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

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Disclosures

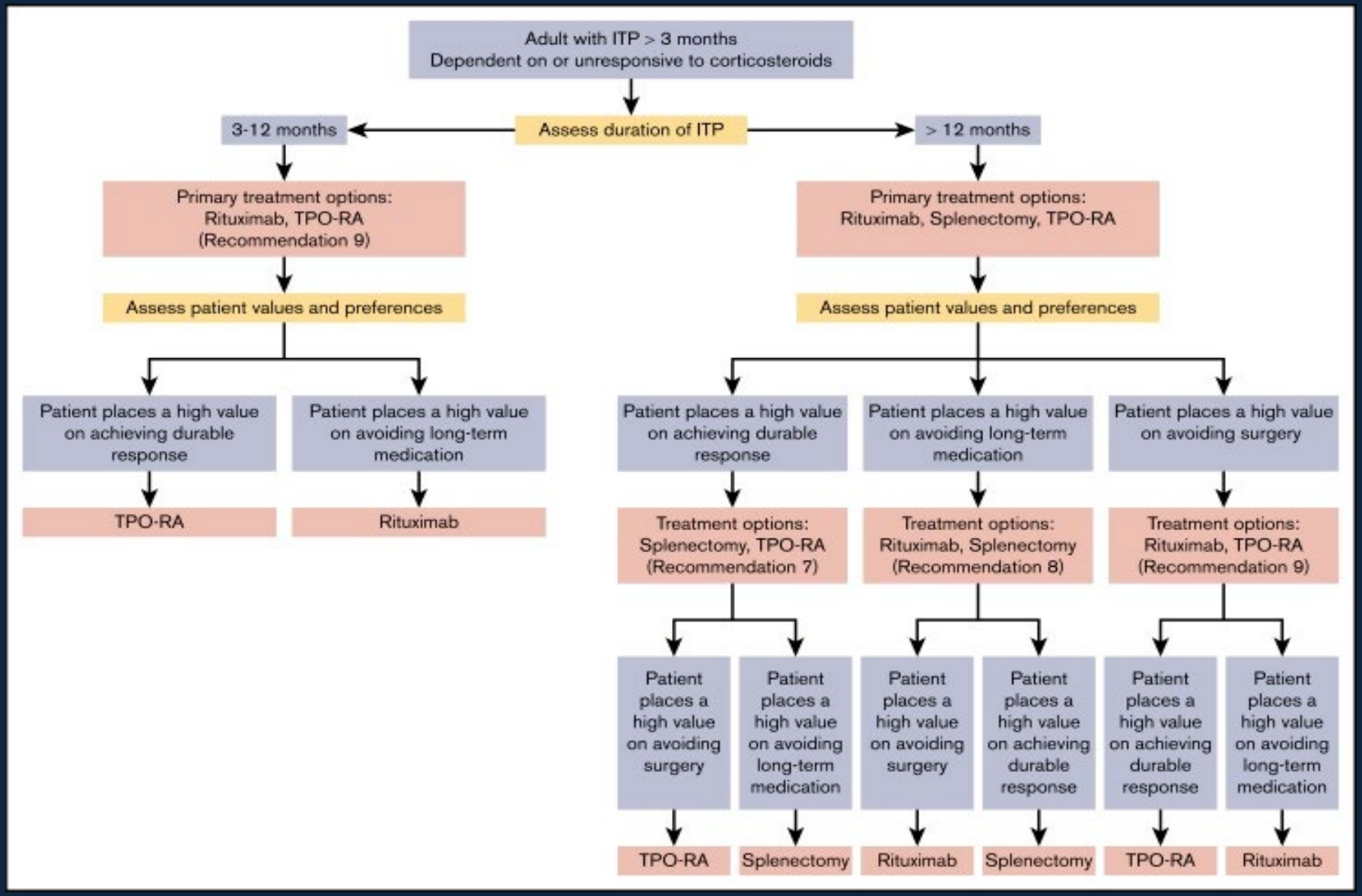
- Research- Takeda, Genentech, Bayer, NovoNordisk, Octapharma, Sangamo
- Advisory Boards-Baxalta, Bayer, Biogen, Biomarin, Genentech, NovoNordisk, Octapharma, Pfizer, Sangamo, Rigel, Novartis
- DSMB- NIH, Dimension, Octapharma, Revo, Georgetown
- Stock- Not applicable
- Employment – Not applicable
-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

