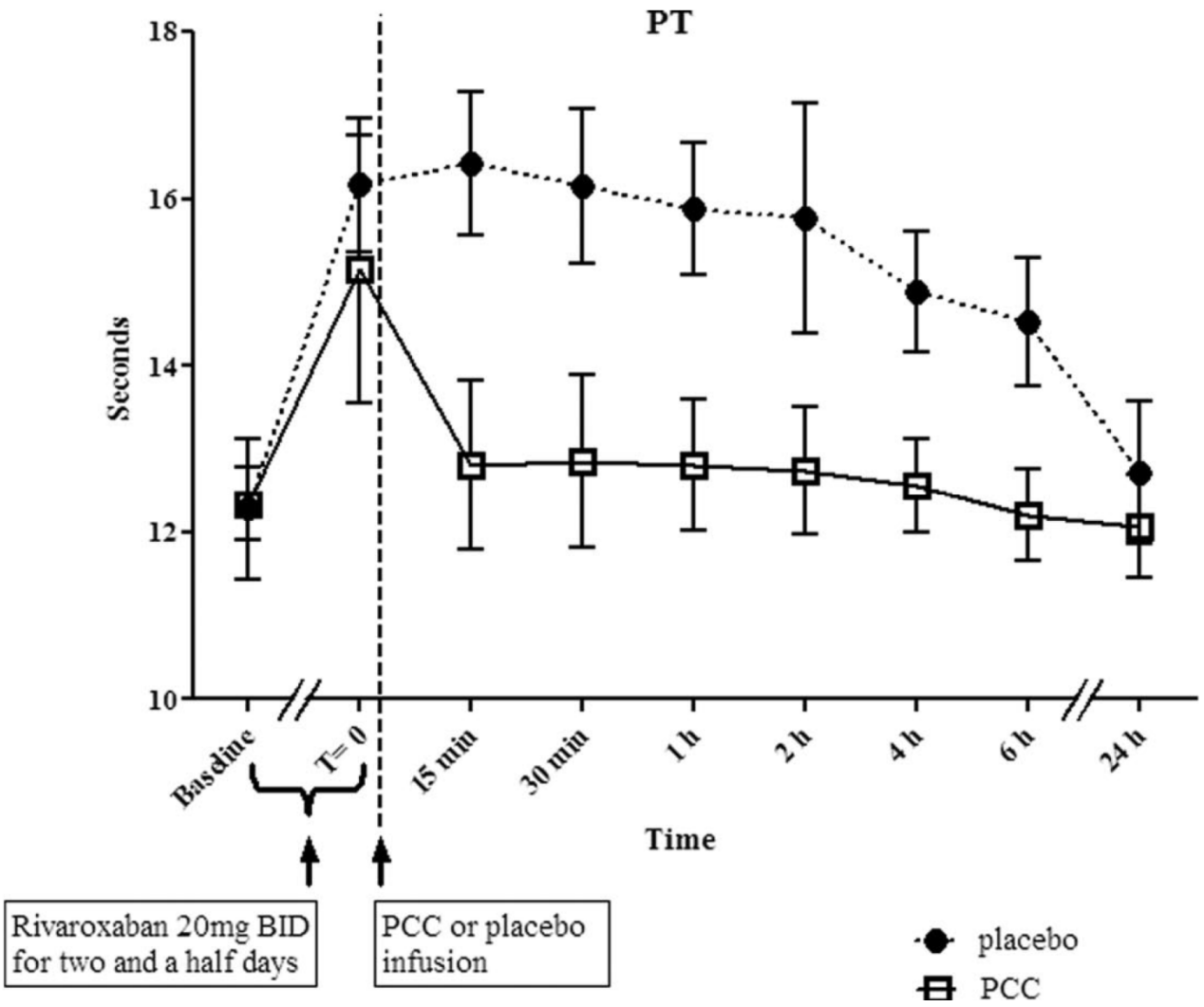
Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

- 12 healthy males
- 20 mg PO BID x 2.5 days
- PCC 50 units/kg or placebo x1 dose
- Measurements of Reversal



