Direct Oral Anticoagulants

Current indications and practical aspects

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Disclosures

- Research support: NIH, PCORI, Stago, Siemens, Instrumentation Laboratory
- Consultant positions: None

- Off-label medication use: none

Direct Oral Anticoagulants

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability	6.5%	80%	50%	62%
Time to peak plasma concentration	0.5-2 hr	2-4 hr	3-4 hr	1-2 hr
Half-life	12-14 hr	7-13 hr	8-13 hr	8-10 hr
Routine monitoring	No	No	No	No
Elimination	80% renal	67% renal	25% renal	50% renal
Potential drug interactions*	P-glycoprotein inhibitors and inducers	Inhibitors of CYP3A4 and P-glycoprotein	Inhibitors of CYP3A4 and P-glycoprotein	Strong P-glycoprotein inhibitors

* Inhibitors of p-glycoprotein include ketoconazole, quinidine, and amiodarone. Inhibitors of CYP3A4 include macrolide antibiotics, ritonavir. Rifampicin is an inducer of p-glycoprotein and CYP3A4.

Devabhakthuni S, et al., J Pharm Prac, 2015

Clinical Indications for DOAC's

- Thromboprophylaxis after orthopaedic surgery
- Stroke prevention in patients with atrial fibrillation
- Treatment of acute venous thromboembolism

- Treatment of venous thromboembolism in patients with cancer

Patient presentation

- 45 year old woman presents with progressive dyspnea, is found to have bilateral segmental pulmonary emboli
- She is treated with rivaroxaban, 15 mg twice daily for three weeks, then switched to 20 mg daily
- She is referred to see you after completing six months of anticoagulant therapy, at which time she feels back to her baseline level of activity

- What would you recommend for her now?

Treatment Duration for Unprovoked VTE: ACCP Guidelines

- In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation … for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).
- In patients with a first unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Kearon C, et al. Chest, 2016; 149: 315-52

Unprovoked VTE: how long to treat?

Apixaban 10 mg BID x 7 d; Rivaroxaban 15 mg BID x 21 d; LMWH for min 5 d* and INR ≥ 2 for 2 d

Apixaban 5 mg BID; Dabigatran 150 mg BID; Edoxaban 60 mg daily†; Rivaroxaban 20 mg daily; Warfarin for INR 2-3

What are the best options for indefinite anticoagulation in order to provide effective anticoagulation with minimal bleeding risk?

The NEW ENGLAND JOURNAL of MEDICINE

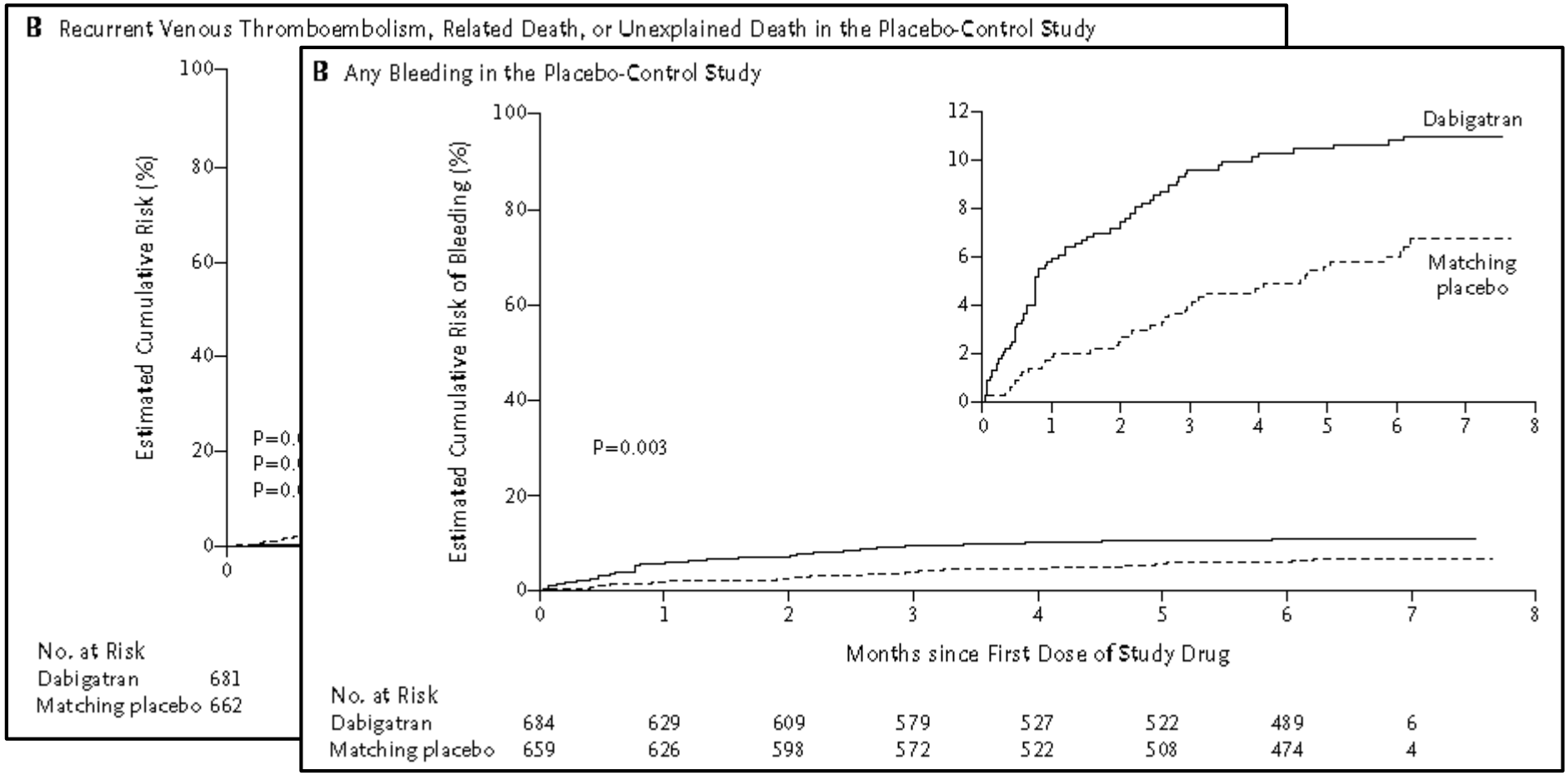
ORIGINAL ARTICLE

Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism

Sam Schulman, M.D., Ph.D., Clive Kearon, M.D.,
Ajay K. Kakkar, M.B., B.S., Ph.D., Sebastian Schellong, M.D.,
Henry Eriksson, M.D., Ph.D., David Baanstra, M.Sc.,
Anne Mathilde Kvamme, M.Sc.Pharm., Jeffrey Friedman, M.D.,
Patrick Mismetti, M.D., and Samuel Z. Goldhaber, M.D.,
for the RE-MEDY and the RE-SONATE Trials Investigators*

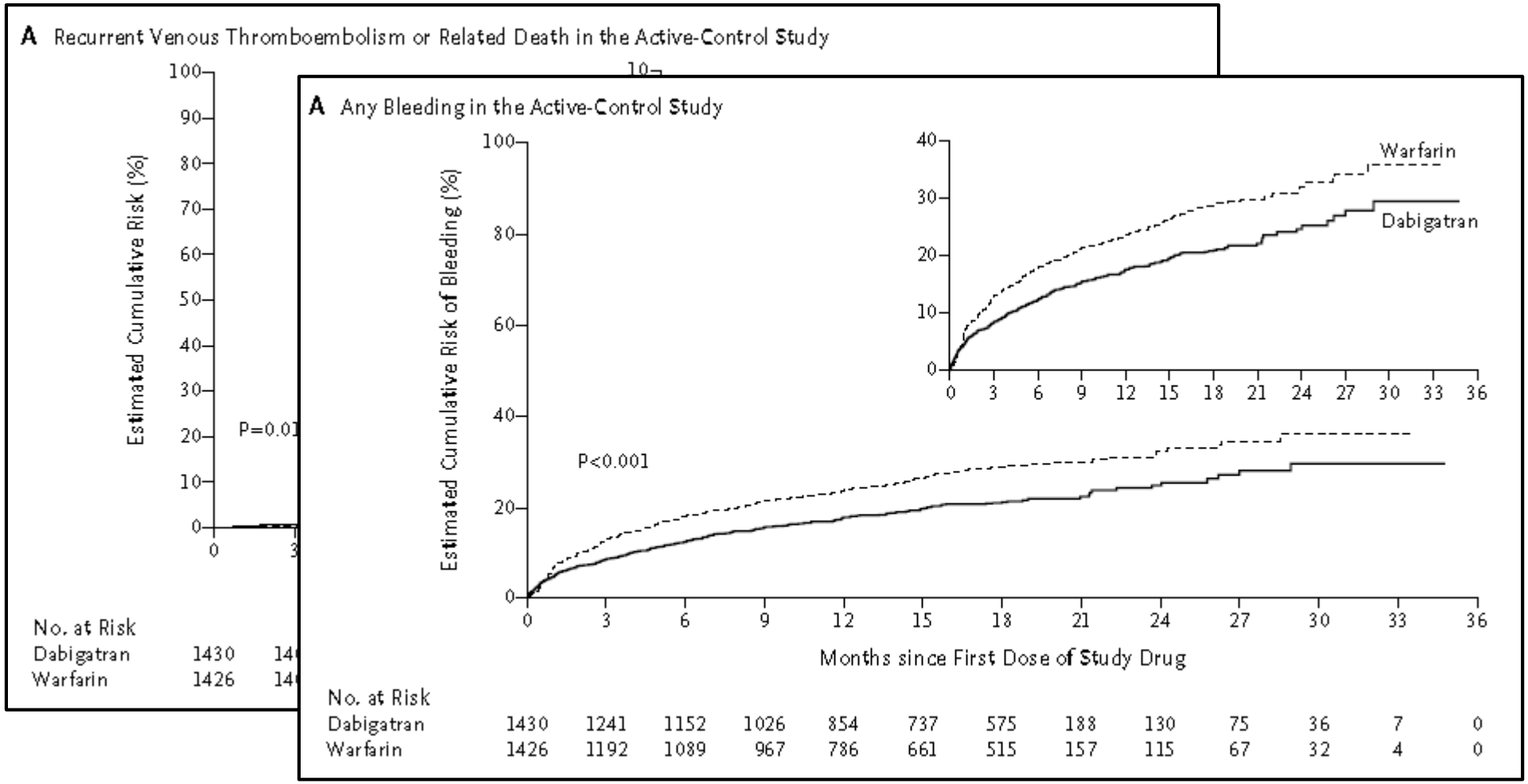
Schulman S, *et al*. N Engl J Med; 2013; 368: 709-18