Topics

- Advances in ITP
- Advances in Sickle Cell disease
- Target specific oral anticoagulation
- New antidotes to direct oral acting anticoagulants (DOACs)
- DOACS in cancer and beyond
- COVID and coagulation

Algorithm for the selection of second-line therapy in adults with ITP

American Society of Hematology 2019 Guidelines



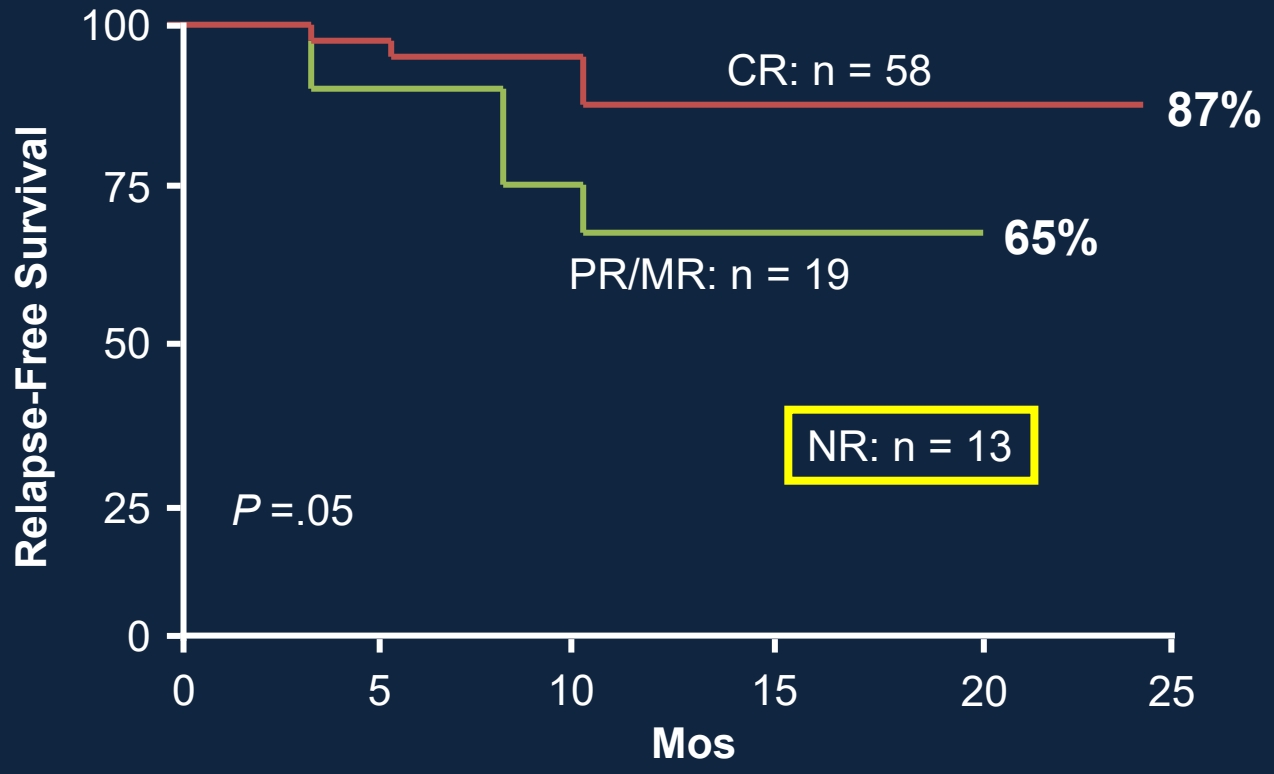
Neunert *Blood Advances* (volume 3 issue 23 pages 3829) 2019

ITP PATHOPHYSIOLOGY: IMPAIRED IMMUNE REGULATION

- Rapid platelet destruction
- Antibodies to platelet membrane antigens
  - GP IIb/IIIa
  - GP Ib/IX
- Suppression of thrombopoiesis
- Antibodies to megakaryocyte antigens
- Requires an intact RE system

