Non-Malignant Hematology: What have we learned this year?

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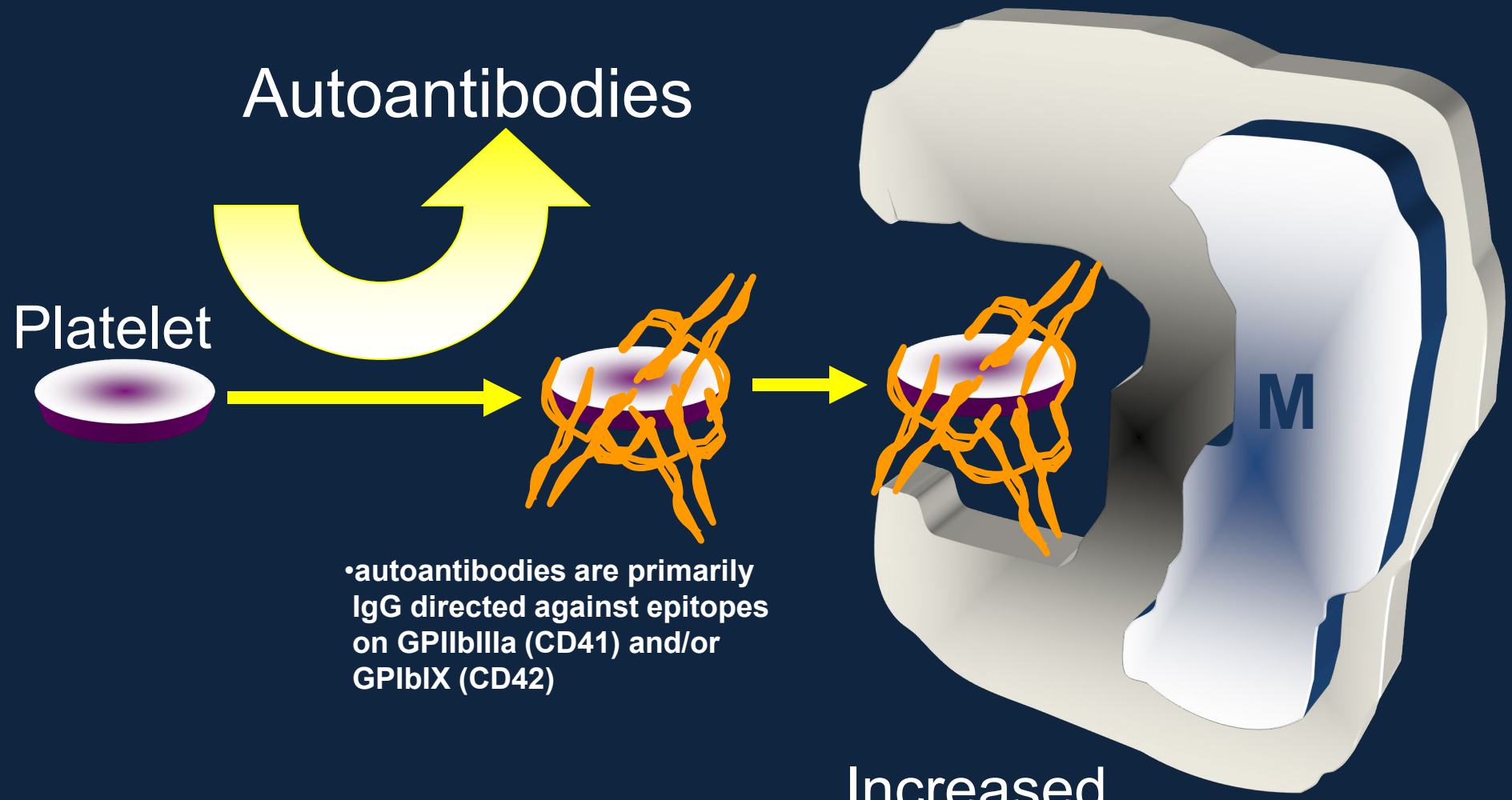
Disclosures

- Research- Baxalta, Bayer, NovoNordisk, Octapharma
- Advisory Boards-Baxalta, Bayer, Biogen, Biomarin, Genentech, NovoNordisk, Octapharma, Pfizer, Sangamo
- DSMB- NIH, Dimension, Octapharma, Revo, Georgetown
- Stock- Not applicable
- Employment – Not applicable
- Speakers' Bureau – Not applicable

Topics

- Target specific oral anticoagulation
- New antidotes to DOACs
- DOACS in cancer and beyond
- Advances in ITP
- Miscellaneous

Classic Immunopathogenesis of ITP:



- autoantibodies are primarily IgG directed against epitopes on GPIIbIIIa (CD41) and/or GPIbIX (CD42)

Increased RES Destruction - Macrophage mediated

Current Guidelines Are Unclear on Sequencing of Therapy in Chronic ITP

1st-line therapy

- **ASH 2011 and IWG 2010 guidelines[1,2]:**
  Steroids (with or without IVIg or anti-D, as clinically indicated)
  If corticosteroids are used, there's little evidence to support any one dose or dosing regimen

2nd-line or later therapy[1,2]

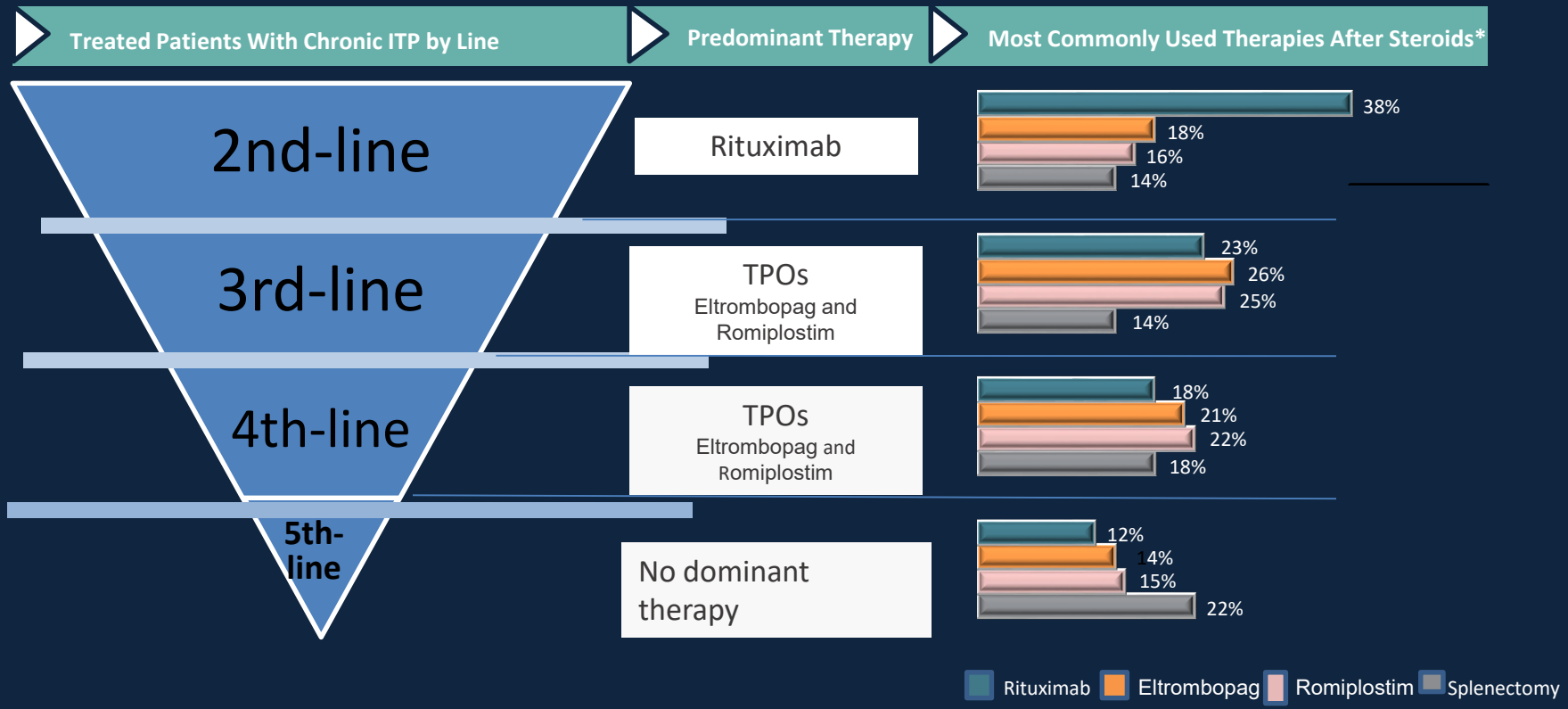
- **ASH 2011 guideline[1]: Splenectomy; if failed or risk of bleeding, then TPO-RAs or rituximab**
- **IWG 2010 guidelines[2]: TPO-RAs, splenectomy, rituximab, immunosuppressants, danazol/dapsone, cyclosporine, etc, *in NO preferential order***

- **Empiric sequencing of therapy by healthcare providers[2,3]**
- **Cycling among treatment options for chronic ITP is common[3]**
- **Response to treatment is hard to predict[4]**

IVIg, intravenous immunoglobulin G; RA, receptor agonist.

1. Neunert C, et al. *Blood.* 2011;117(16):4190-4207. 2. Provan D, et al. *Blood*. 2010;115(2):168-186.
3. Nomura S. *Clin Med Insights Blood Disord.* 2016;9:15-22. 4. Cooper N. *Br J Haematol.* 2017;177(1):39-54.

Post-steroid Lines of Therapy: Treatments Are Currently Diverse and Fragmented



*Other therapeutic options used include chemotherapy, immunosuppressants, and undefined therapies.

Data on file, Rigel Pharmaceuticals, Inc August 2018

ASH Draft Guidelines for ITP-2019

Question 1A: Should adults with newly diagnosed ITP and a platelet count <30 x 10^9/l who are asymptomatic or with minor mucocutaneous bleeding be treated with corticosteroids or observation?

The ASH guideline panel suggests corticosteroids rather than observation in adults with newly diagnosed ITP and a platelet count <30 x 10^9/l who are asymptomatic or with minor mucocutaneous bleeding. (Conditional recommendation, moderate certainty in the evidence about effects)

Question 4: Should adults with newly diagnosed ITP be treated with prednisone (0.5-2mg/kg/day) or dexamethasone (40mg/day x 4 days) as the type of corticosteroid for initial therapy?

The ASH guideline panel suggests either dexamethasone (40 mg/day x 4 days) or prednisone (0.5-2 mg/kg/day) in adults with newly diagnosed ITP as the type of corticosteroid for initial therapy. (Conditional recommendation, very low certainty in the evidence about effects) **Remark:** If a high value is placed on rapidity of platelet count response over concerns for potential side-effects of dexamethasone then an initial course of dexamethasone over prednisone may be preferred.

New Current First Line Therapy for ITP in Adults

- Dex has significantly increased anti-inflammatory effect compared to prednisone
- Laboratory data suggest that dex more effectively modulates the T cell abnormalities seen in ITP
- Given the increased potency of dexamethasone, the adverse effect profile may be less favorable
- Meta-analysis of 9 randomized trials comparing various steroid regimens
  - Initial response rate may be higher in adults treated with dex, but the durable response rates were not significantly different
- Consider dex instead of prednisone in adults if more rapid improvement in platelet count is desired

Liu Z et al. J Transl Med. 2016;14:301
Mithoowani S et al. Lancet Haematol. 2016;3:e489-e496

Which Corticosteroid to Use for ITP?

Responses at 6–12 months in newly diagnosed adults with primary ITP

Treatment	6 months (%)	12 months (%)
Prednis(ol)one 1 mg/kg/day	36–59	24
HDD × one to two cycles	25–40	33[a]
HDD × at least three cycles	60	40
HDD and rituximab	58–63	53
Romiplostim	32[b]	–
HDD and eltrombopag	75	67

HDD, high-dose dexamethasone.
[a]Patients received one to five cycles of HDD.
[b]At 24 weeks.

Cuker A et al. Current opinion in hematology, 23(5), 479-485, 2016

Refractory ITP: What to do next?