Dabigatran vs. placebo for indefinite anticoagulation



Schulman S, *et al*. N Engl J Med; 2013; 368: 709-18

Dabigatran vs. warfarin for indefinite anticoagulation



Schulman S, *et al*. N Engl J Med; 2013; 368: 709-18

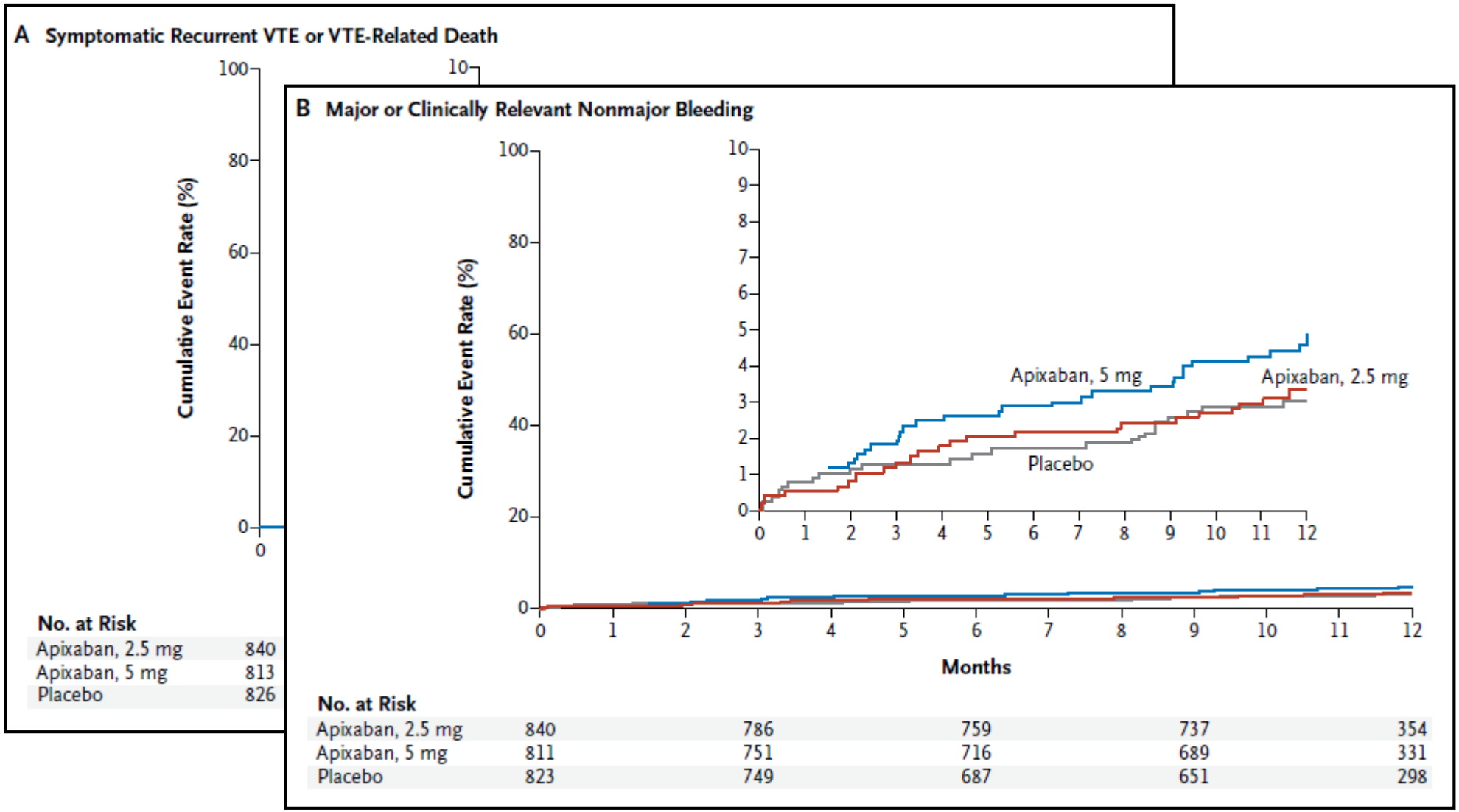
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 21, 2013 VOL. 368 NO. 8

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

AMPLIFY EXTEND



Agnelli G, *et al*. N Engl J Med; 2013; 368: 699-708

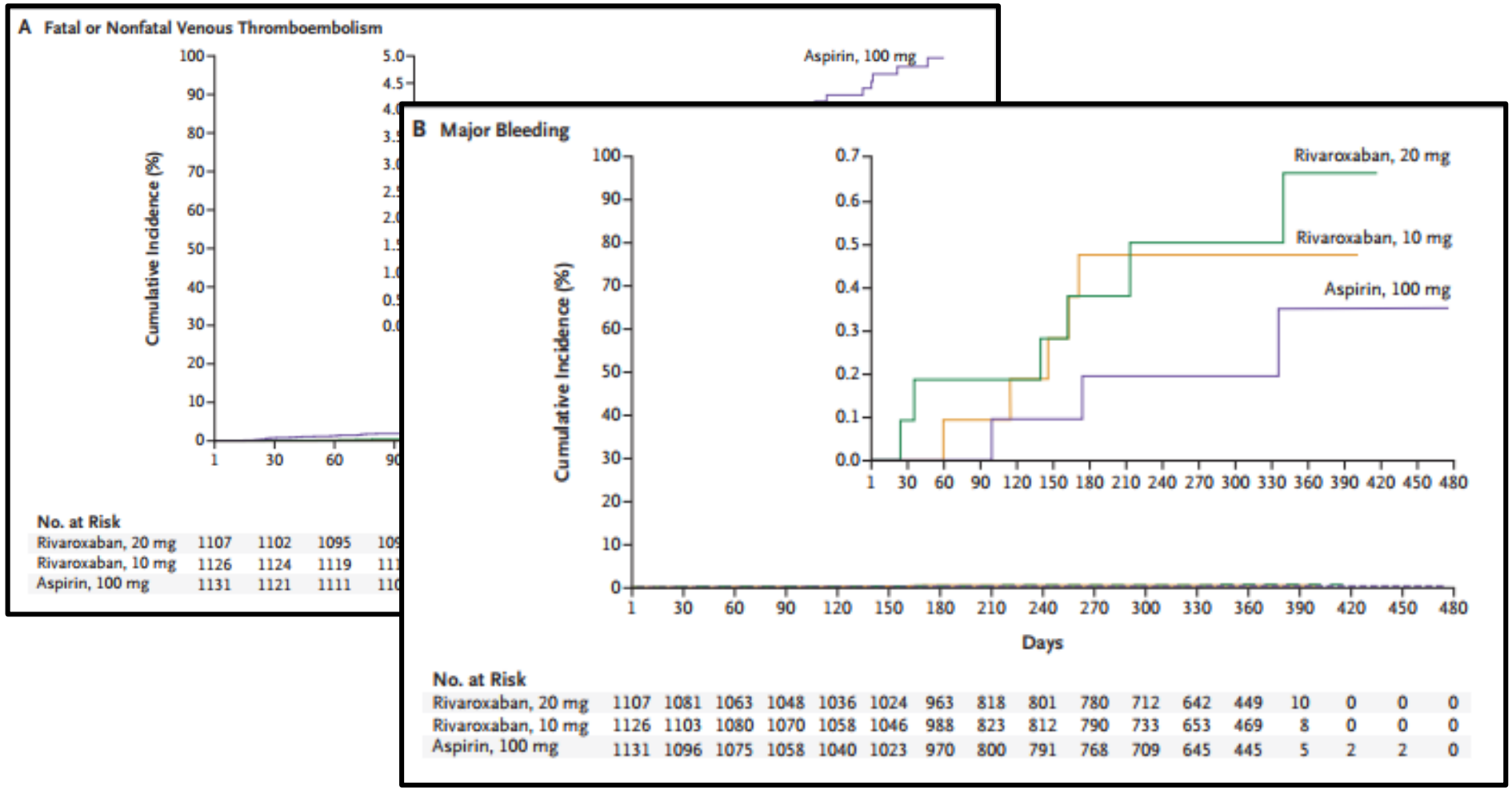
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 30, 2017 VOL. 376 NO. 13

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

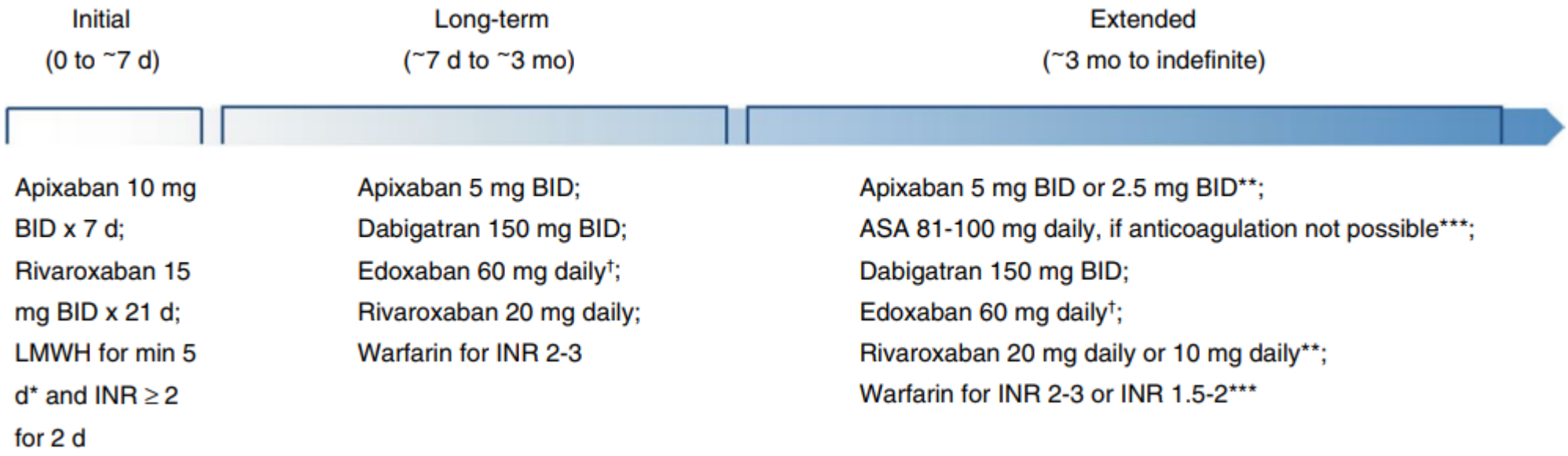
J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

EINSTEIN-CHOICE



Weitz JI, *et al*, N. Engl J Med, 2017; 376: 1211-22

Unprovoked VTE: how long to treat?