GP= glycoprotein; RE= reticuloendothelial

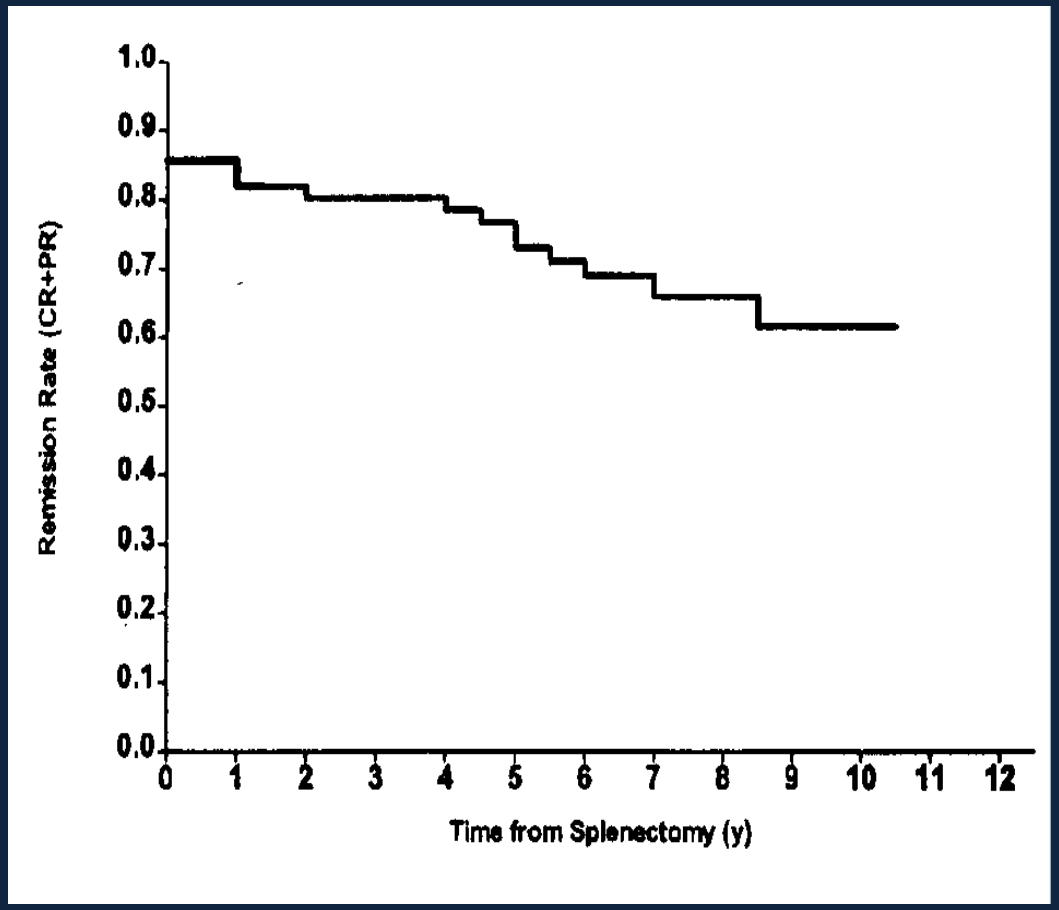
Multicenter Study: Response to High-Dose Dexamethasone



- At 15 mos of follow-up, 5 relapses each among subjects who achieved CR or PR/MR

Blood. Mazzucconi M, et al. Blood. 2007;109:1401-1407.