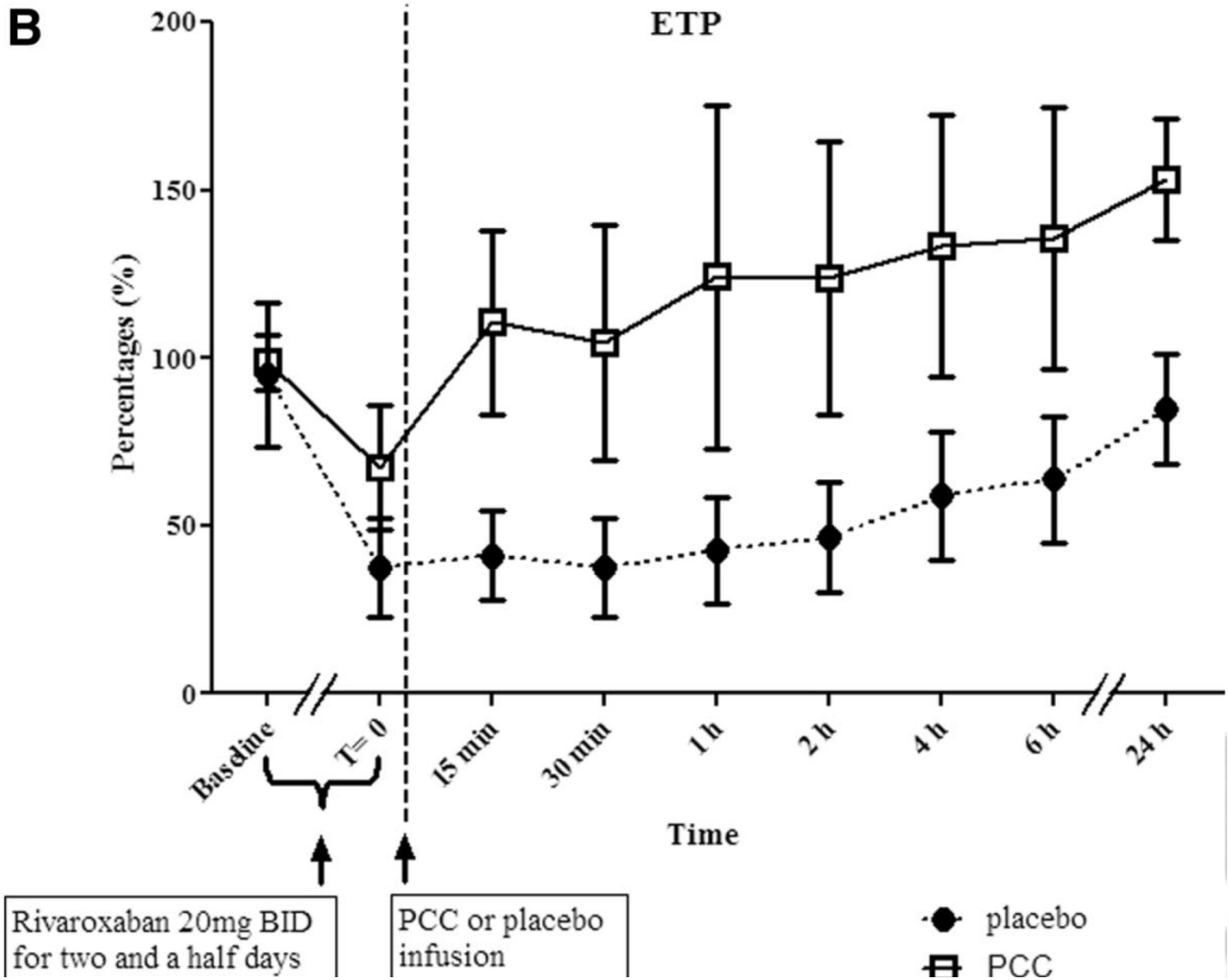
Published ahead of print. *Circulation*. 2011:124.

Correction of PT with PCC



Published ahead of print. *Circulation*. 2011:124.

Correction of ETP with PCC



Published ahead of print. *Circulation*. 2011:124.