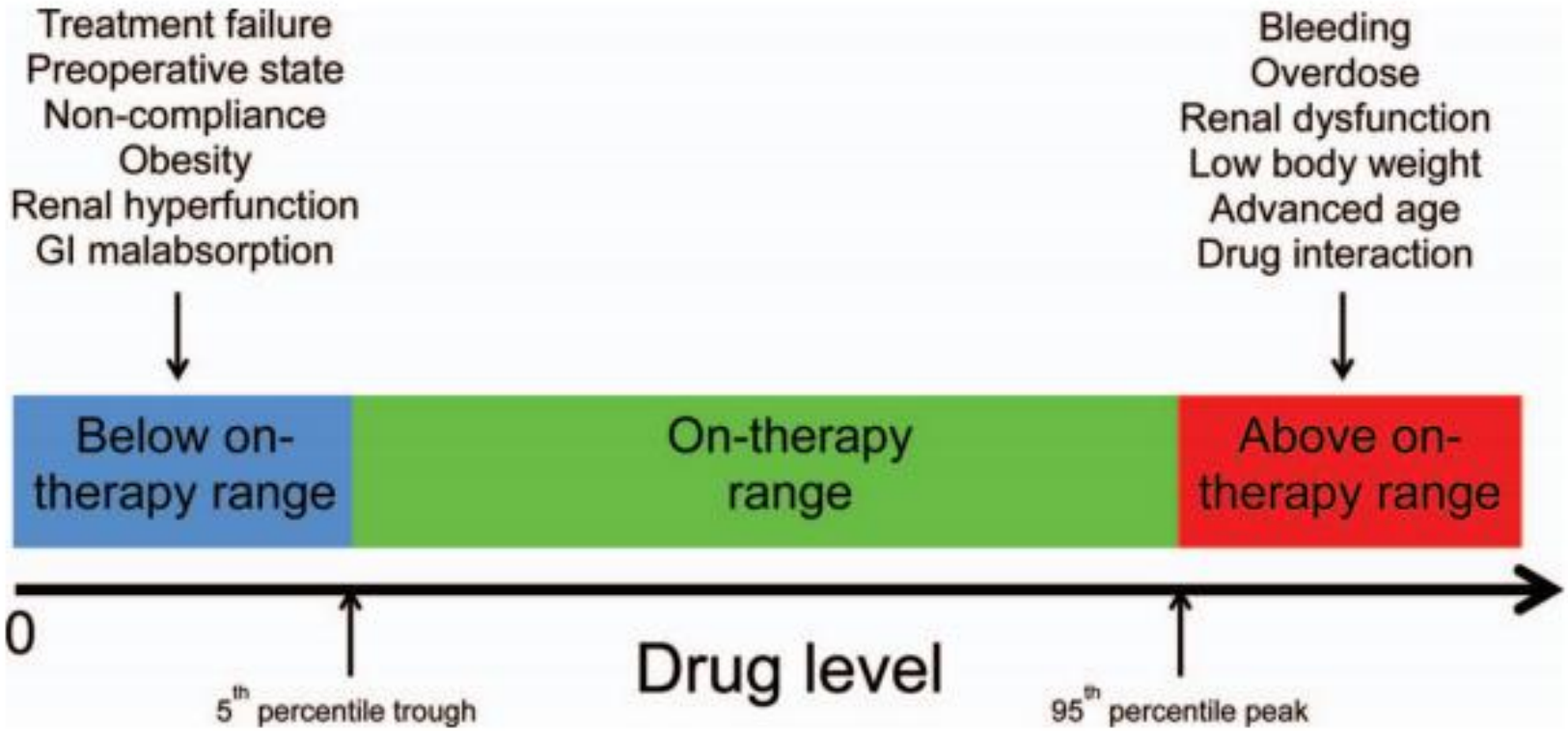


Patient 2 presentation

- A 72 year old man developed an unprovoked left leg DVT from the common femoral vein to the popliteal vein
- He is started on apixaban 10 mg twice daily for 7 days, and is now on 5 mg twice daily
- He is also on aspirin 81 mg daily for a bare metal stent placed in his right coronary artery two years ago
- He complains about increased bruising and two episodes of epistaxis since starting the apixaban

- How could you assess this patient's apixaban level?

Why might one want to measure a DOAC level?



Cuker A and Siegal D. Hematology 2015, 2015; 117-24

Laboratory Testing for DOACs

- Screening coagulation tests

Coagulation Assay	Relationship to Expected 'On Therapy' Range	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
APTT					
	Below	Normal or prolonged[a]	Normal limits	Normal limits	Normal limits
	Within	Prolonged	Normal or prolonged[b]	Normal or prolonged[b]	Normal limits
	Above	Prolonged	Normal or prolonged[b]	Prolonged	Normal or prolonged[c]
PT/INR					
	Below	Normal limits	Normal limits	Normal limits	Normal limits
	Within	Normal or prolonged[d]	Normal or prolonged	Normal or prolonged[e]	Normal or prolonged[f]
	Above	Normal or prolonged[d]	Normal or prolonged	Normal or prolonged[e]	Normal or prolonged[f]

Samuelson BT, et al. Chest, 2017; 151: 127-38

Laboratory Testing for DOACs

- Specialty coagulation tests

Coagulation Assay	Relationship to Expected 'On Therapy' Range	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dilute TT					
	Below	Normal or prolonged[g]	Not indicated	Not indicated	Not indicated
	Within	Prolonged[g]	Not indicated	Not indicated	Not indicated
	Above	Prolonged[g]	Not indicated	Not indicated	Not indicated
Anti-Xa					
	Below	Not indicated	Normal or increased[h]	Normal or increased[i]	Normal or increased
	Within	Not indicated	Increased	Increased	Increased
	Above	Not indicated	Increased	Increased[e]	Increased[j]

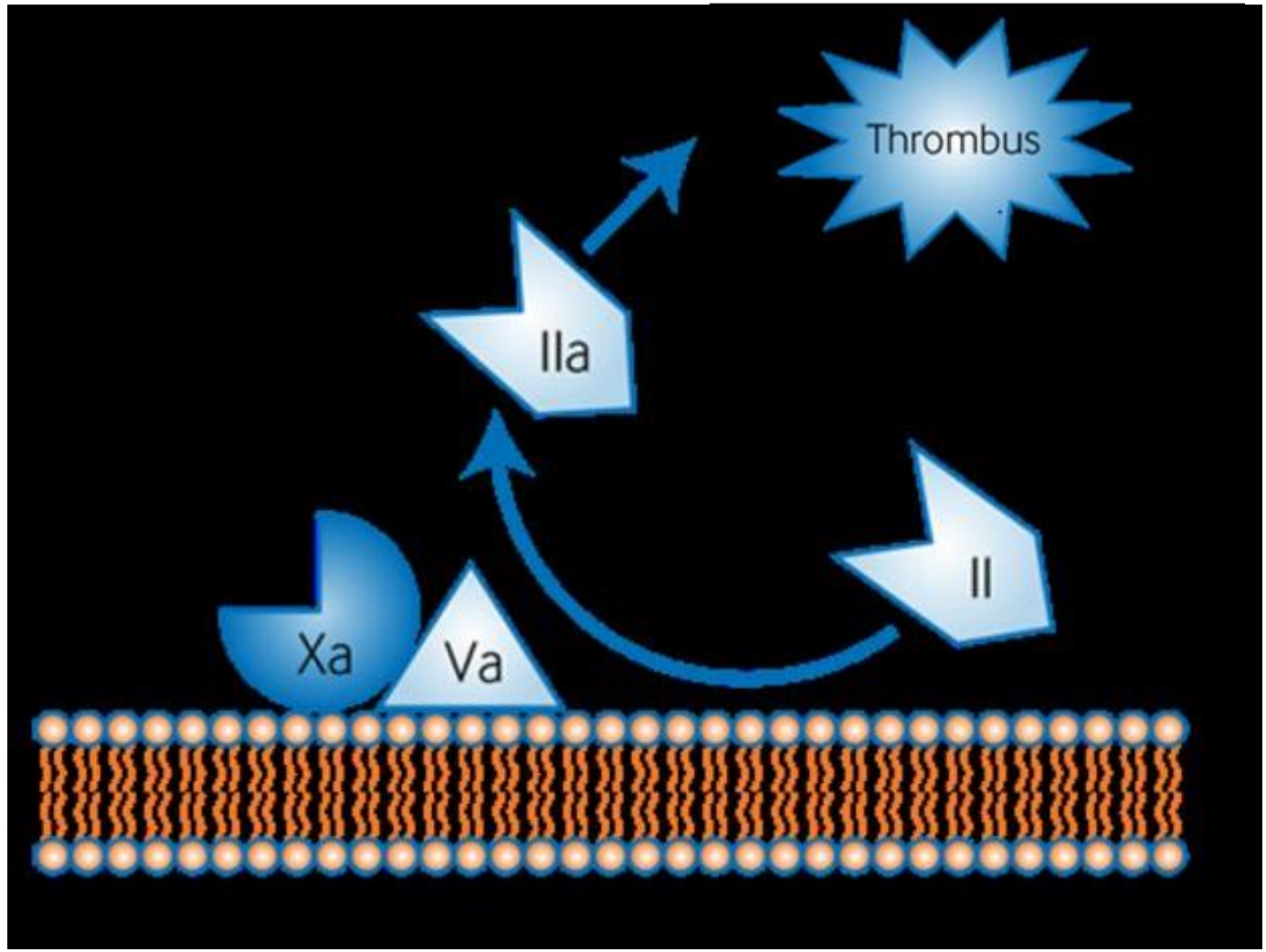
Samuelson BT, et al. Chest, 2017; 151: 127-38

Patient 2 Presentation

- Two days later, the patient is in the emergency department with an acute hemorrhagic stroke