Splenectomy: Long Term Outcome



Schwartz et al. Am J. Hematol, 72:94-98, 2003

- Early response rate ~80%
- Responses usually rapid
- 15% relapse rate in first year, more later
- Laparoscopic splenectomy less morbid
- Predictors of response controversial
- Immunize with Pneumococcal, HIb, Meningococcal vaccine

Rituximab response in chronic ITP

CR100=48.1%; CR150=31.8%

OR30=67.7%; OR50= 60.4%

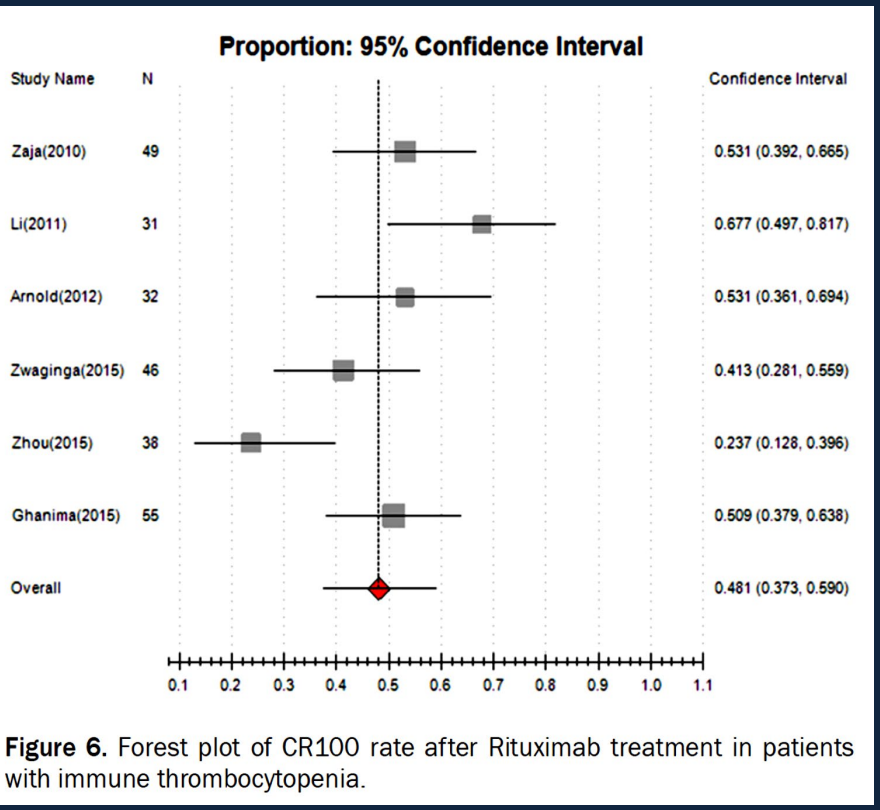


Figure 6. Forest plot of CR100 rate after Rituximab treatment in patients with immune thrombocytopenia.