- Splenectomy-60% long term responses; poor predictability for success; lifelong increased risk of sepsis and thrombosis

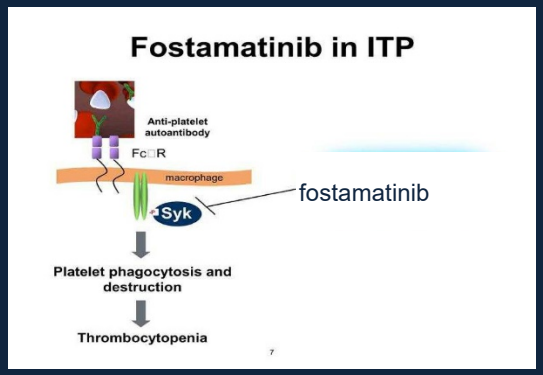
- TPO-mimetics- 20-30% long term cures; Non-immunosuppressive; long term safety remains uncertain; increased risk for thrombosis? Increased risk for sepsis

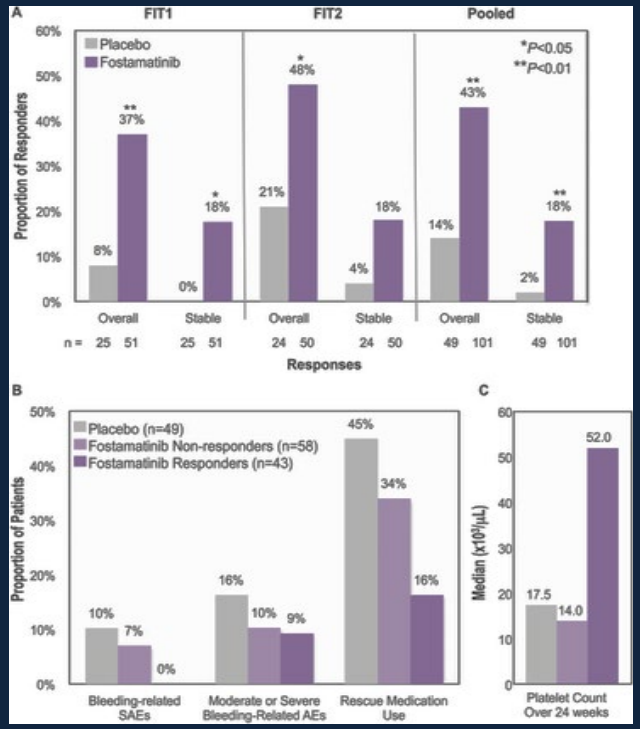
- Rituxamab- Immunosuppressive; 60% long term success (70% in women); hypogammaglobulinemia; risks of PML, HBV, HCV;

- Mycophenolate- 50% response; reversible immunosuppression; not in pregnancy; slow response rate (8 wks); Secondary malignancies?

New TPO-mimetics/New agents

- Avatrombopag (Doptelet®)- for CLD; orally bioavailable; no divalent cation interactions limiting timing of meals or potential for hepatotoxicity as seen with eltrombopag; rapid response (65% at 1 wk)
- BKI analogs – in clinical trials
- Fostamatinib- syk inhibitor





Bussel J et al. Am J Hematol. 2018 Jul;93(7):921-930

Abs 289: Romiplostim for Chemotherapy-Induced Thrombocytopenia (CIT). Results of a Phase 2 Trial Soff GA et al

TABLE 1A. Primary Endpoint of Randomized Patients: (ITT, Intention To Treat)

	Platelet Count Corrected to >100,000/mcL, within 3 weeks	Fail To Correct within 3 weeks	Total
Romiplostim	14 (93.3%)	1	15
Observation	1 (12.5%)	7	8

P = <0.001

TABLE 1B. Primary Endpoint of All Patients: (ITT, Intention To Treat)

	Platelet Count Corrected to >100,000/mcL, within 3 weeks	Fail To Correct within 3 weeks	Total
Romiplostim	27 (84.4%)	5	32
Observation	1 (12.5%)	7	8

P = <0.001

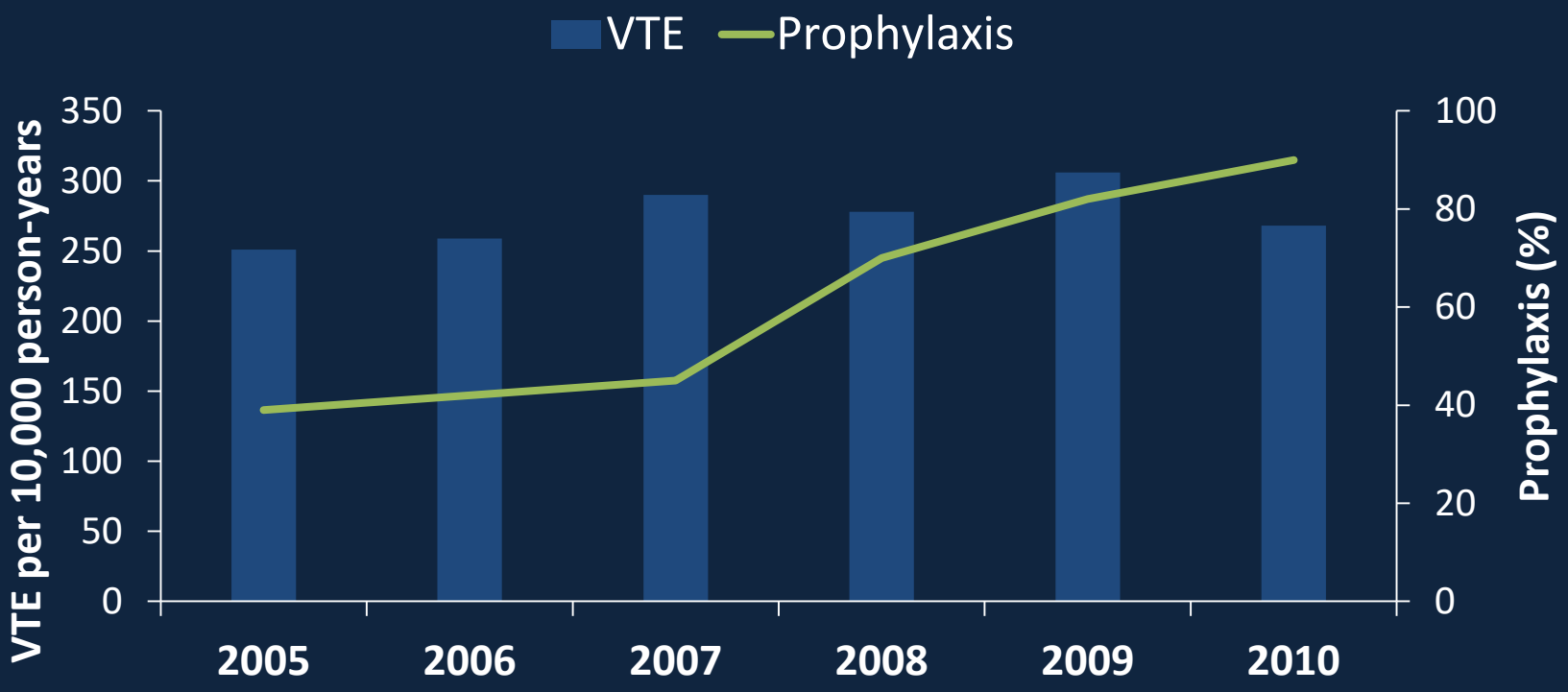
4/32 (12.5%) romiplostim pts developed VTE. One with symptomatic PE; one with asx incidental PE; 2 with distal DVTs. These pts all high risk for VTE with metastatic or locally advanced pancreas (2), colorectal, and hepatocellular carcinoma

The Pharmacological Landscape of the DOACs- 2019

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	IIa	Xa	Xa	Xa	Xa
Bioavailability	6%–7%	66%	50%	62%	34%
Protein binding	35%	92%–95%	87%	40%–59%	60%
T_{max} (h)	2	2–4	1–3	1–2	3–4
Metabolism via CYP450	<2%	57%	<32%	<25%	<1%
Renal excretion	>80%	66%	25%	35%	6%–13%
Fecal excretion	82%–88%	26.4%	46.7%–56%	62.2%	82%–89%
$T_{1/2}$ (h)	12–14	9–13	8–15	9–11	37 (PD $T_{1/2}$=20 h)

Inpatient Prophylaxis Alone is Insufficient to Reduce Hospital-Acquired Venous Thromboembolism

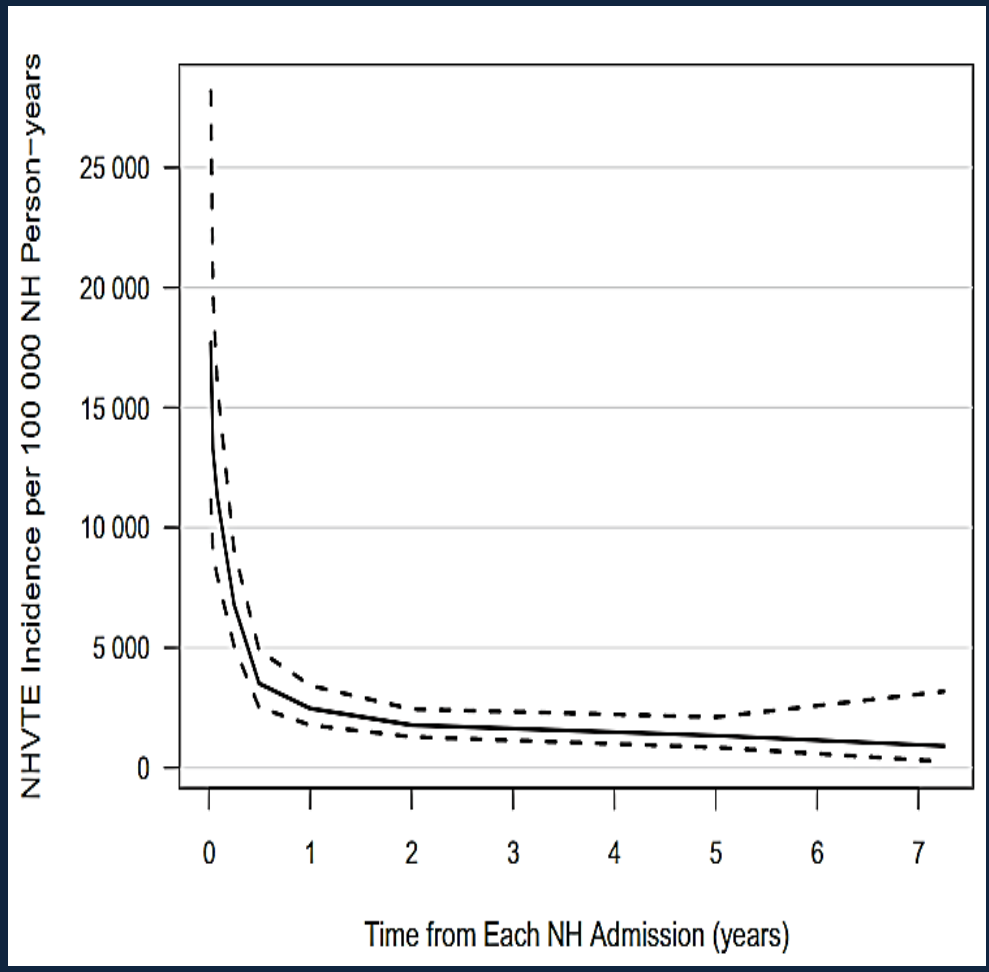
Median LOS 3 days! Median duration of VTE prophylaxis 70 hrs!



- Heit JA, et al. *Blood* 2017 130:109-114

Nursing Home Residents are at High Risk for VTE

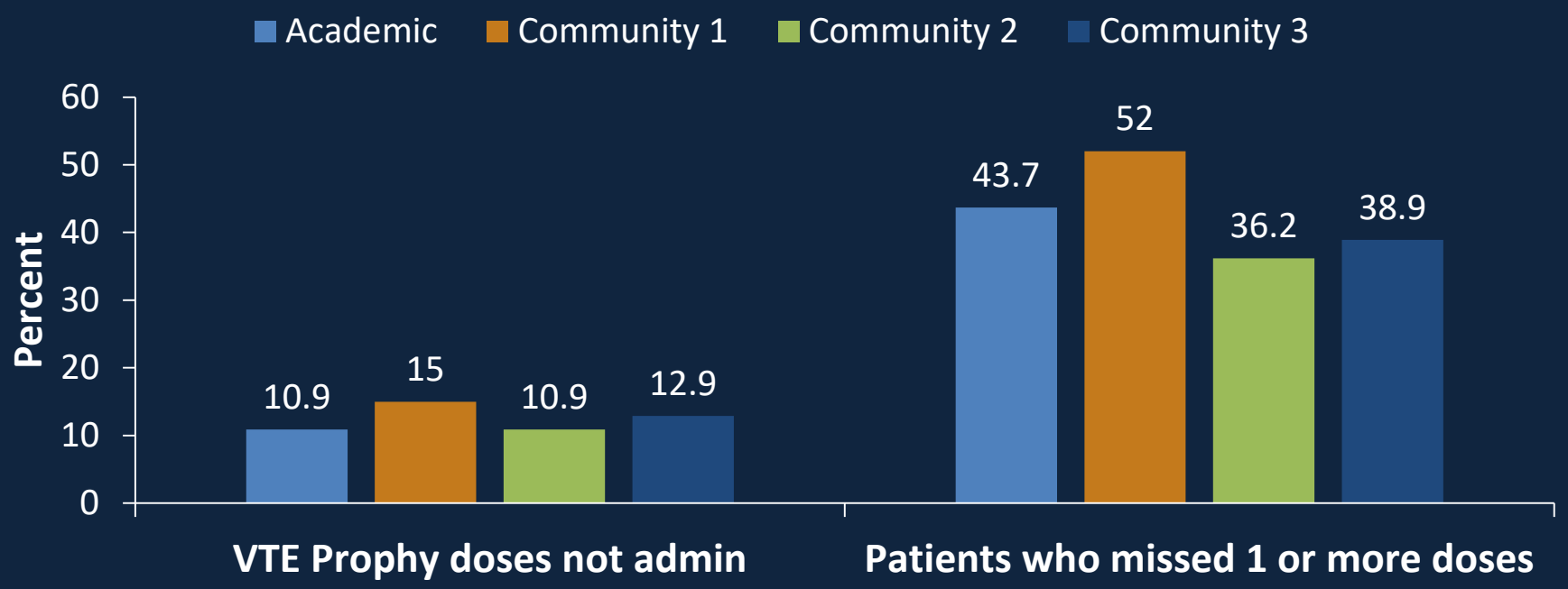
- Mayo Clinic population-based retrospective cohort 1998-2005
- 3465 nursing home residents with median age 82 and 1 year follow up
- VTE occurred in 2.3% of nursing home stays
- Nursing home VTE incidence 30-fold general population
- Nursing home VTE associated with 1.9-fold risk of death
- Nursing home residents are at high risk for VTE



- Petterson TM, et al. *Thromb Haemost* 2018;118:1316-1328.