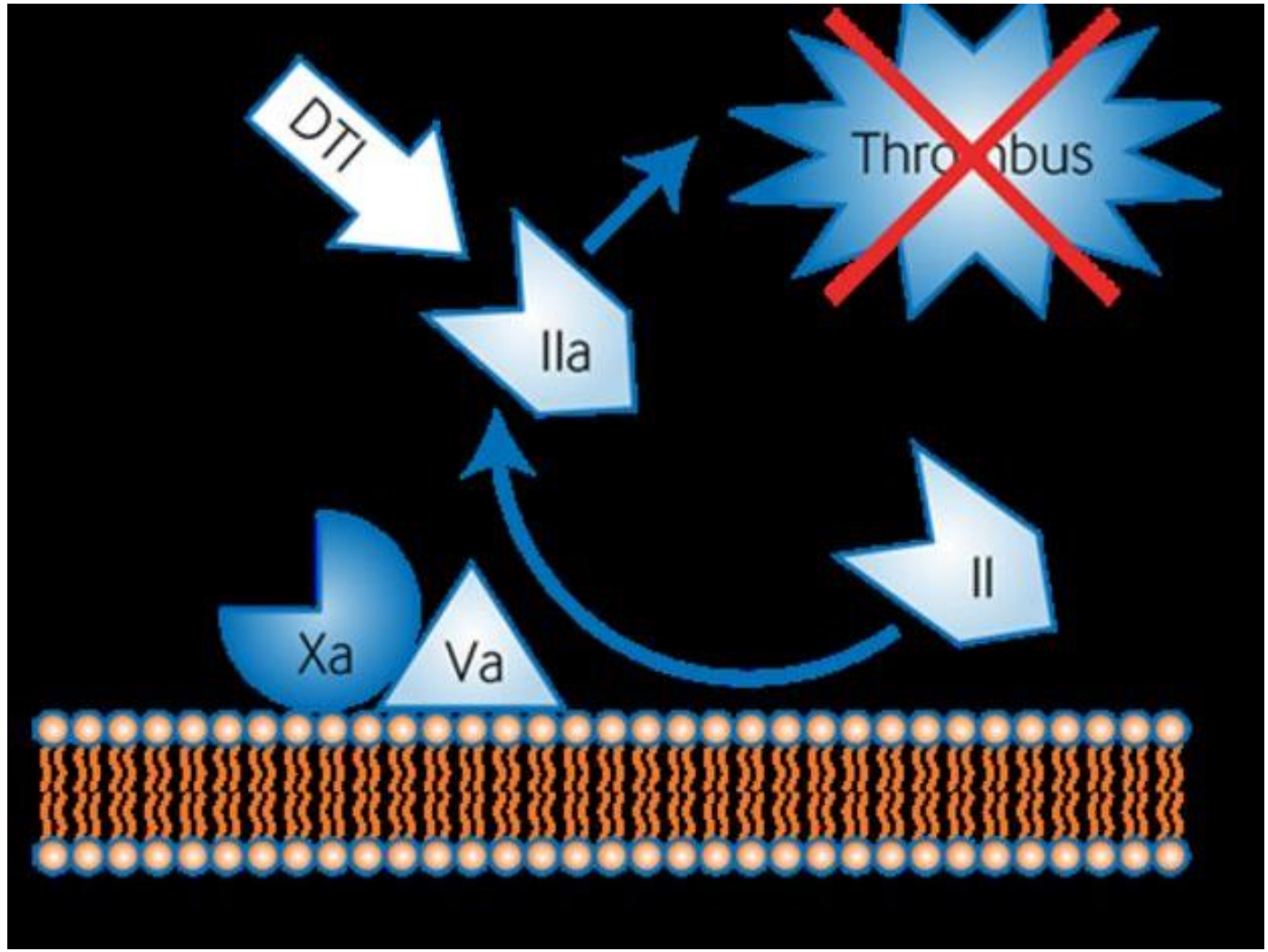
- What can be done to reverse his anticoagulant effect?

Hemostatic reactions and thrombosis



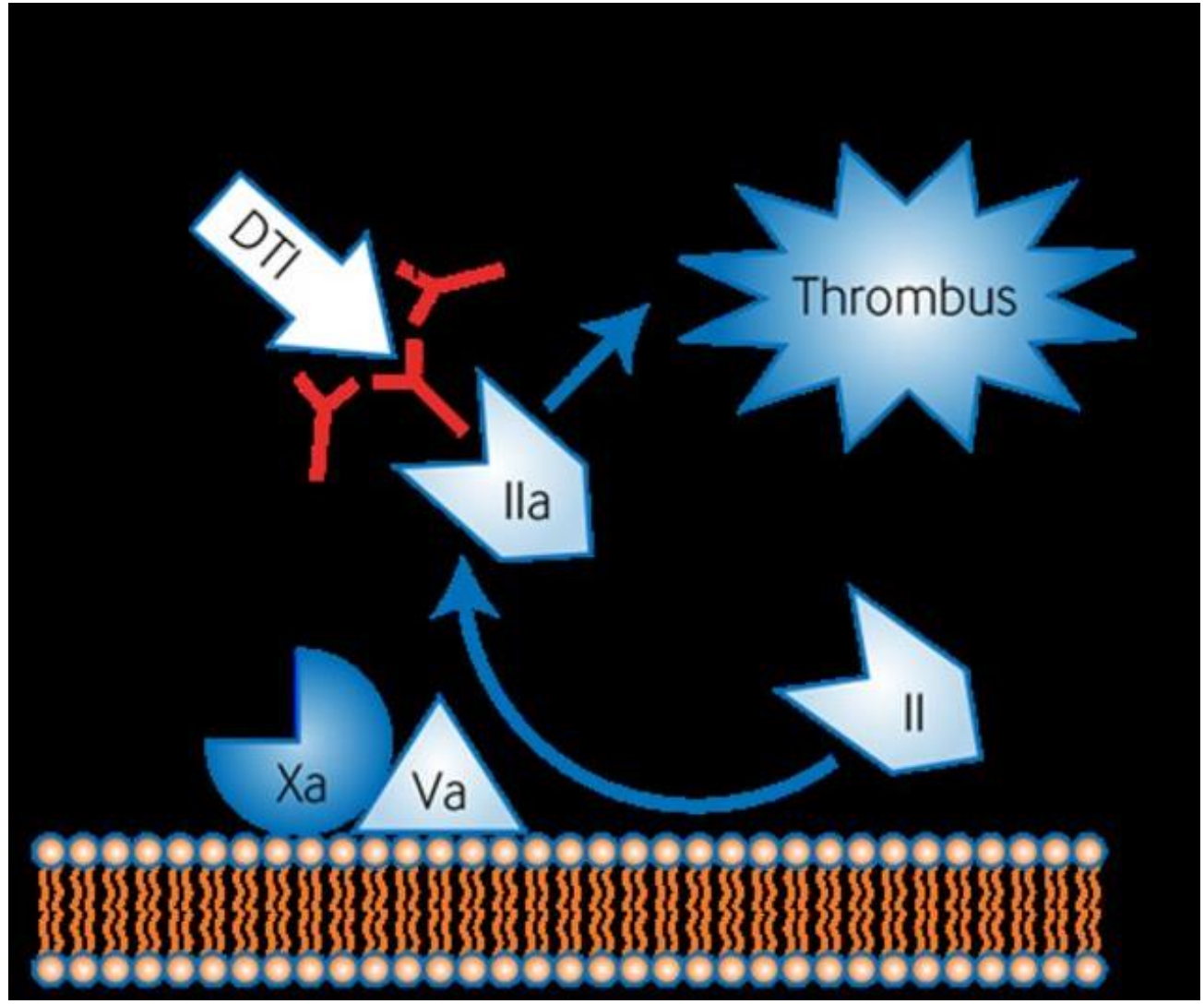
Burnett A, et al. BMJ, 2017; 357: 2216

Inhibiting thrombin blocks hemostasis



Burnett A, et al. BMJ, 2017; 357: 2216

Reversing Dabigatran: Antibodies



Burnett A, et al. BMJ, 2017; 357: 2216

The NEW ENGLAND JOURNAL of MEDICINE

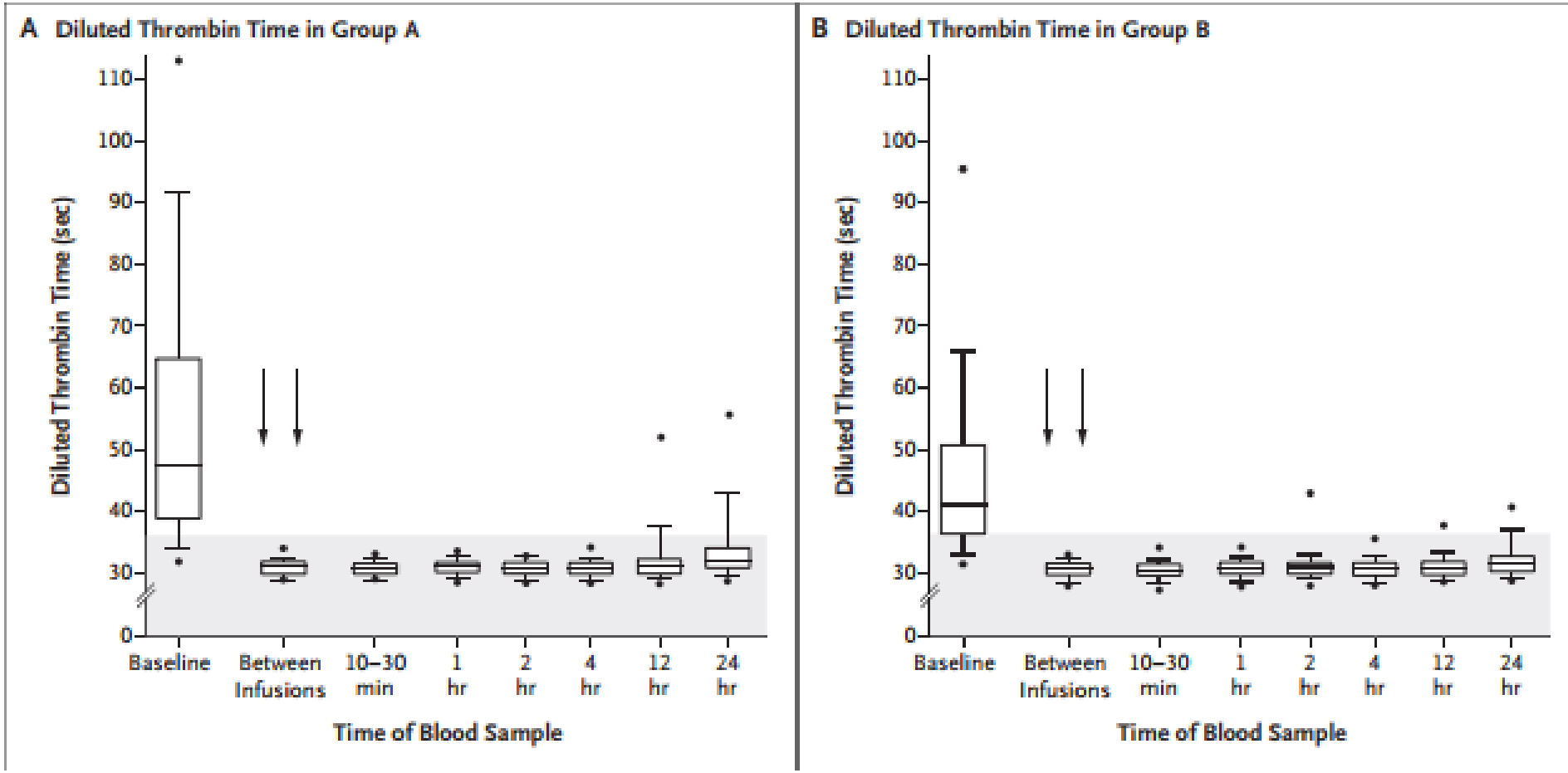
ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