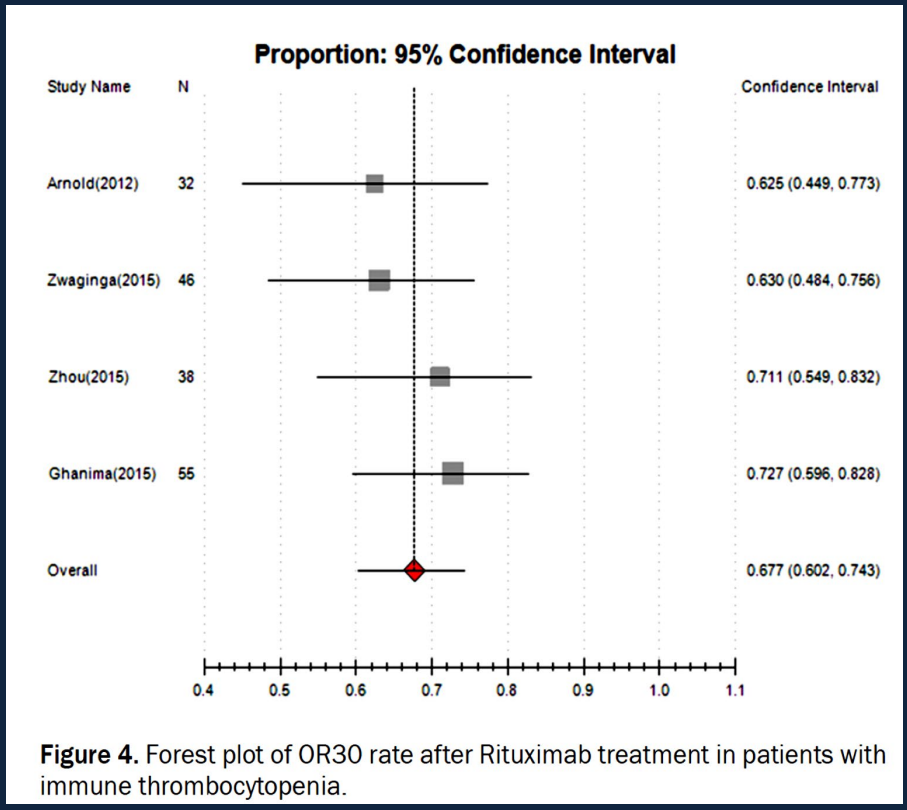
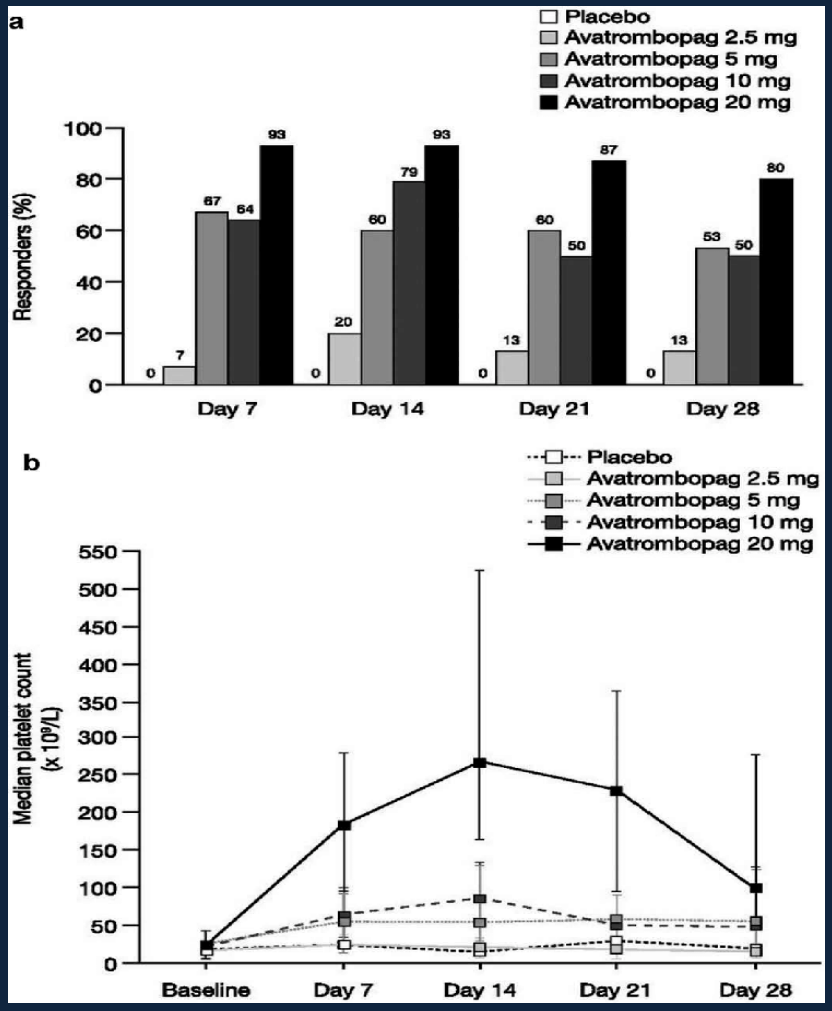