VTE Prophylaxis Non-Administration is Common Care Defect

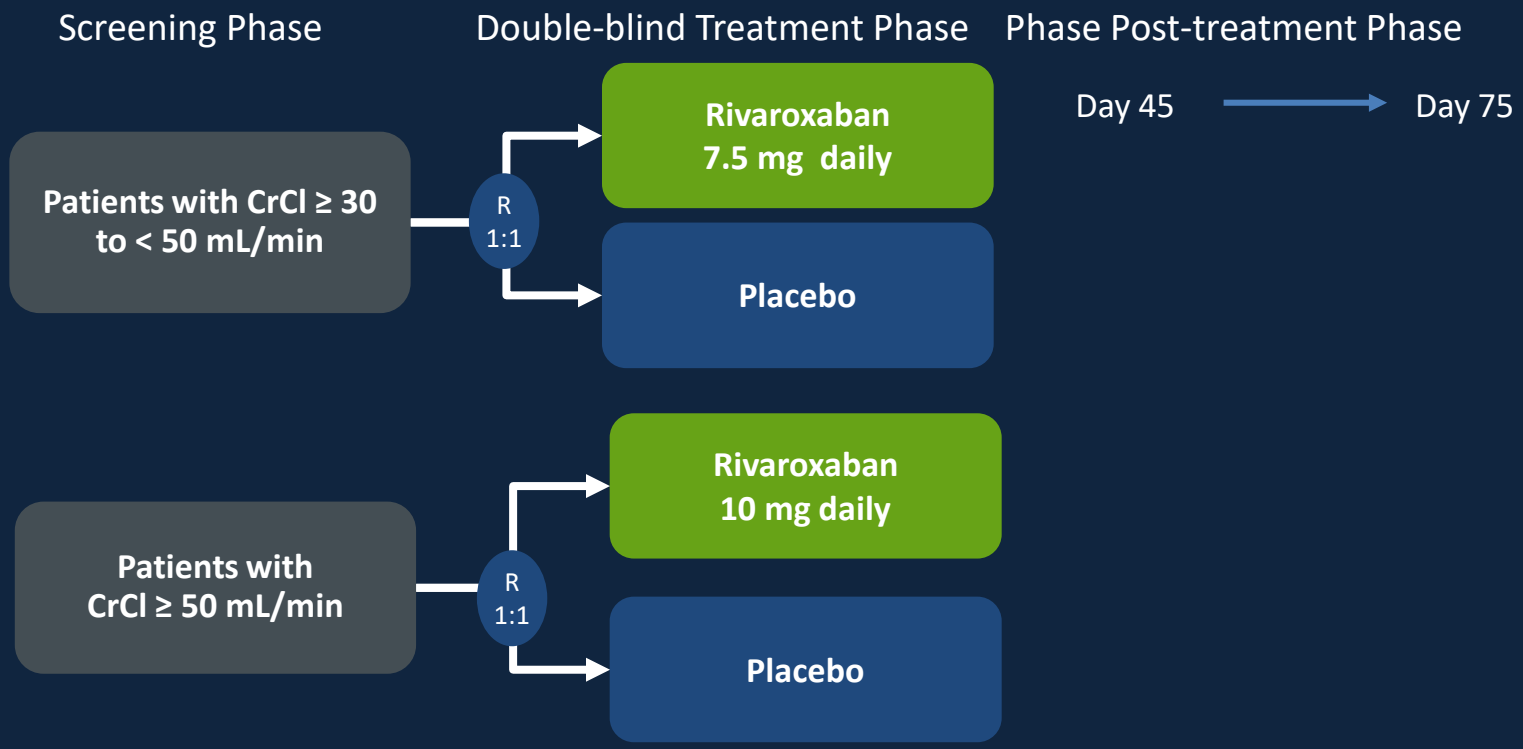
Retrospective dose administration survey January 1, 2015-December 31,2015



- Lau BD, et al. *J Gen Intern Med* 2018;33:19-20

MARINER Trial

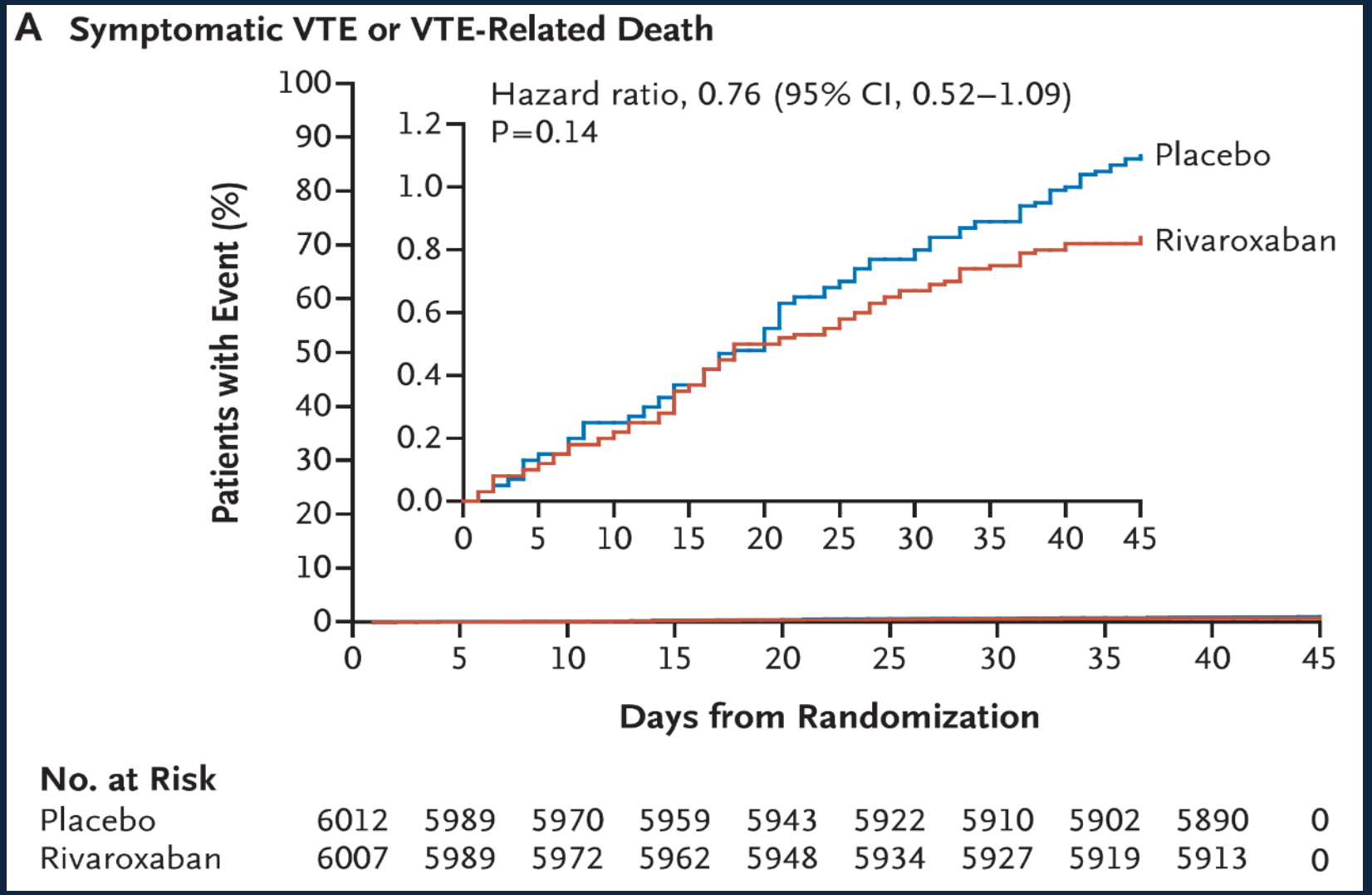
Rivaroxaban (N = 12,024)



- Raskob GE, et al. *Thromb Haemost* 2016; 115: 1240–1248

MARINER Trial

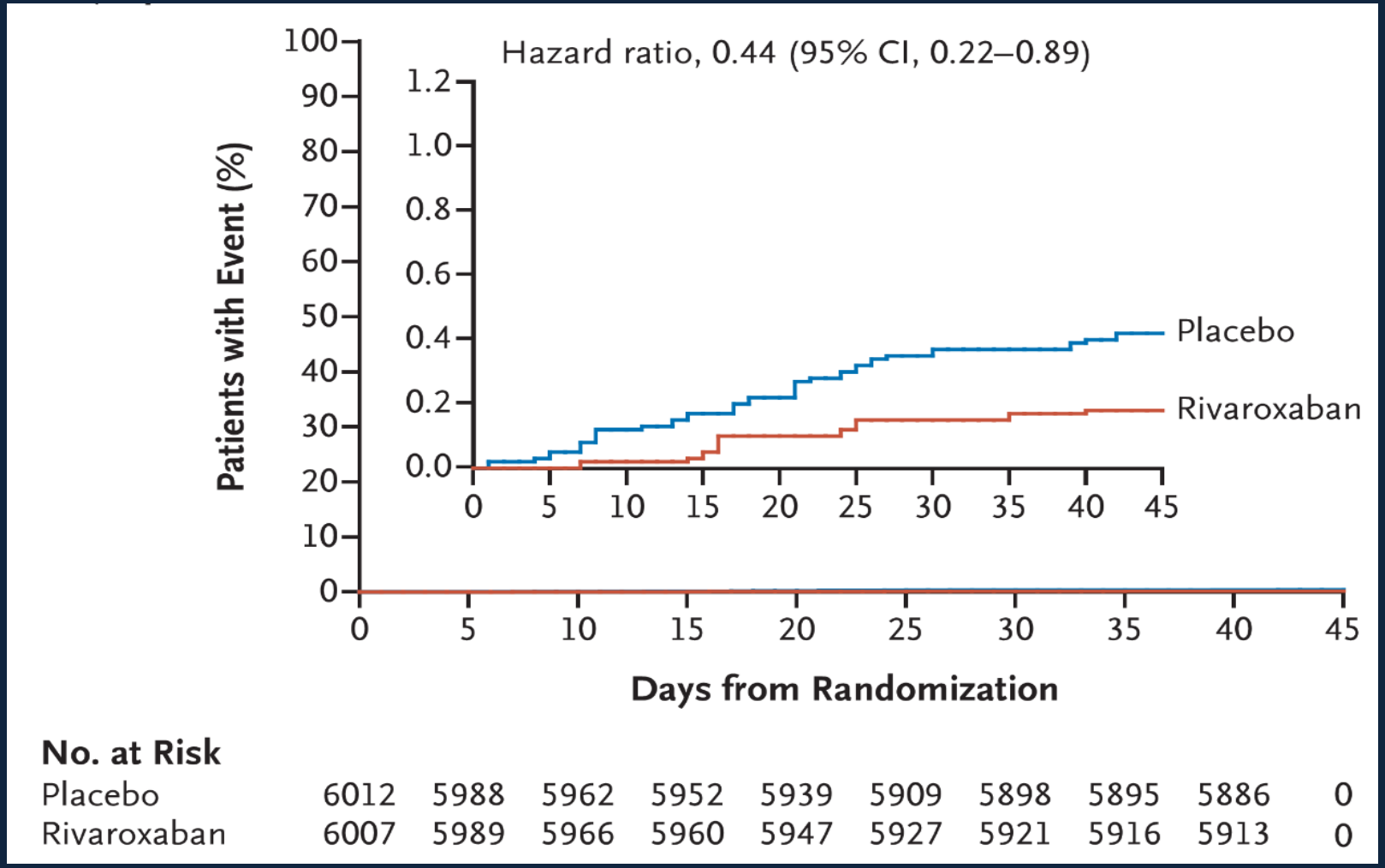
Primary Efficacy Endpoint



- Spyropoulos AC, et al. *N Eng J Med*. 2018;379:1118-1127.