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

Pollack C, et al. N Engl J Med, 2017; 377: 431-41

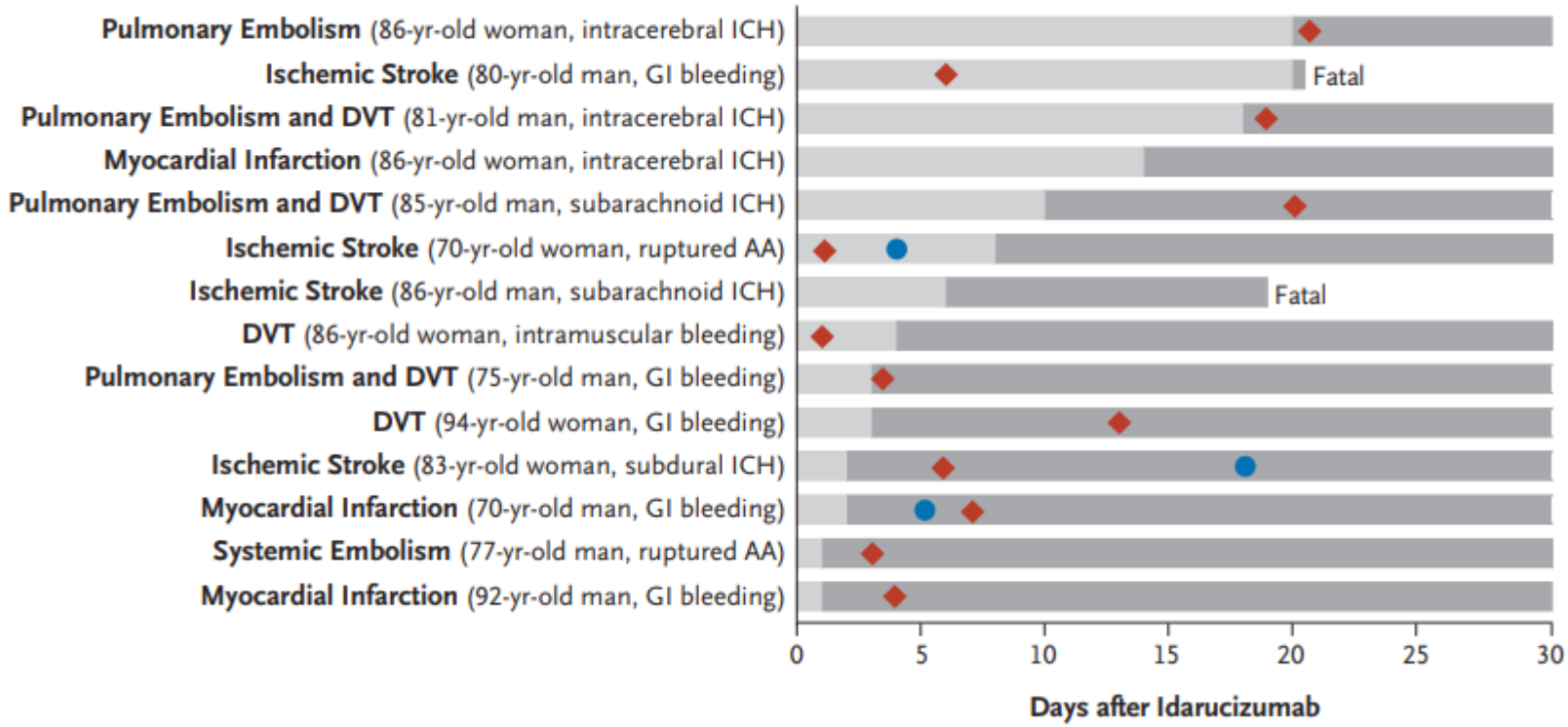
Idarucizumab for Dabigatran Reversal



Pollack C, et al. N Engl J Med, 2017; 377: 431-41

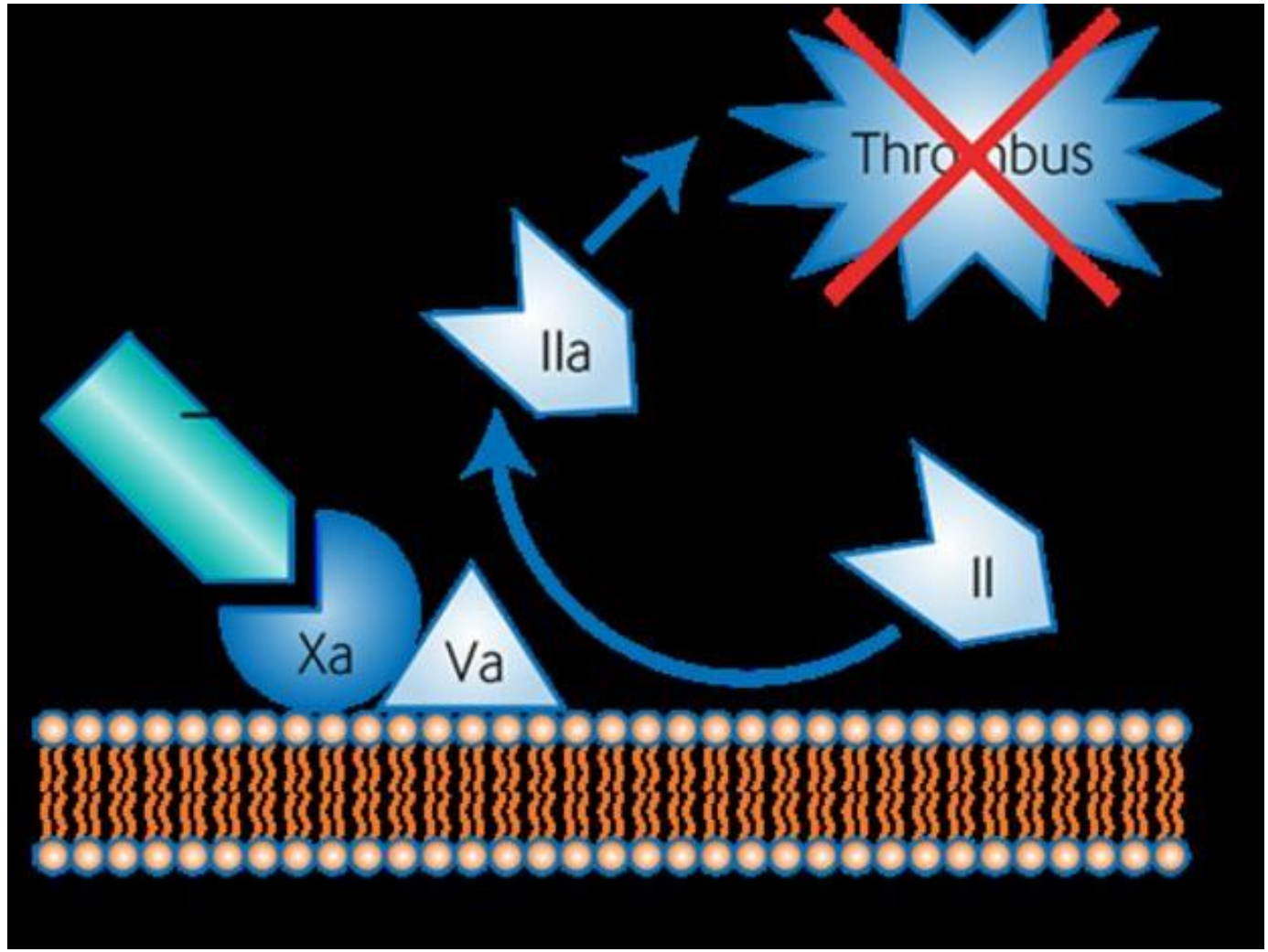
Thrombotic Events in Patients Receiving Idarucizumab

- 301 patients taking dabigatran treated for uncontrolled bleeding



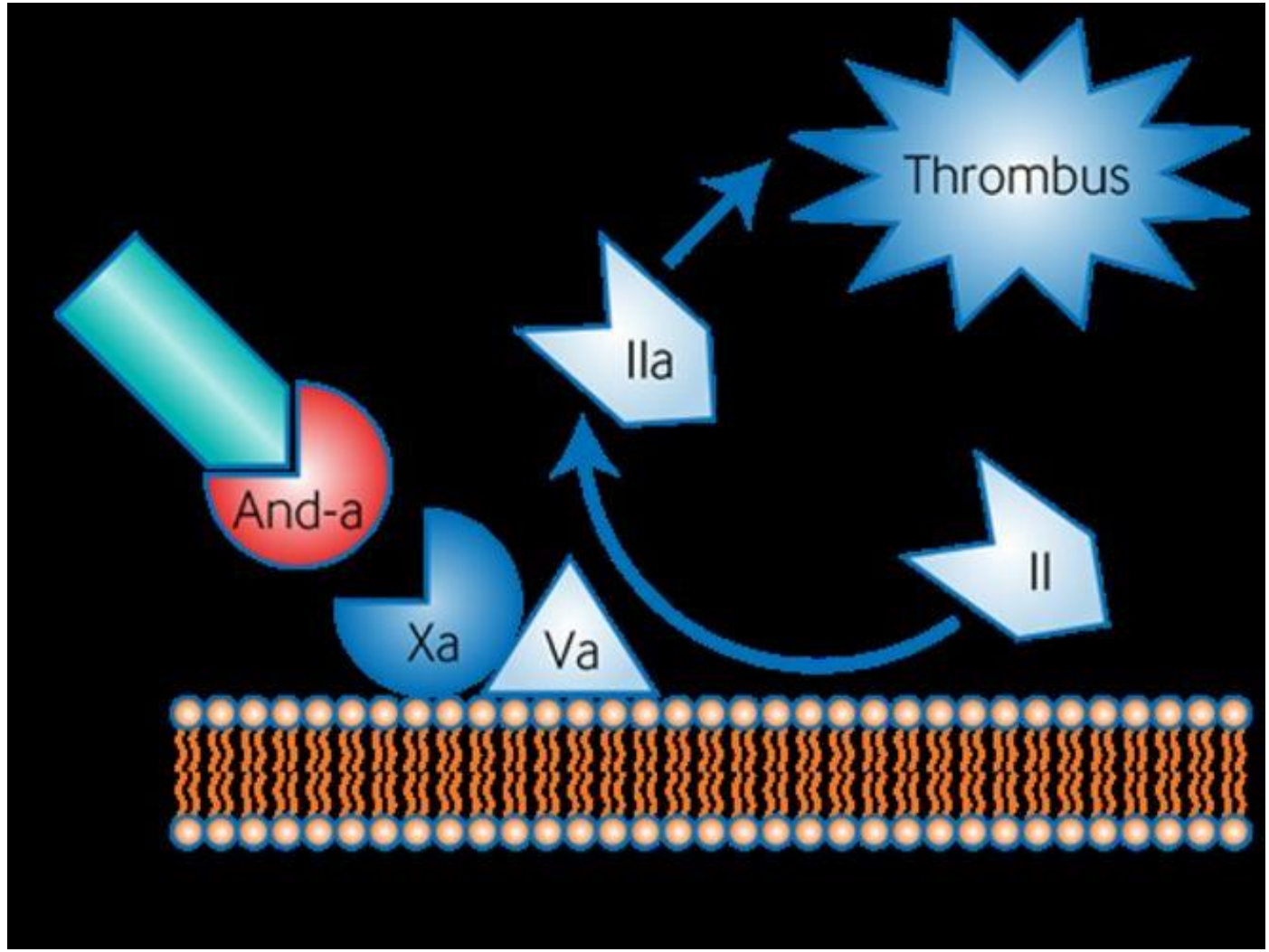
Pollack C, et al. N Engl J Med, 2017; 377: 431-41