MARINER Trial

Symptomatic VTE



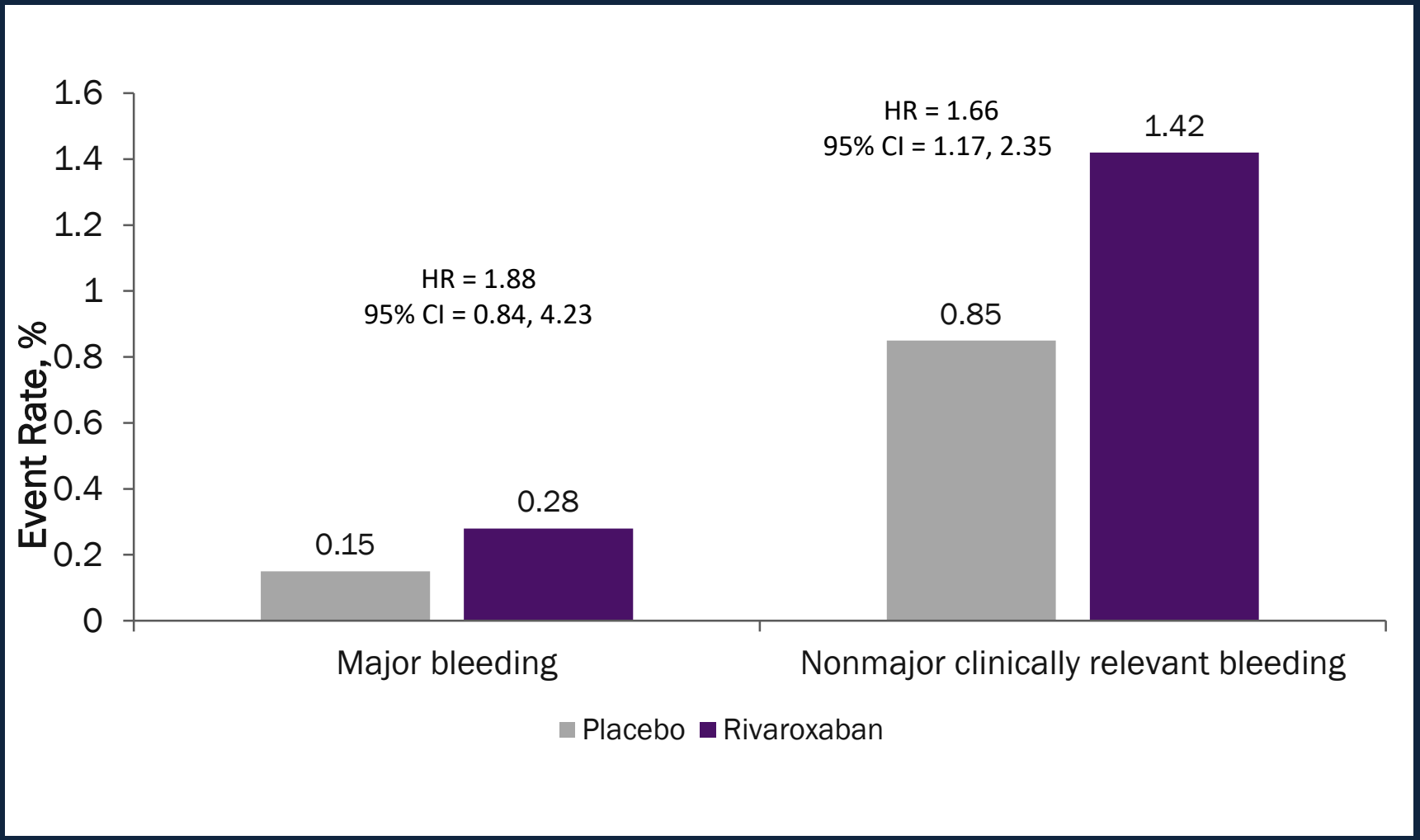
No. at Risk

Placebo	6012	5988	5962	5952	5939	5909	5898	5895	5886	0
Rivaroxaban	6007	5989	5966	5960	5947	5927	5921	5916	5913	0

- Spyropoulos AC, et al. *N Eng J Med*. 2018;379:1118-1127.

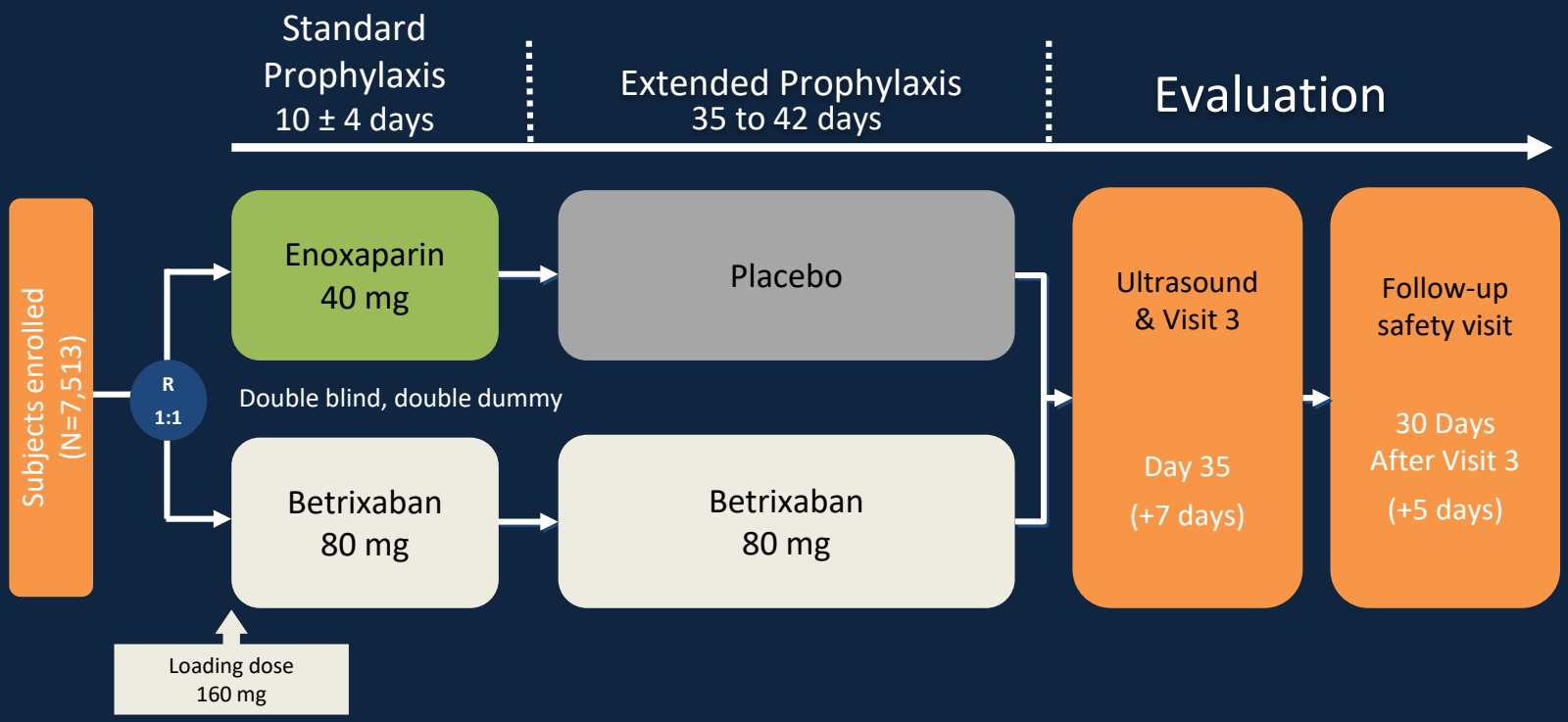
MARINER Trial

Bleeding Complications



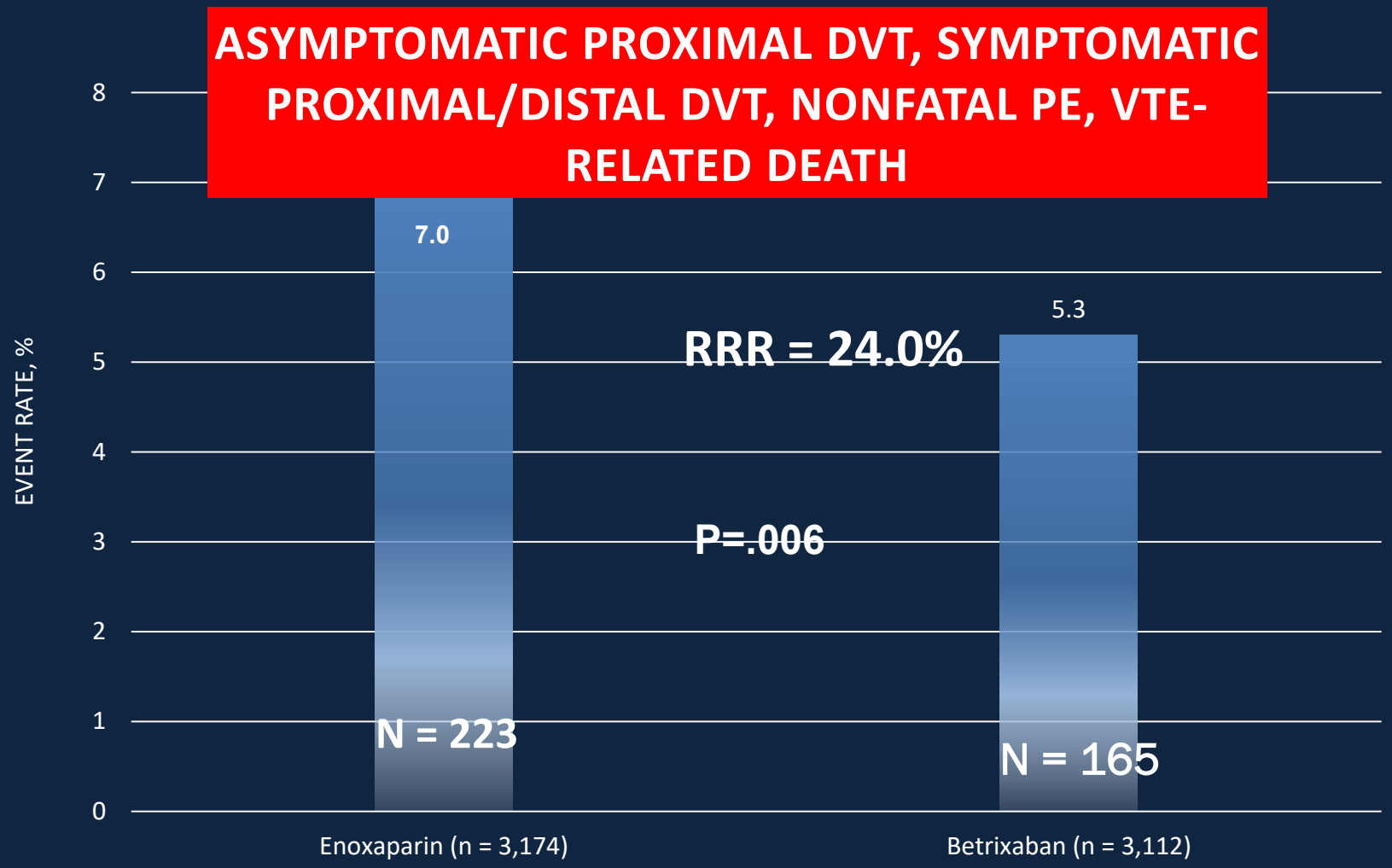
- Spyropoulos AC, et al. *N Eng J Med*. 2018;379:1118-1127.

APEX Study Design



- Cohen AT, et al. *N Engl J Med* 2016; 375: 534-544.

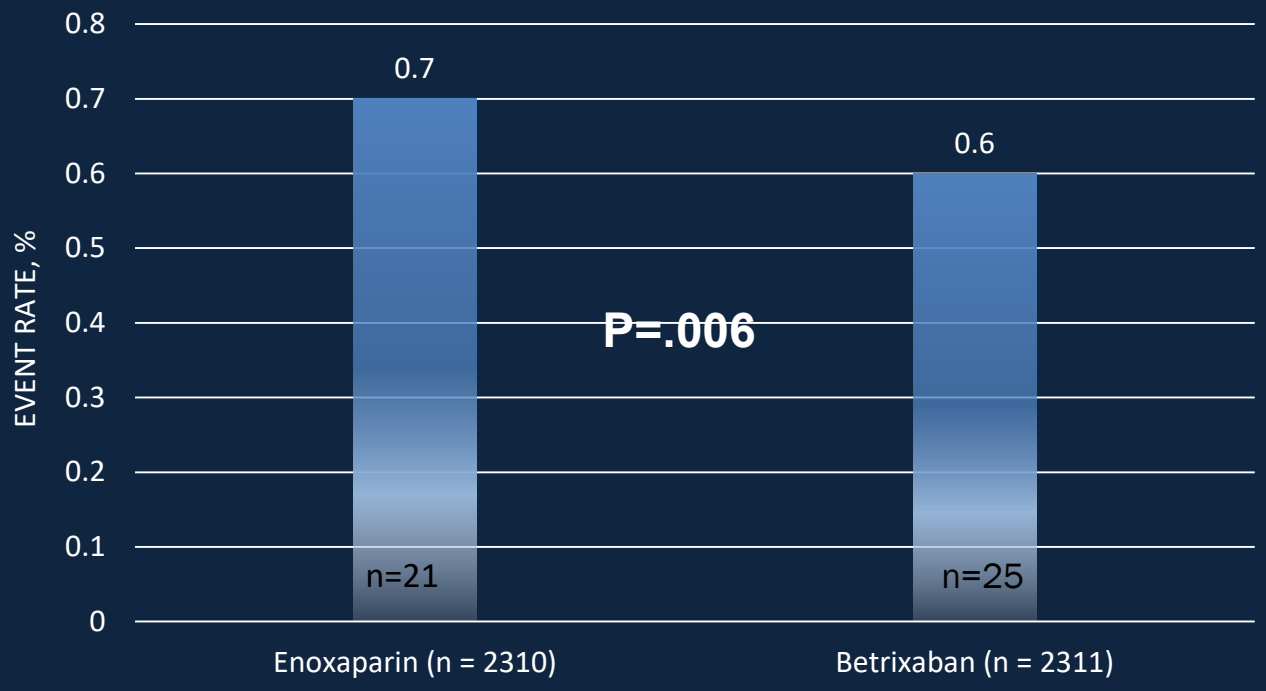
APEX *Primary Efficacy Endpoint*



- Cohen AT, et al. *N Engl J Med*. 2016;375:534-544.

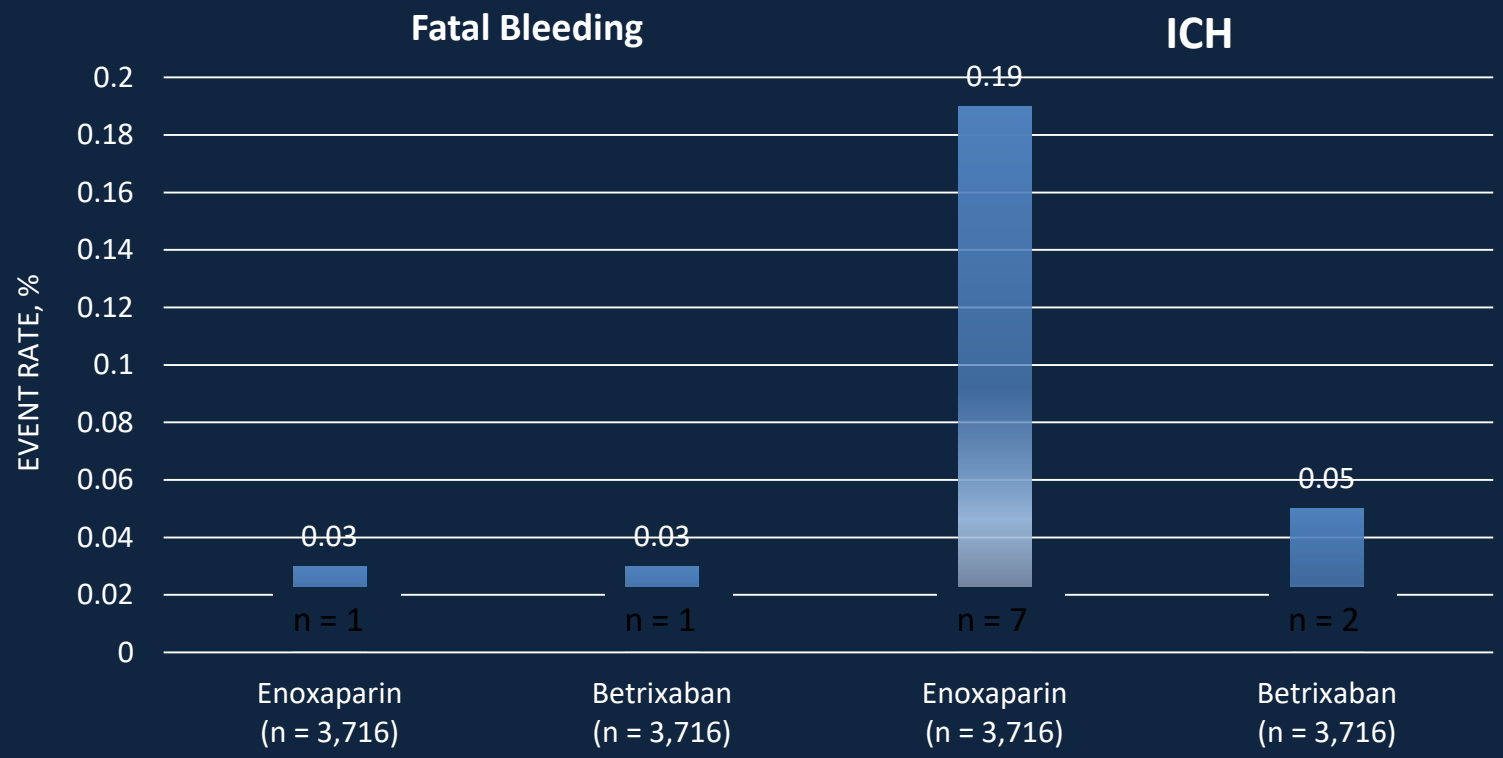
APEX: Primary Safety Endpoint:

Major Bleeding



- Cohen AT, et al. *N Engl J Med*. 2016;375:534-544.

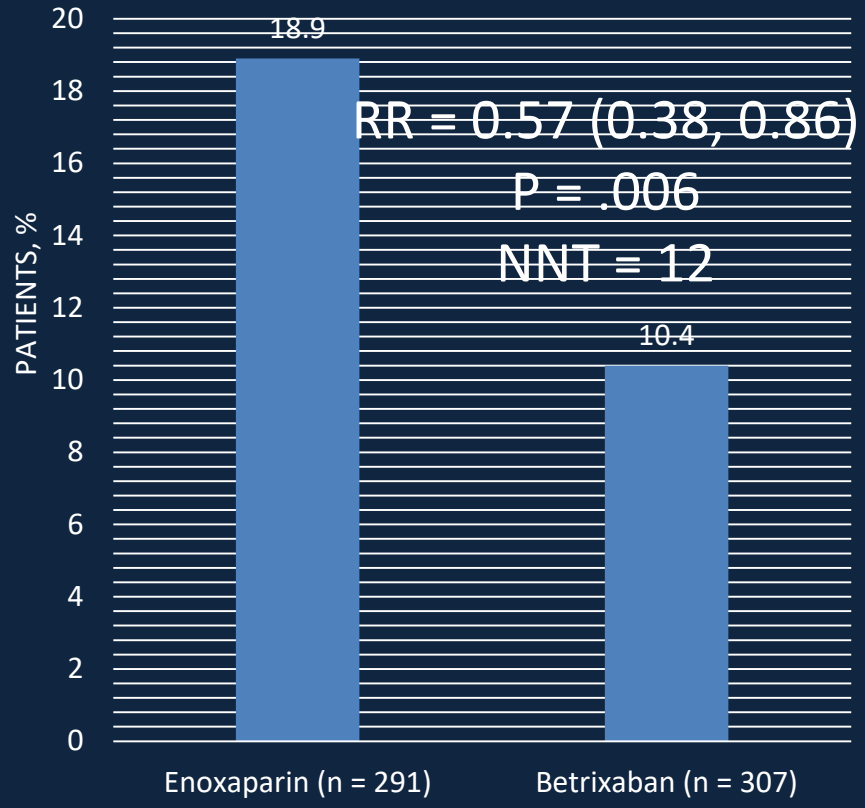
APEX: Fatal Bleeding and ICH: Safety Population



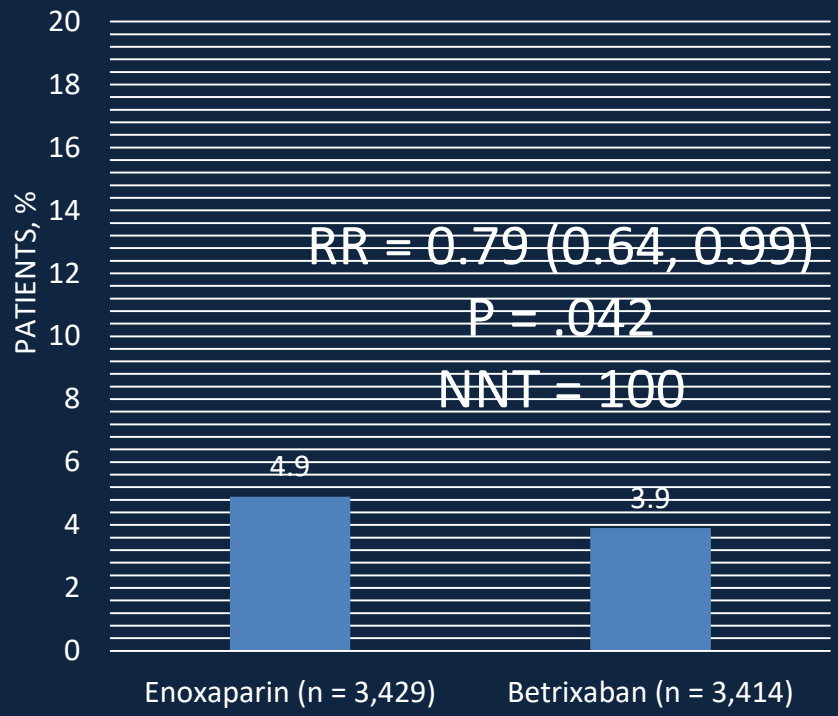
- Gibson CM et al. *J Am Heart Assoc*. 2017;6(7)