Inhibiting factor Xa blocks hemostasis



Burnett A, et al. BMJ, 2017; 357: 2216

Reversing Factor Xa Inhibitors: Decoys



Burnett A, et al. BMJ, 2017; 357: 2216

The NEW ENGLAND JOURNAL of MEDICINE

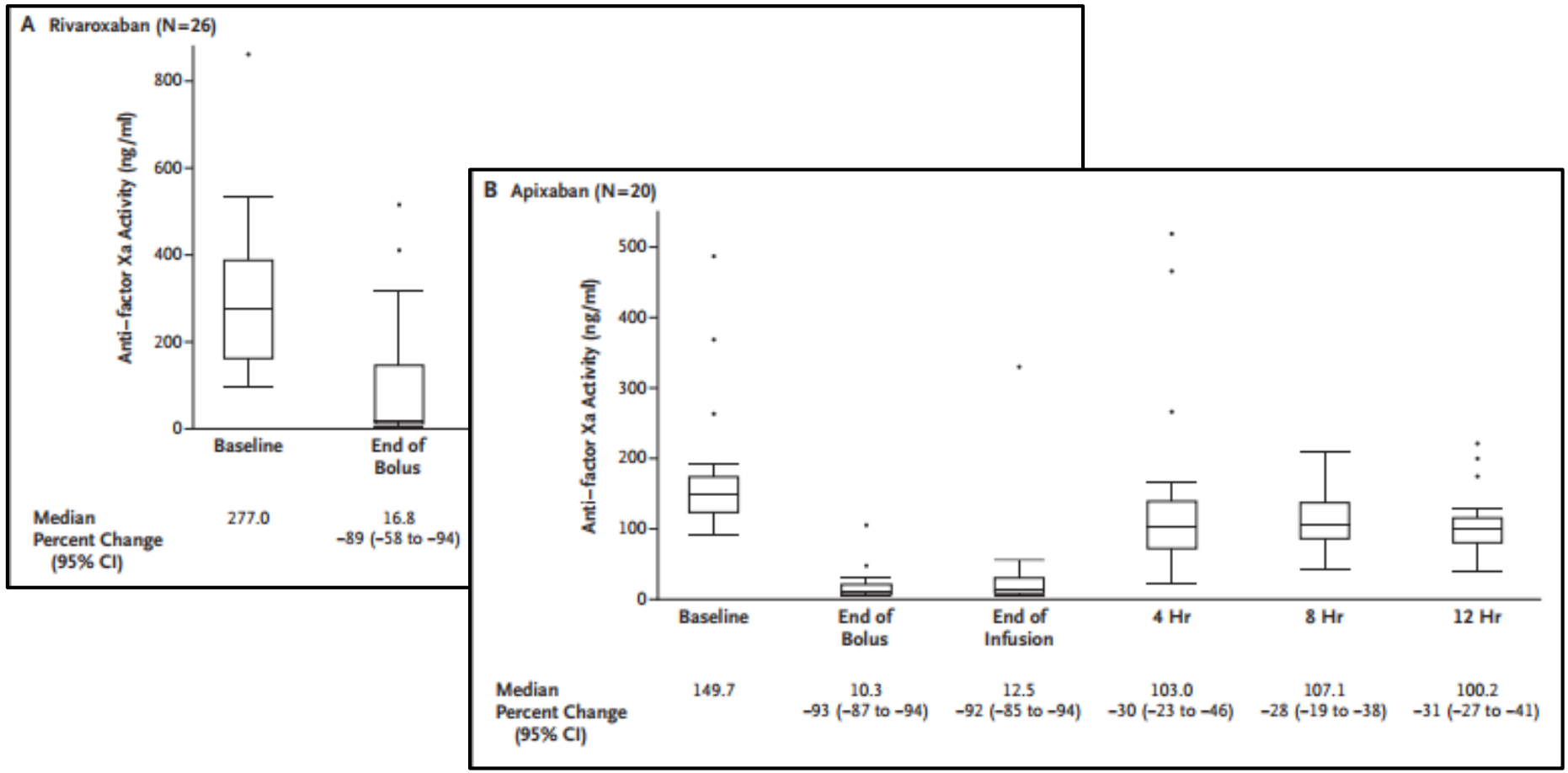
ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

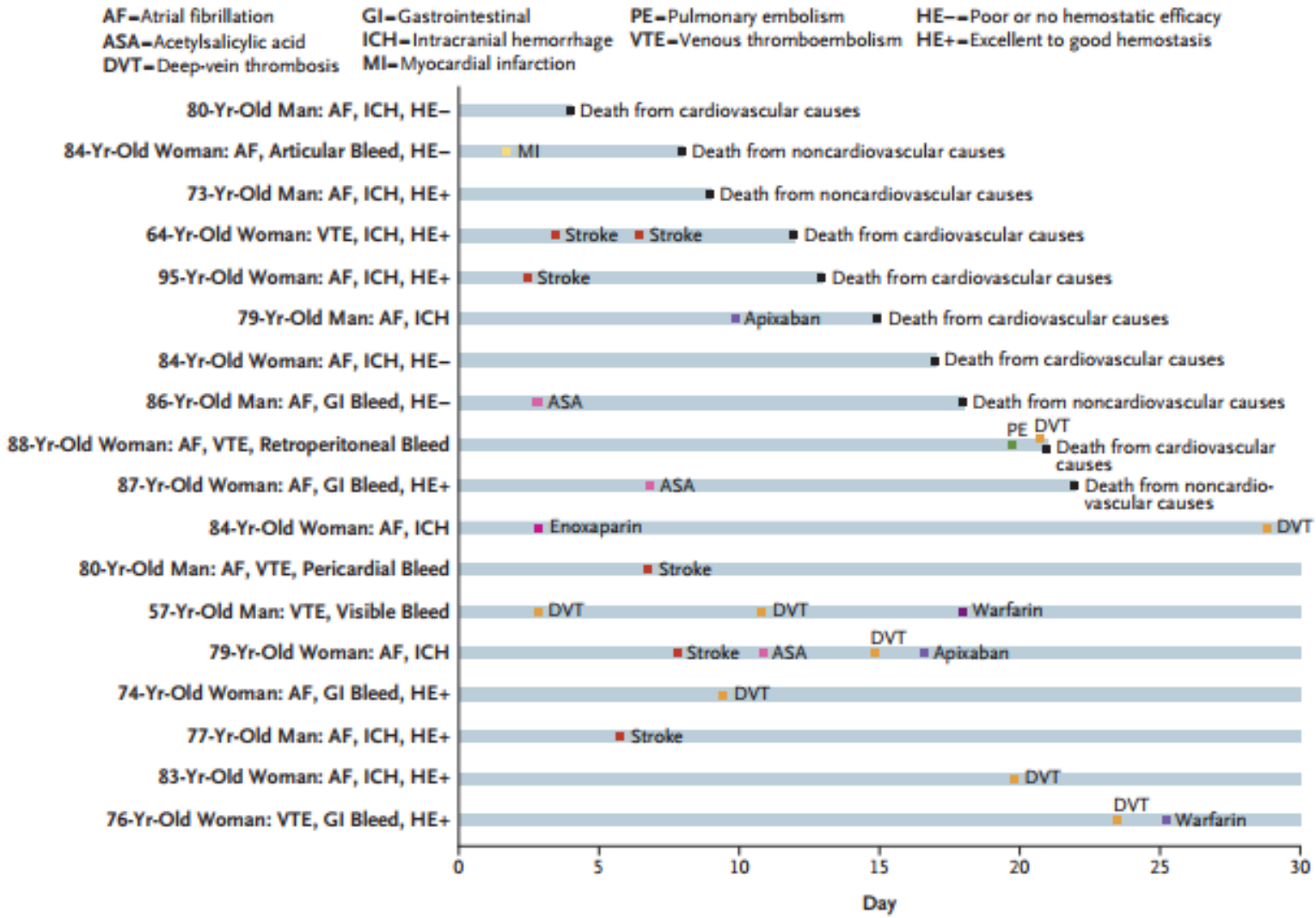
Connolly SJ, et al. N Engl J Med, 2016; 375: 1131-41

Andexanet Alfa for Acute Bleeding with Factor Xa Inhibitors



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

TE or Death with Andexanet Alfa



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

Approved Products

Resources for You

- Approved Cellular and Gene Therapy Products
- Licensed Biological Products with Supporting Documents

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo)

STN: BLA 125586
Proper Name: coagulation factor Xa (recombinant), inactivated-zhzo
Trade Name: ANDEXXA
Manufacturer: Portola Pharmaceuticals, Inc.
Indication:

- For patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

Product Information

- Package Insert - ANDEXXA (PDF - 582KB)
- Demographic Subgroup Information – coagulation factor Xa (recombinant), inactivated-zhzo [ANDEXXA] (PDF - 2.1MB)
  Refer to Section 1.1 of the Clinical Review Memo for information about participation in the clinical trials and any analysis of demographic subgroup outcomes that is notable.