APEX: Primary Efficacy Outcome by History of VTE

- History of VTE

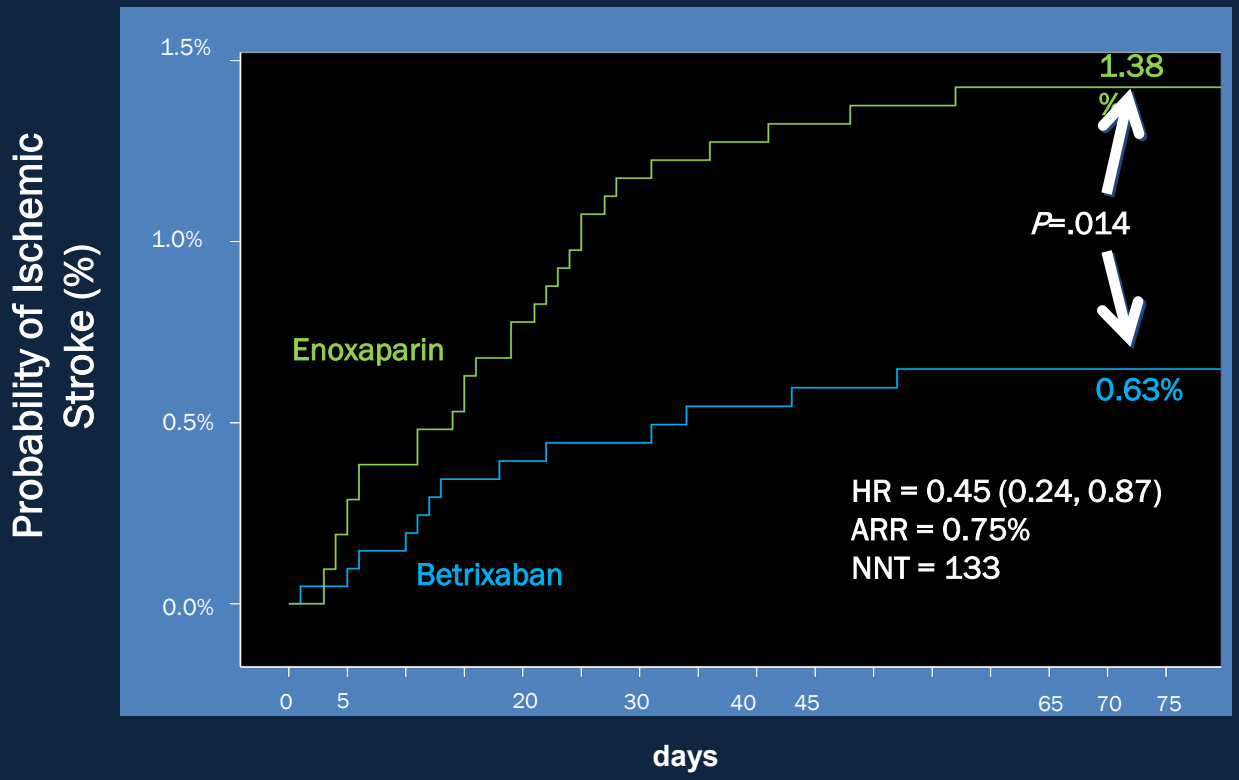


- No History of VTE



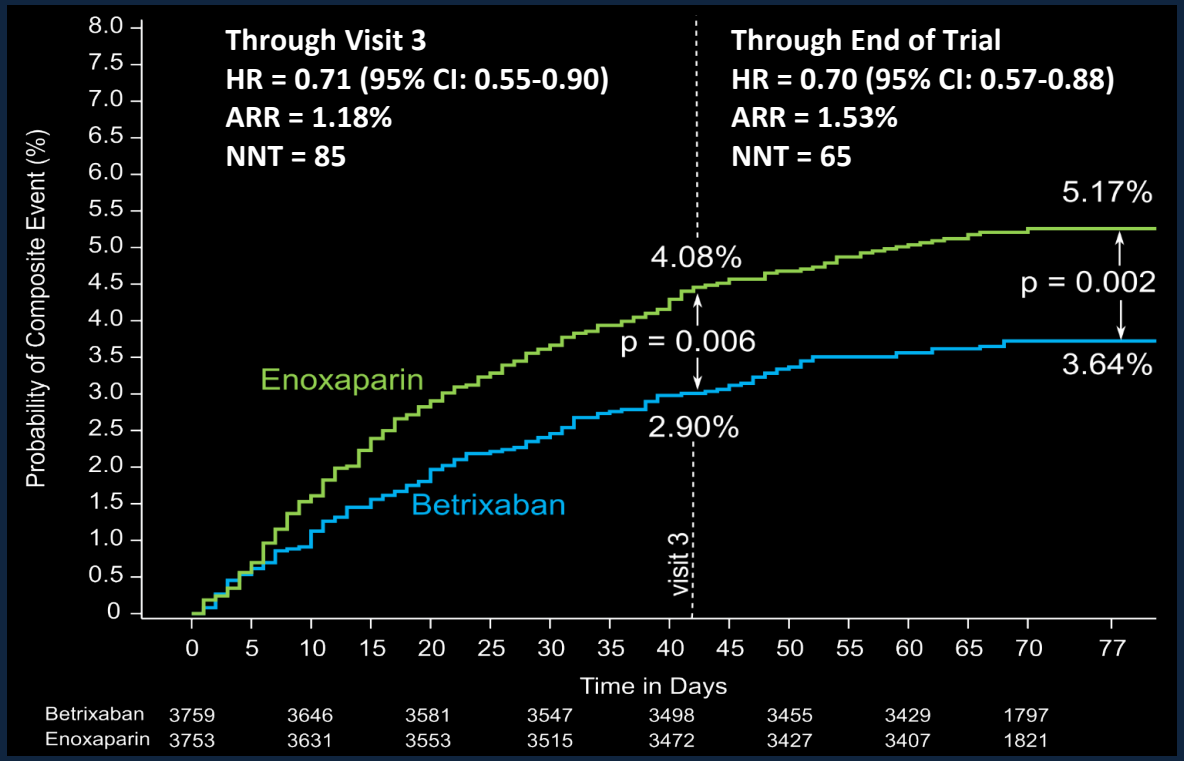
- Yee MK, et al. *J Thromb Thrombolysis*. 2018;45:1-8.

APEX: Ischemic Stroke or CHF as Index Event



- Gibson CM, et al. *Circulation* 2017;135:648-655

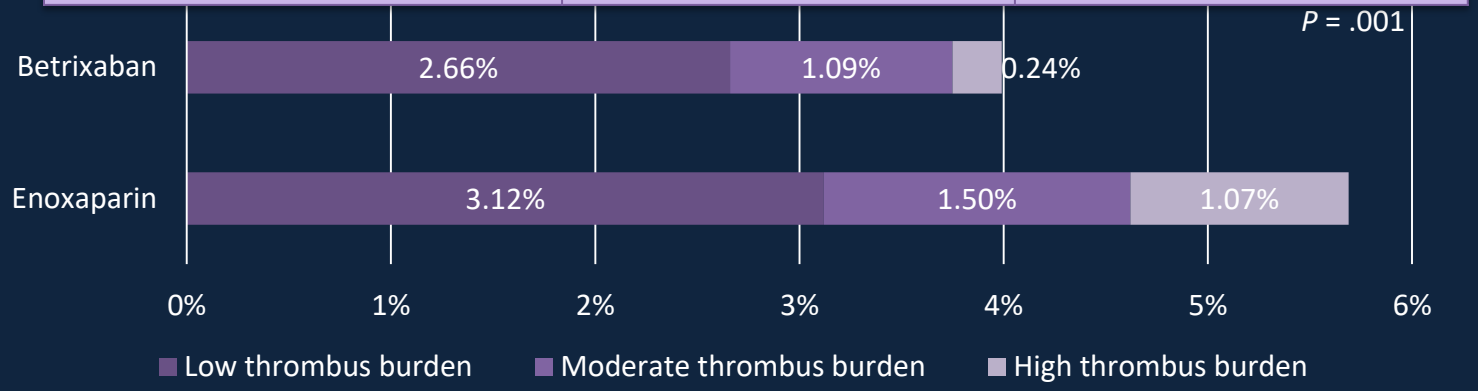
APEX: Fatal or Irreversible Outcomes: Legacy Effect



- Gibson CM, et al. *Circulation* 2017;135:648-655

Betrixaban vs Enoxaparin on Thrombus Burden (80 mg) Modified ITT Population

Thrombus burden	Enoxaparin (n = 2532)	Betrixaban (n = 2485)
No DVT	94.31% (2388)	96.02% (2386)
Low thrombus burden	3.12% (79)	2.66% (66)
Moderate thrombus burden	1.50% (38)	1.09% (27)
High thrombus burden	1.07% (27)	0.24% (6)



- Chi G. *Thromb Haemost* 2017; 117: 2389-2395.

Major Bleeding Events With DOACs vs VKA

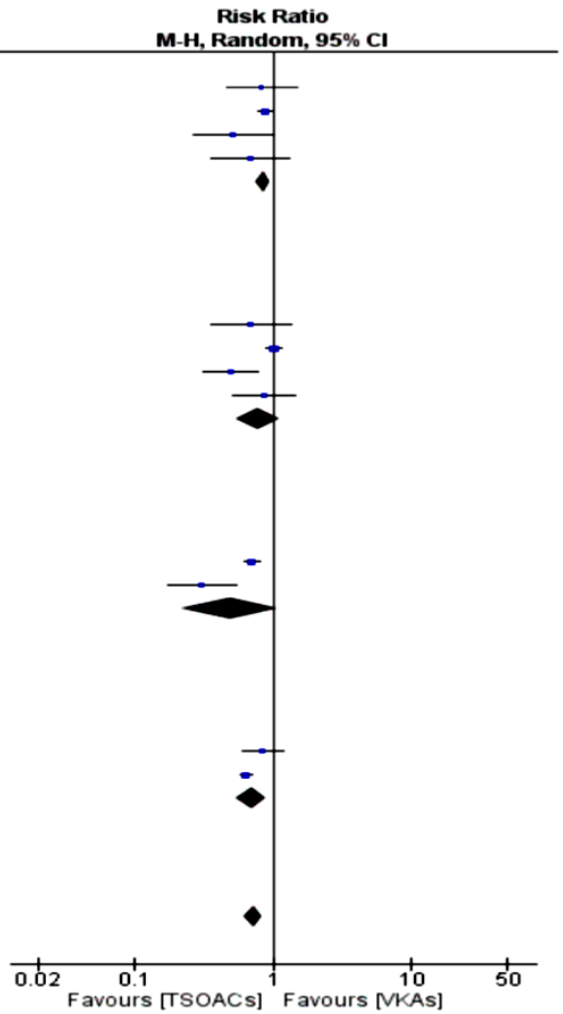
Meta-analysis of Data From 12 RCTs - 9/12 Blinded

	DOACs (N = 57,850)	VKA (N = 44,757)	Pooled RR
Major bleeds	4.0%	4.64%	0.72
Fatal bleeding	0.30%	0.52%	0.53
Intracranial bleeding	0.51%	1.08%	0.43
Major GI bleeding	**2.09%**	**1.70%**	0.94

- Chai-Adisaksopha C, et al. *Blood*. 2014;124:2450-2458.

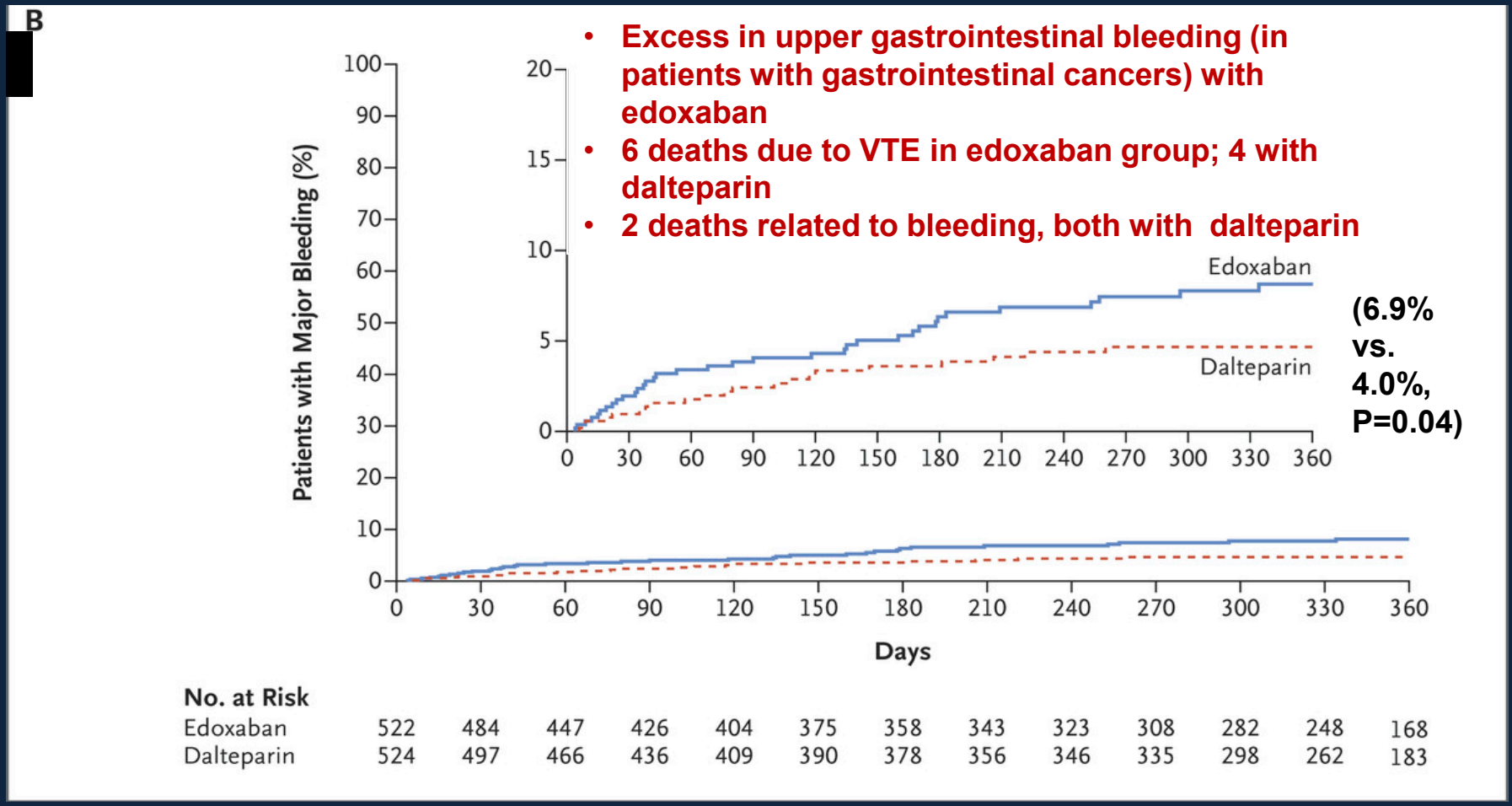
Supplemental Figure 5. Subgroup analysis: Major bleeding according to types of target-specific oral anticoagulant