Andexanet alfa: dosing and price

Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
FXa inhibitor			
Apixaban			
Rivaroxaban	>10 mg/unknown	High dose	

Pricing: US

Solution (reconstituted) (Andexxa Intravenous)

100 mg (per each): $3,300.00

Andexanet alfa Dosing Regimens:

Low dose: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed 2 minutes later by 4 mg/minute IV infusion for up to 120 minutes

High dose: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed 2 minutes later by 8 mg/minute IV infusion for up to 120 minutes

Source: Lexicomp, accessed 10 August 2018

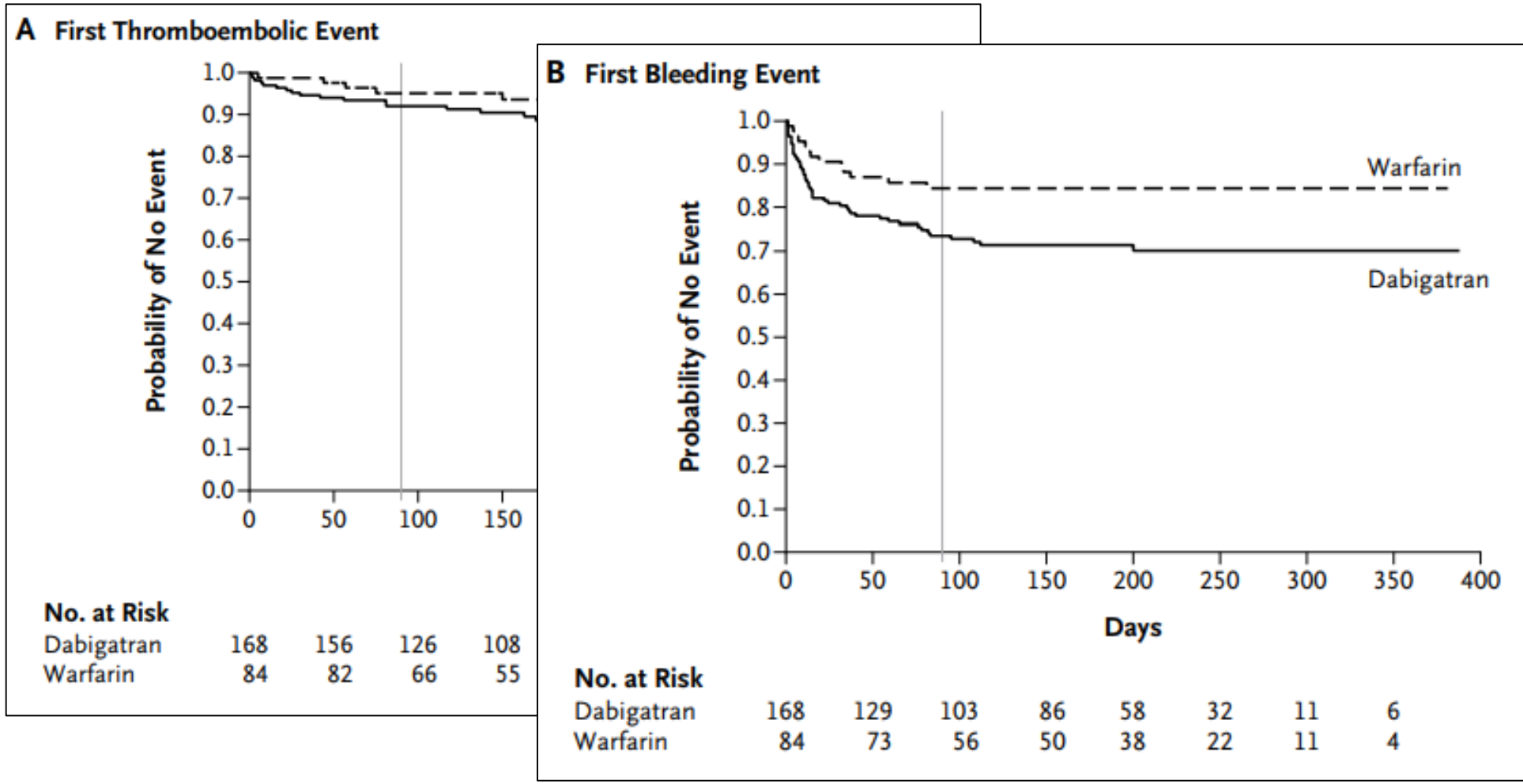
Other options to reverse DOAC's…

- Time
- Prothrombin complex concentrates
- Fresh frozen plasma is generally not helpful

- Hemodialysis has been used to acutely remove dabigatran
- Plasma exchange has been used to acutely remove rivaroxaban

What other indications are being explored for the direct oral anticoagulants?

RE-ALIGN



Eikelboom JW, et al. N Engl J Med, 2013; 369: 1206-14

COMPASS

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  vs… …n
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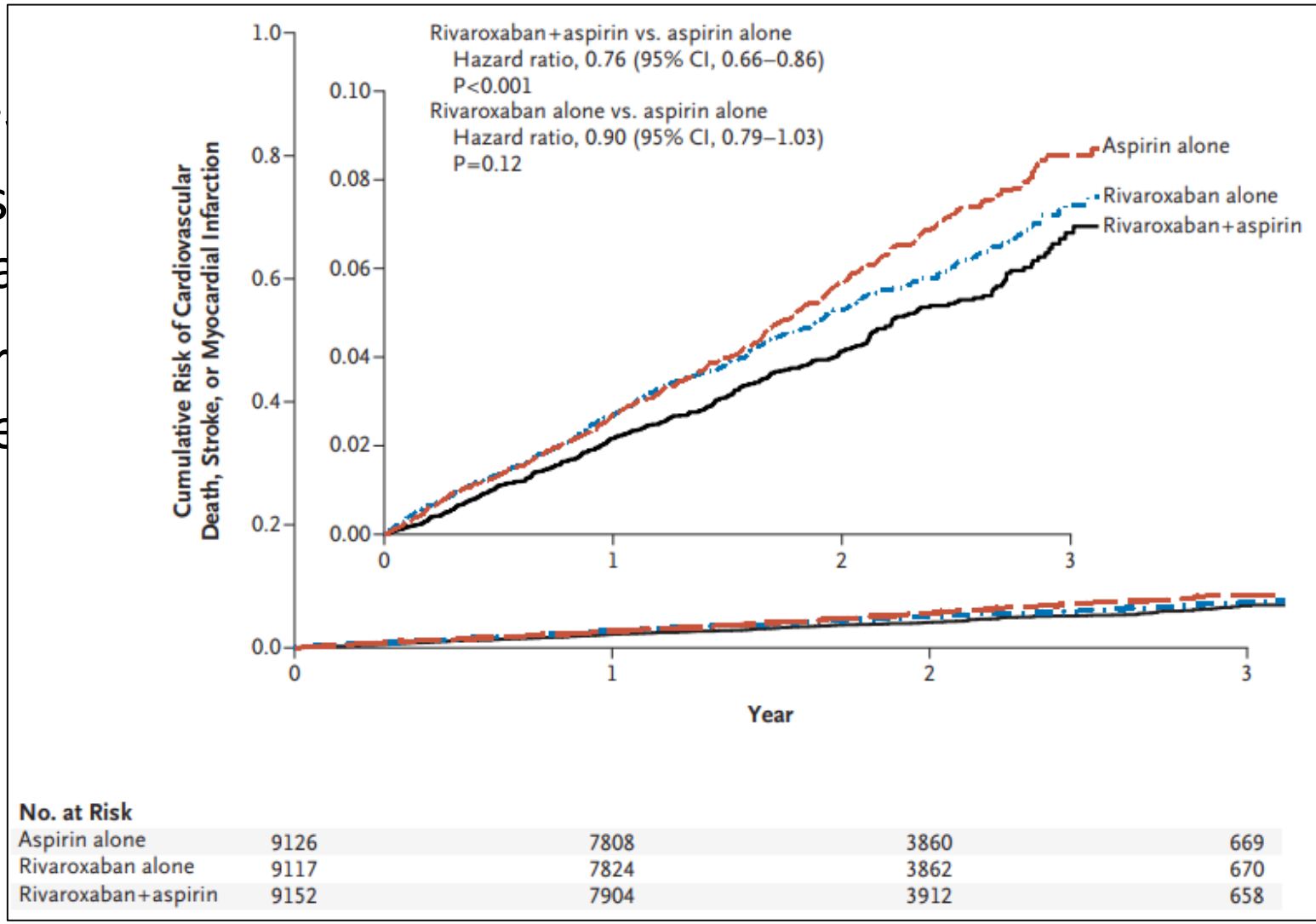


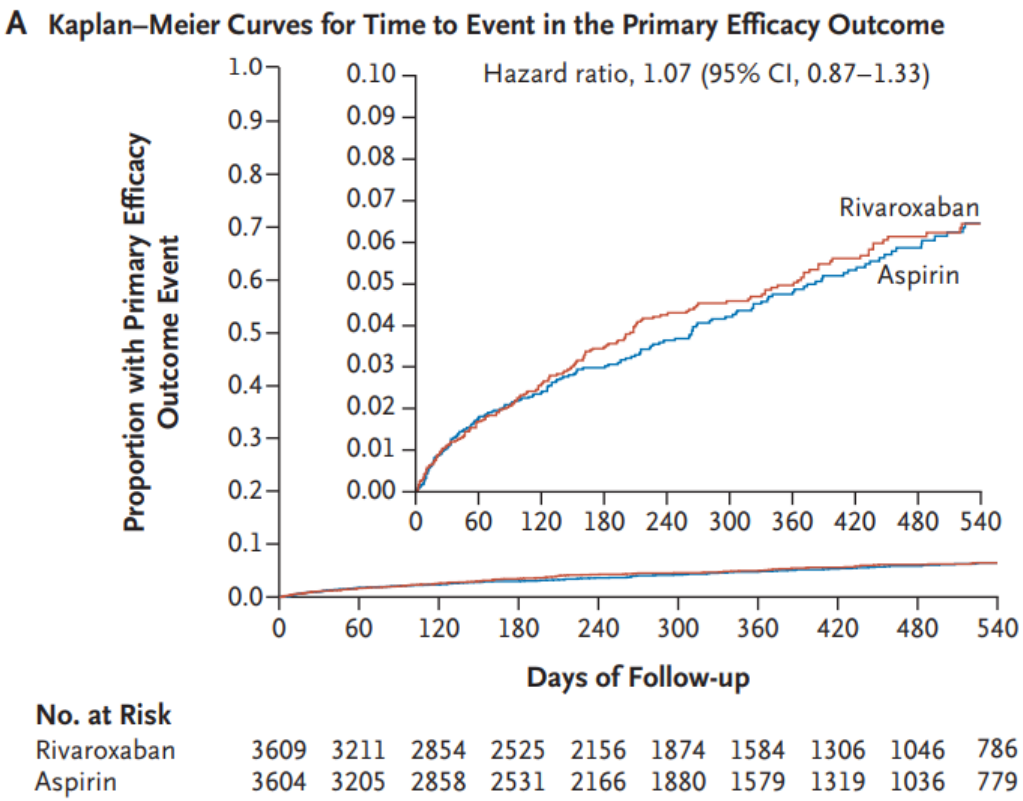
Eikelboom JW, et al. N Engl J Med, 2017; 377: 1319-30