Study or Subgroup	TSOACs Events	TSOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 Dabigatran							
RE-COVER, 2009	20	1274	24	1265	5.0%	0.83 [0.46, 1.49]	2009
RE-LY, 2009	741	12091	421	6022	14.2%	0.88 [0.78, 0.98]	2009
RE-MEDY, 2013	13	1430	25	1426	4.2%	0.52 [0.27, 1.01]	2013
RE-COVER II, 2014	15	1279	22	1289	4.3%	0.69 [0.36, 1.32]	2014
Subtotal (95% CI)		**16074**		**10002**	**27.7%**	**0.86 [0.77, 0.96]**	
Total events	789		492				
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 3 (P = 0.43); I² = 0%							
Test for overall effect: Z = 2.76 (P = 0.006)							
1.2.2 Rivaroxaban							
EINSTEIN-DVT, 2010	14	1718	20	1711	4.0%	0.70 [0.35, 1.38]	2010
ROCKET AF, 2011	395	7111	386	7125	13.8%	1.03 [0.89, 1.18]	2011
EINSTEIN-PE, 2012	26	2412	52	2405	6.6%	0.50 [0.31, 0.80]	2012
J-ROCKET AF, 2012	26	639	30	639	5.9%	0.87 [0.52, 1.45]	2012
Subtotal (95% CI)		**11880**		**11880**	**30.4%**	**0.78 [0.54, 1.12]**	
Total events	461		488				
Heterogeneity: Tau² = 0.09; Chi² = 9.44, df = 3 (P = 0.02); I² = 68%							
Test for overall effect: Z = 1.33 (P = 0.18)							
1.2.3 Apixaban							
ARISTOTLE, 2011	327	9088	462	9052	13.8%	0.70 [0.61, 0.81]	2011
AMPLIFY, 2013	15	2676	49	2689	5.1%	0.31 [0.17, 0.55]	2013
Subtotal (95% CI)		**11764**		**11741**	**18.9%**	**0.49 [0.22, 1.10]**	
Total events	342		511				
Heterogeneity: Tau² = 0.30; Chi² = 7.55, df = 1 (P = 0.006); I² = 87%							
Test for overall effect: Z = 1.73 (P = 0.08)							
1.2.4 Edoxaban							
HOKUSAI-VTE, 2013	56	4118	66	4122	8.8%	0.85 [0.60, 1.21]	2013
ENGAGE-AF-TIMI-48, 2013	672	14014	524	7012	14.3%	0.64 [0.57, 0.72]	2013
Subtotal (95% CI)		**18132**		**11134**	**23.1%**	**0.70 [0.54, 0.90]**	
Total events	728		590				
Heterogeneity: Tau² = 0.02; Chi² = 2.20, df = 1 (P = 0.14); I² = 55%							
Test for overall effect: Z = 2.73 (P = 0.006)							
Total (95% CI)		**57850**		**44757**	**100.0%**	**0.72 [0.62, 0.85]**	
Total events	2320		2081				
Heterogeneity: Tau² = 0.04; Chi² = 48.96, df = 11 (P < 0.00001); I² = 78%							
Test for overall effect: Z = 3.98 (P < 0.0001)							
Test for subgroup differences: Chi² = 3.70, df = 3 (P = 0.30), I² = 19.0%							



Chatree Chai-Adisaksopha et al. Blood 2014;124:2450-2458

Major bleeding is increased in cancer VTE patients: Hokusai VTE Cancer Study

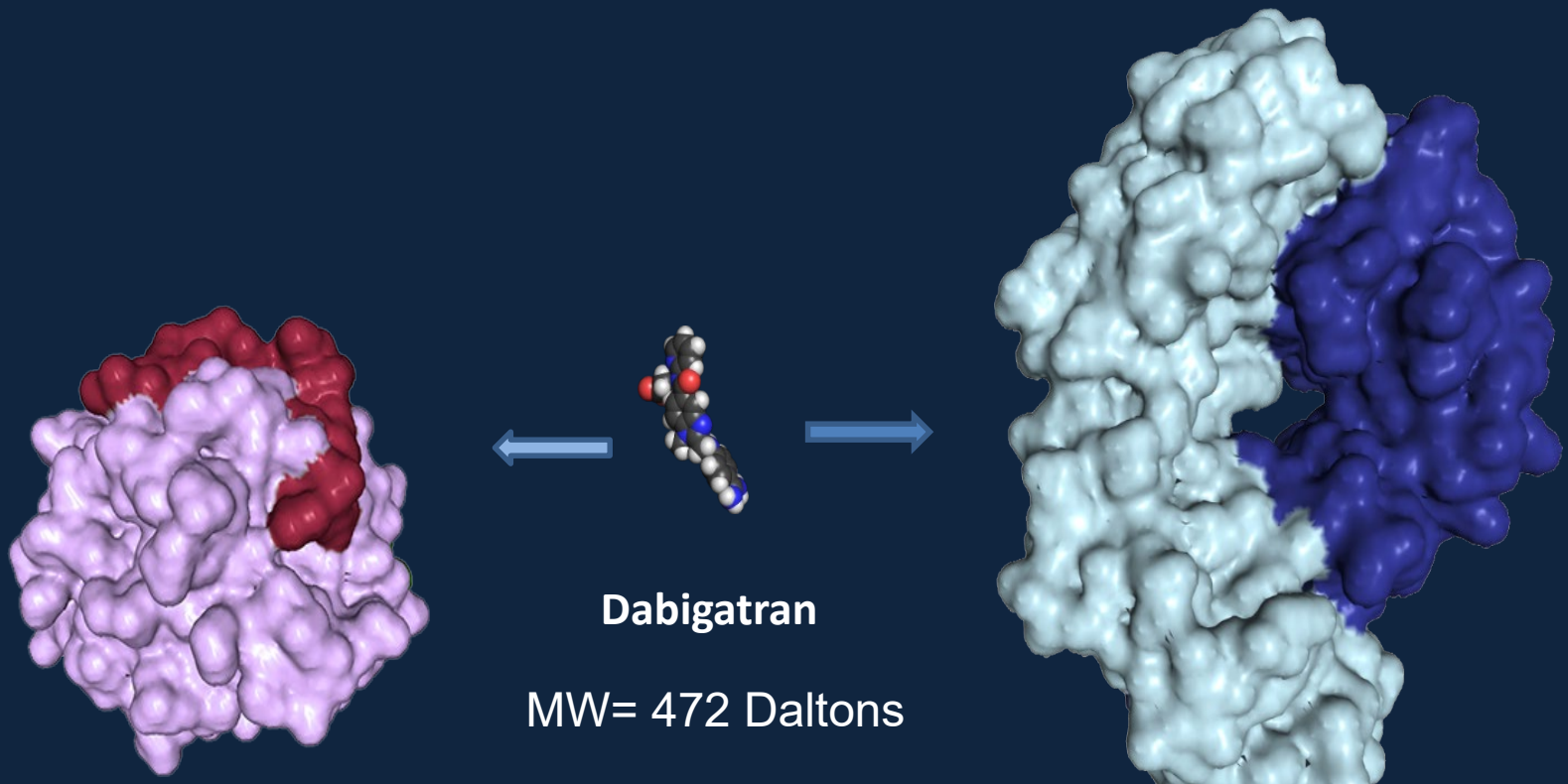


- **Excess in upper gastrointestinal bleeding (in patients with gastrointestinal cancers) with edoxaban**
- **6 deaths due to VTE in edoxaban group; 4 with dalteparin**
- **2 deaths related to bleeding, both with dalteparin**

(6.9% vs. 4.0%, P=0.04)

N Engl J Med 2018;378:615-24. DOI: 10.1056/NEJMoa1711948

Idarucizumab Is a Humanized Monoclonal Antibody Fragment (Fab)



Thrombin

MW~ 37 kD

Dabigatran

MW= 472 Daltons

Idarucizumab

MW ~ 48 kD

https://reference.medscape.com/drug/andexxa-andexanet-alfa-coagulation-factor-xa-recombinant-inactivated-zhzo-999945

Idrucizimab Full Cohort

- N =503, 301 Group A, 202 Group B
- 100% reversal by ecarin, DTT, aPTT
- Median time bleeding cessation 2.5 h
- Median time initiate procedure 1.6 h
- Periprocedural hemostasis 93.4%
- Thrombotic events 90 days –
- 6.3% Group A, 7.4% Group B
- Mortality rate 18.8% and 18.9% respectively
- Anticoagulation restarted in 72% at mean of 13.2 days Group A and in 90% at mean 3.5 days Group B

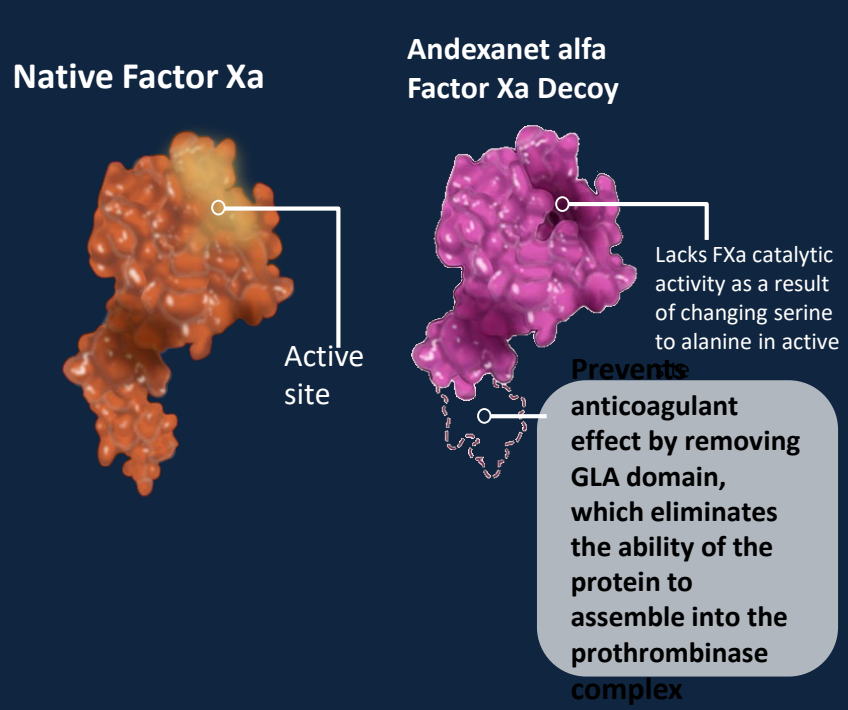
New England Journal of Medicine

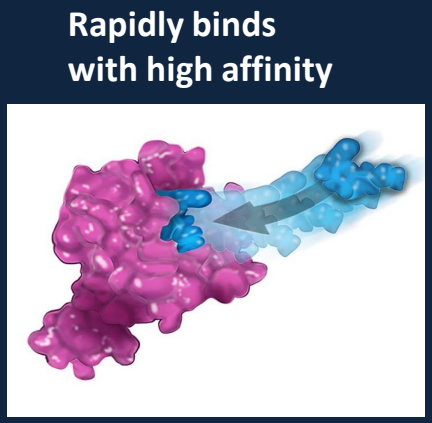
Idarucizumab for dabigatran reversal -- full cohort analysis

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

• Pollack CV, et al. *N Engl J Med*. 2017;377:431-441.

Novel Mechanism of Action Provides Rapid Reversal of FXa Inhibitor Activity Without Prohemostatic or Anticoagulant Effects





Binds to Factor Xa inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban
- Enoxaparin*
- Betrixaban

- Engineered to remove any pro- or anticoagulant effects:
  - Prothrombotic effects are eliminated by modification of the catalytic domain
  - Anticoagulant effects are eliminated by deletion of GLA domain

- * Exerts its effect by binding to the ATIII complex.
- AndexXa™ PI 2018.

https://reference.medscape.com/drug/andexxa-andexanet-alfa-coagulation-factor-xa-recombinant-inactivated-zhzo-999945

ANNEXA-4

- Patients with major bleeding on apixaban and rivaroxaban
- Received andexanet alfa within 18 hours of last dose
- About 60% cerebral bleeds, 35% GI
- End points hemostatic efficacy, survival, thrombotic complications

- Connolly, SJ, et al. *N Engl J Med* 2016; 375:1131-1141

Safety Assessment

- Thrombotic events occurred within 3 days of andexanet alfa in 6/227 (2.6%) patients and by 30 days in 24 (11%)
- Anticoagulation re-started in 129 patients (57%) by 30 days
- Therapeutic anticoagulation was restarted in 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

- Stuart J. Connolly, MD. As Presented at the ACC Scientific Sessions, 12 March 2018.

Prothrombin Complex Concentrate-DOAC Reversal

Vitamin K-dependent coagulation factors II,VII, IX and X

Treatment: 4 factor PCC ~ 25 IU/kg protocol
< 65 kg: 1500 IU
>65 kg: 2000 IU

3 patients developed thromboembolic events (5-15 days after PCC

	Apixaban n = 39		Rivaroxaban n = 45	
	Effective	Ineffective	Effective	Ineffective
Bleeding location, n (%)				
ICH	21 (72.4)	8 (27.6)	22 (73.3)	8 (26.7)
GI	3 (60.0)	2 (40.0)	5 (62.5)	3 (37.5)
Visceral	0 (0.0)	2 (100.0)	1 (33.3)	2 (66.7)
Genitourinary	1 (50.0)	1 (50.0)	2 (100.0)	0 (0.0)
Musculoskeletal	1 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)
Hemoglobin drop, n (%)	2 (33.3)	4 (66.7)	3 (37.5)	5 (62.5)
Any invasive procedure, n (%)				
None	17 (68.0)	8 (32.0)	23 (74.2)	1 (25.0)
Craniotomy	5 (71.4)*	2 (28.6)	6 (100.0)*	0 (0.0)
Gastroscopy	3 (75.1)†	1 (25.0)	1 (33.3)†	2 (66.7)
Embolization	0 (0.0)	2 (100.0)	1 (50.0)*	1 (50.0)
Fasciotomy	1 (100.0)*	0 (0.0)	0 (0.0)	0 (0.0)
Laparotomy	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
Thoracotomy	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Length of hospital stay, d, median (IQR)	7.0 (3.0-15.0)	4.5 (2.0-7.0)	9.0 (4.0-16.0)	2.5 (2.0-5.0)
Discharge destination, n (%)				
Home	14 (93.3)	1 (6.7)	10 (90.9)	1 (9.1)
Rehabilitation facility	7 (63.6)	4 (36.4)	13 (92.9)	1 (7.1)
Other hospital	2 (66.7)	1 (33.3)	1 (100.0)	0 (0.0)
Deceased	3 (33.3)	6 (66.7)	5 (35.7)	9 (64.3)
Unknown	0 (0.0)	1 (100.0)	1 (33.3)	2 (66.7)

3 patients developed thromboembolic events (5-15 days after PCC)

Majeed A, et al. *Blood*. 2017;130:1706-1712.

How About FEIBA and rVIIa for DOAC Reversal?

- Probably useful
- Probably thrombogenic: case reports of thrombotic complications with each

Bottom Line for DOAC Reversal

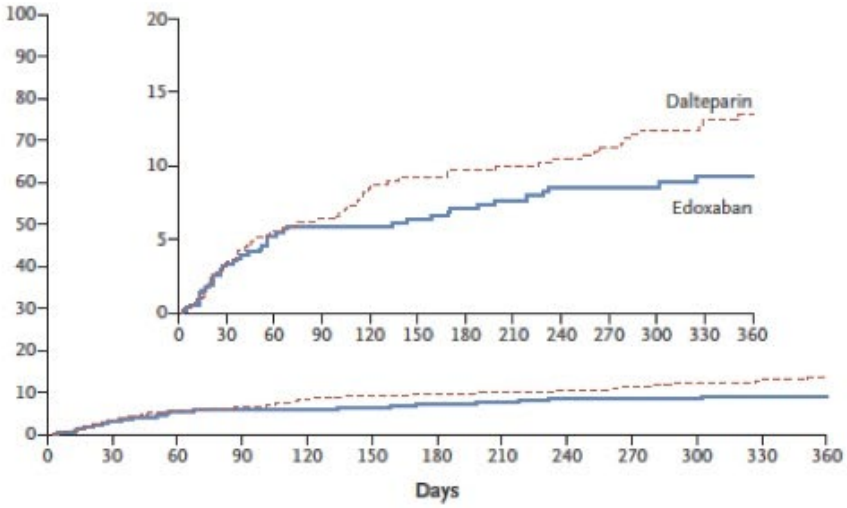
- Supportive therapy may be all that is necessary
- Delay surgery by at least 12 h
- Seek interventional radiology options
- Check mode of metabolism of DOAC - hemodialysis, charcoal, etc, may be options
- Dose reversal agent according to clinical scenario and DOAC in question

Are Direct Acting Oral Anticoagulants Ready for Prime-Time Use in Cancer-Related Thrombosis?

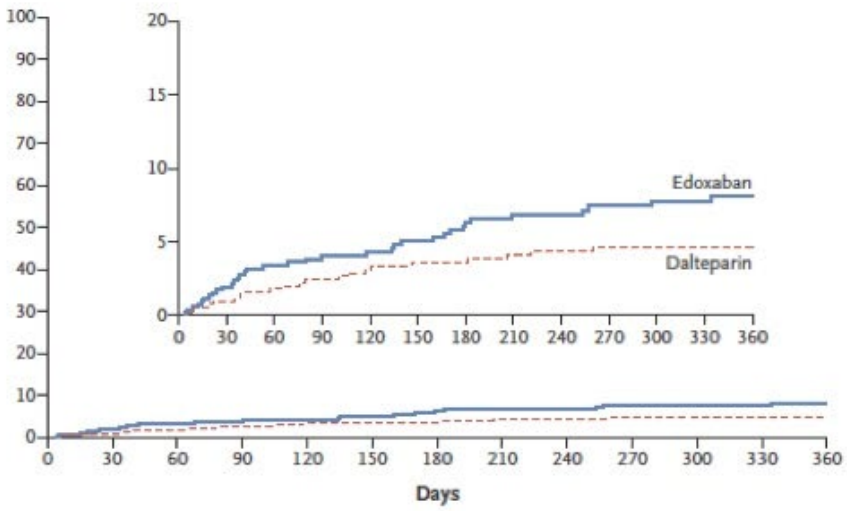
- Basic Facts
  - 20-25% of VTE occur in individuals with malignancies
  - Patients with cancer have a 4- to 7-fold increased risk for VTE compared with the general population
  - Different types of cancer vary dramatically in their propensity to cause thrombosis

Hokusai VTE Cancer

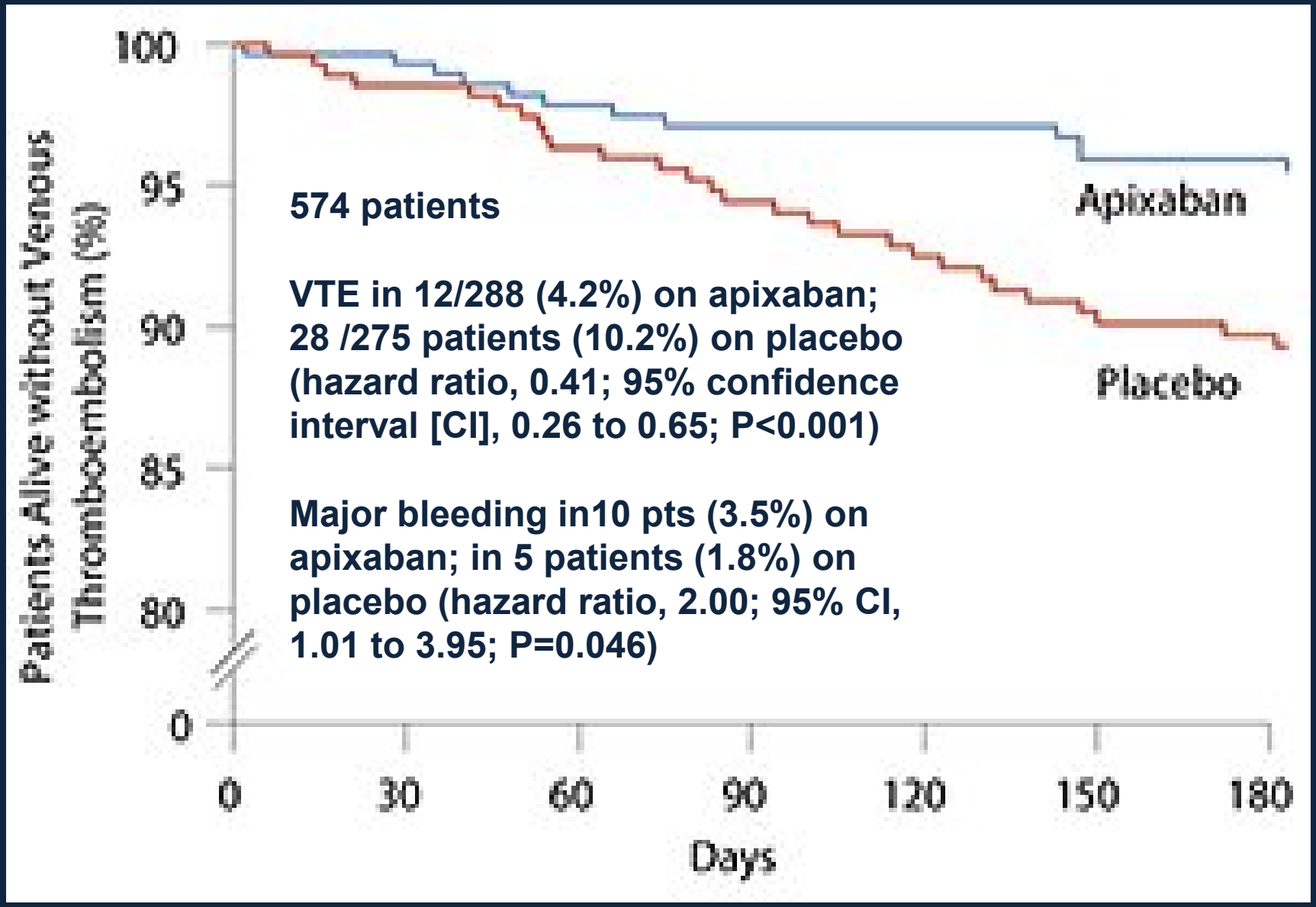
Recurrent venous thromboembolism



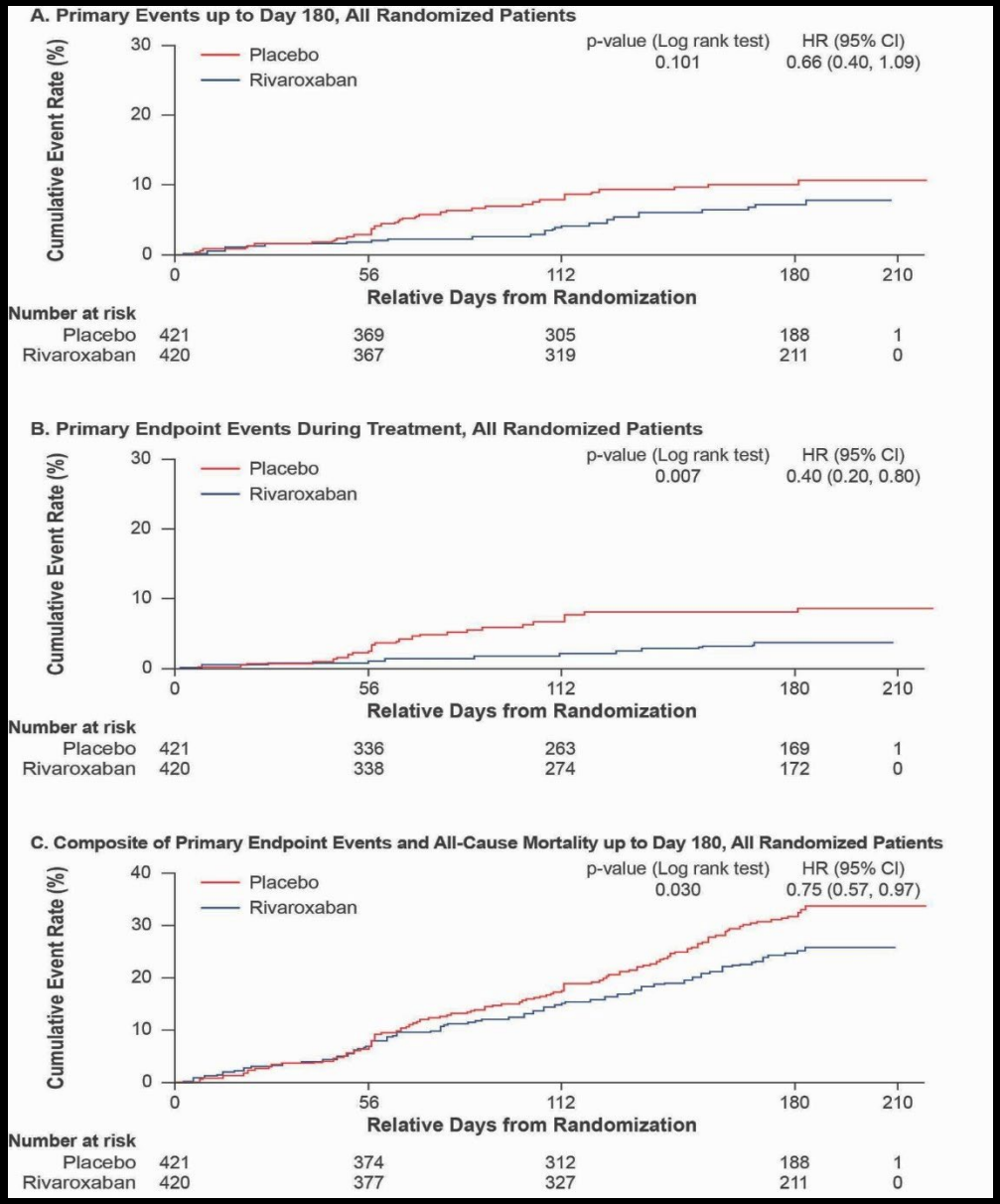
Major bleeding



Raskob G.E. et al. N Engl J Med, December 12, 2017



AVERT trial: Apixaban 2.5 mg bid vs placebo N Engl Med.2018 Dec 4



Major bleeding:

1.98% with Riva

.99% with placebo

P=.265

177 pts stopped Riva (43.7%) and 203 pt stopped placebo (50.2%) before 180 d endpoint

Primary composite endpoint not statistically significant

Secondary endpoint of while on drug/placebo: P=.007

Khorana AA et al. ASH 2018; abstract LBA-1