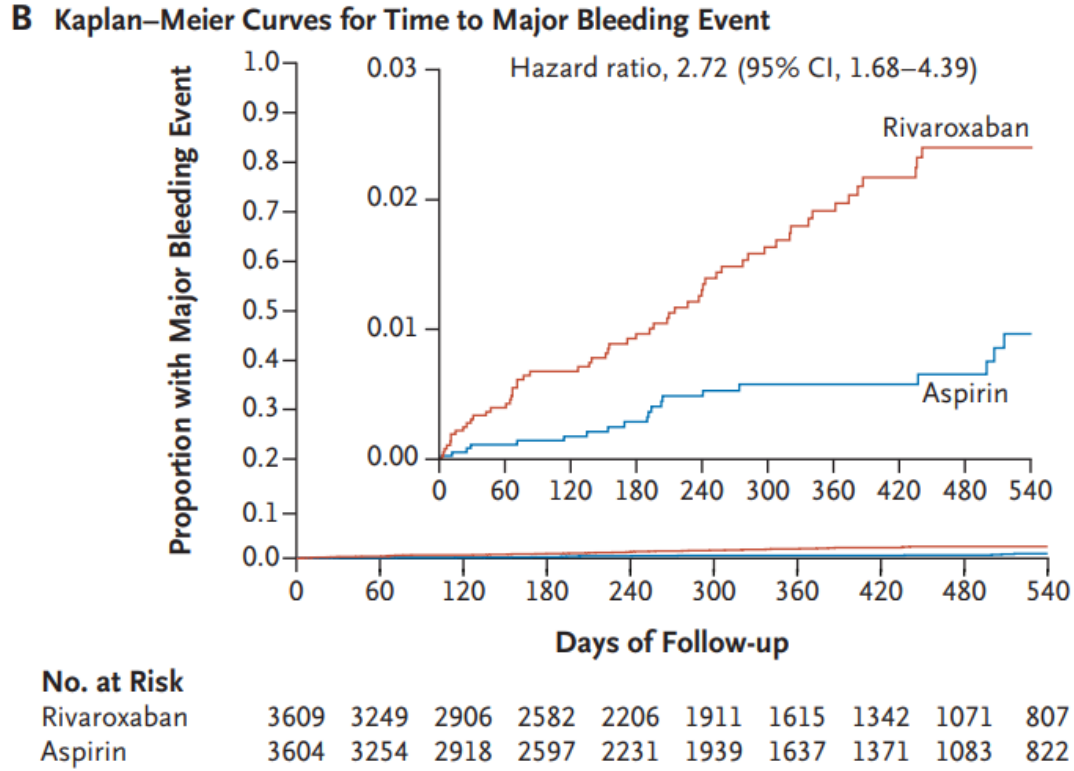
COMPASS

Variable	Rivaroxaban + ASA (n=9152)	ASA alone (n=9126)	Hazard ratio (95% CI), p value
Major bleeding	288 (3.1%)	170 (1.9%)	1.70 (1.40-2.05), p<0.001
Site: GI	140 (1.5%)	65 (0.7%)	2.15 (1.60-2.89), p<0.001
Minor bleeding	838 (9.2%)	503 (5.5%)	1.70 (1.52-1.90), p<0.001

Eikelboom JW, et al. N Engl J Med, 2017; 377: 1319-30

NAVIGATE ESUS





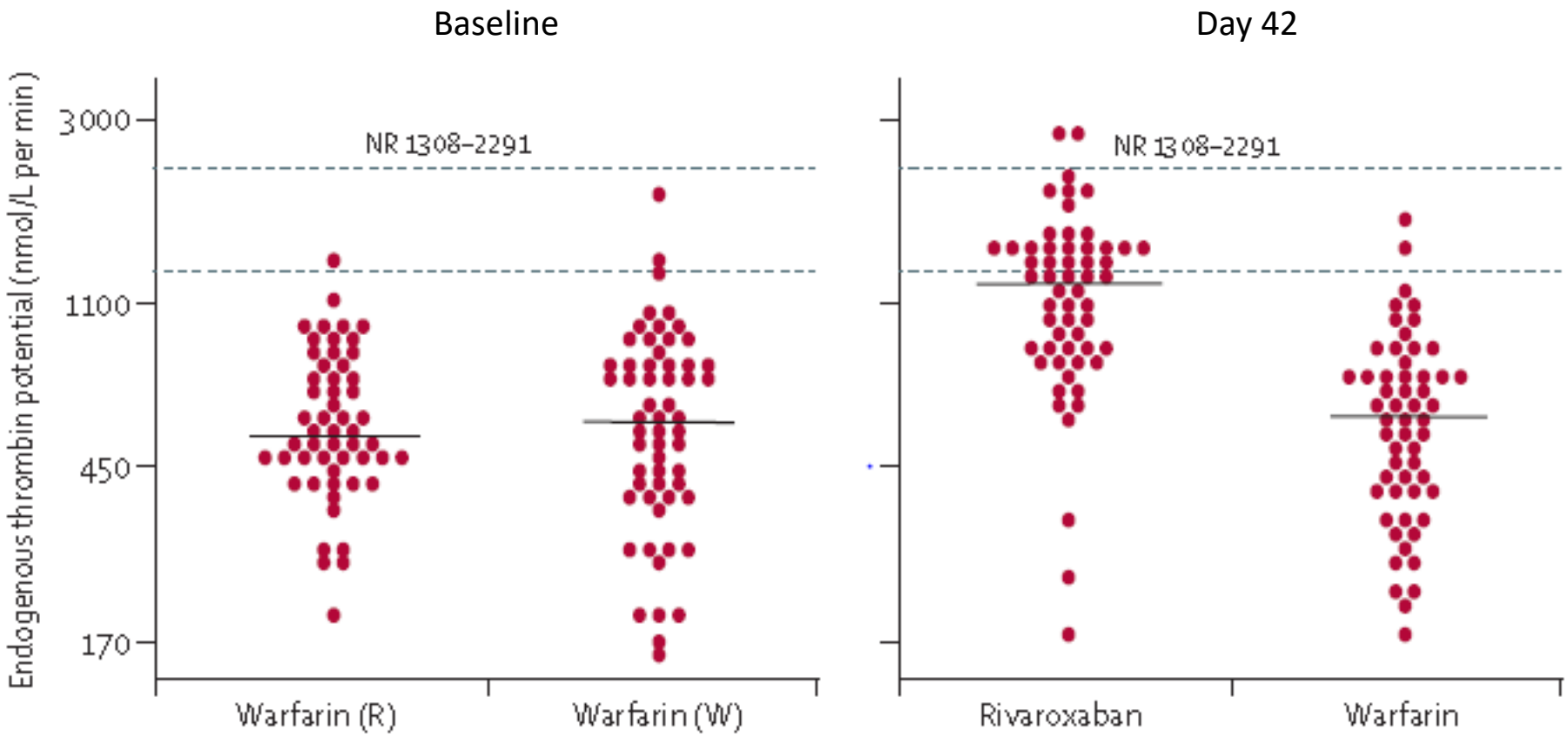
Hart RG, et al. N Engl J Med, 2018; 378: 2191-201

Patient presentation

- 28 year old woman with no prior medical history
- She sustains a left thalamic ischemic stroke
- She is started on anticoagulant therapy with enoxaparin, switched to apixaban prior to discharge

- Hypercoagulable workup revealed markedly positive results for a lupus anticoagulant, anticardiolipin antibody, and anti-β_2-glycoprotein I antibody

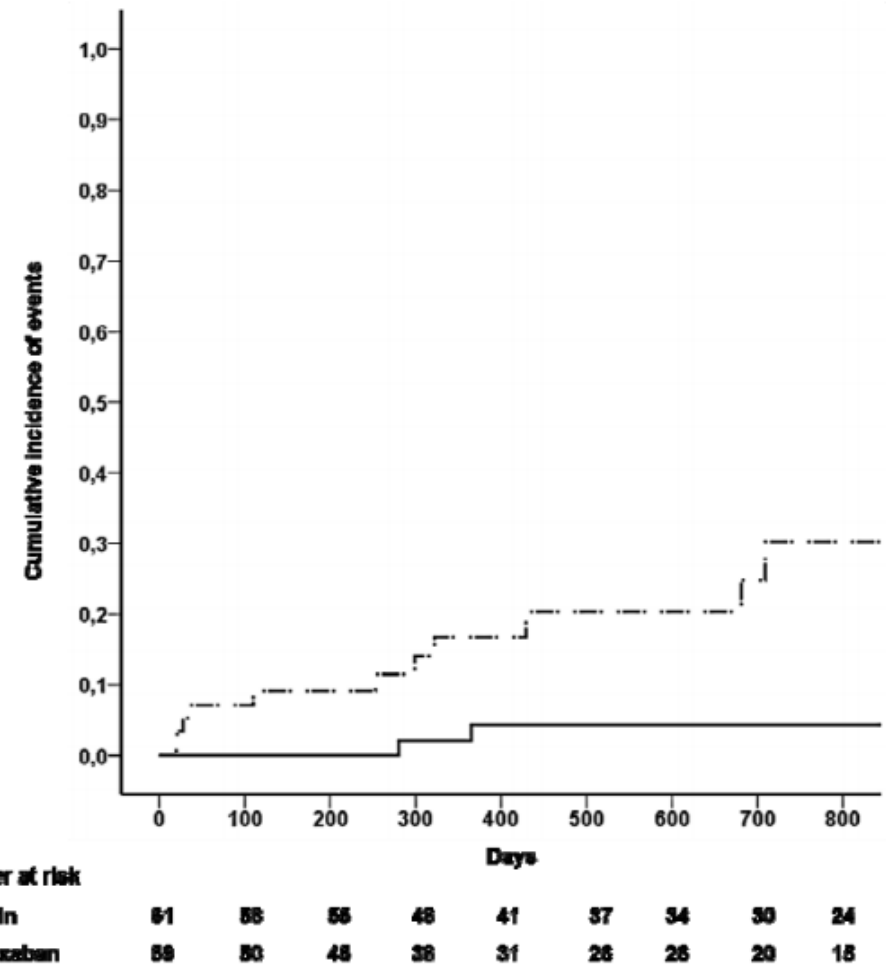
RAPS (Rivaroxaban in APS)



Cohen H, *et al*., Lancet Haematol, 2016; 3: e26-e36

TRAPS (Rivaroxaban in Thrombotic APS)

- 120 patients with ‘triple-positive’ APS randomized to rivaroxaban 20 mg/d vs warfarin, target INR 2-3
- Initial events included venous and arterial thromboembolism
- Study terminated early because of increased frequency of events in the rivaroxaban arm



Pengo V, et al. Blood, 2018; e-pub ahead of print

To summarize new indications…

- Prosthetic cardiac valves: NO
- Stable atherosclerotic vascular disease: Maybe, in selected, low-bleeding risk patients
- Ischemic stroke, non-cardioembolic: NO
- Antiphospholipid Syndrome: NO (for high-risk profile)

Questions?