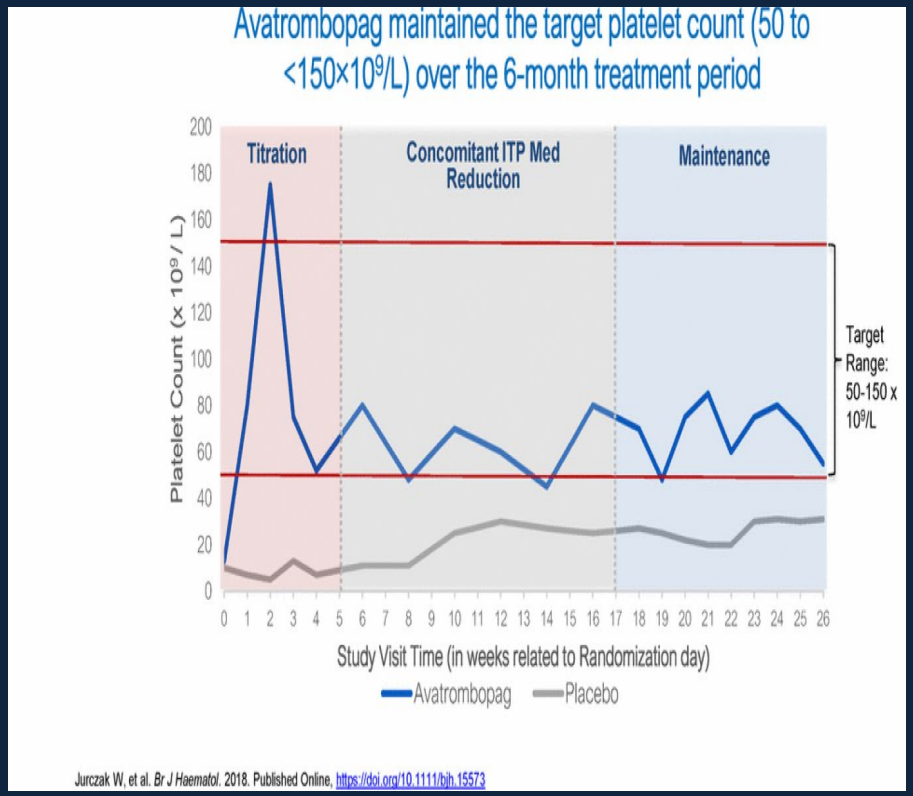
Figure 4. Forest plot of OR30 rate after Rituximab treatment in patients with immune thrombocytopenia.

Feng R et al. Int J Clin Exp Med 2016;9(2):918-926

Avatrombopag-the new TPO-mimetic 2019



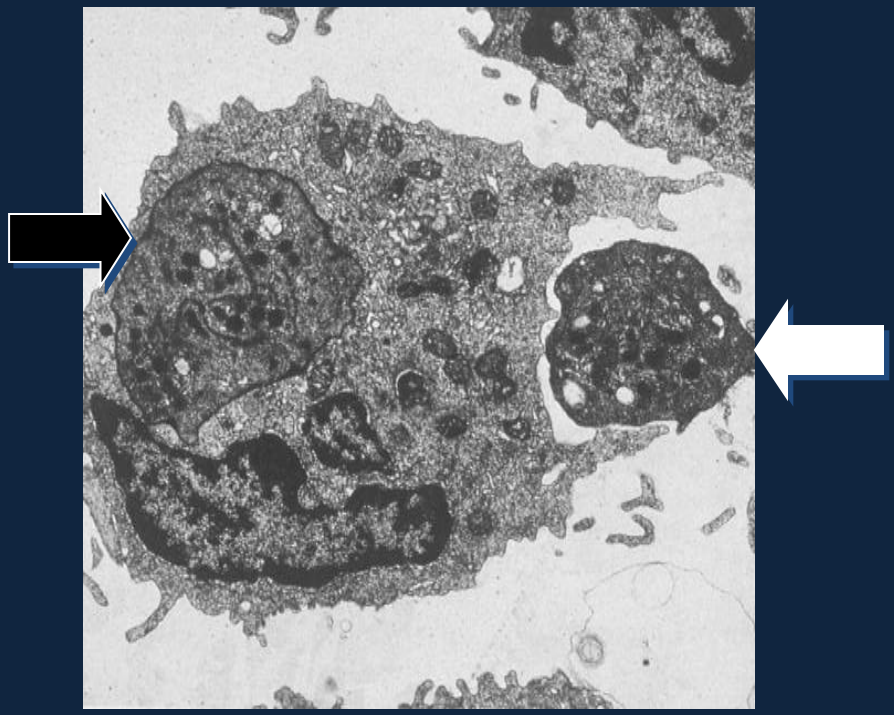
Phase 3 study-medilan platelet counts



Blood. 2014 Jun 19;123(25):3887-94

Pathophysiologic Process

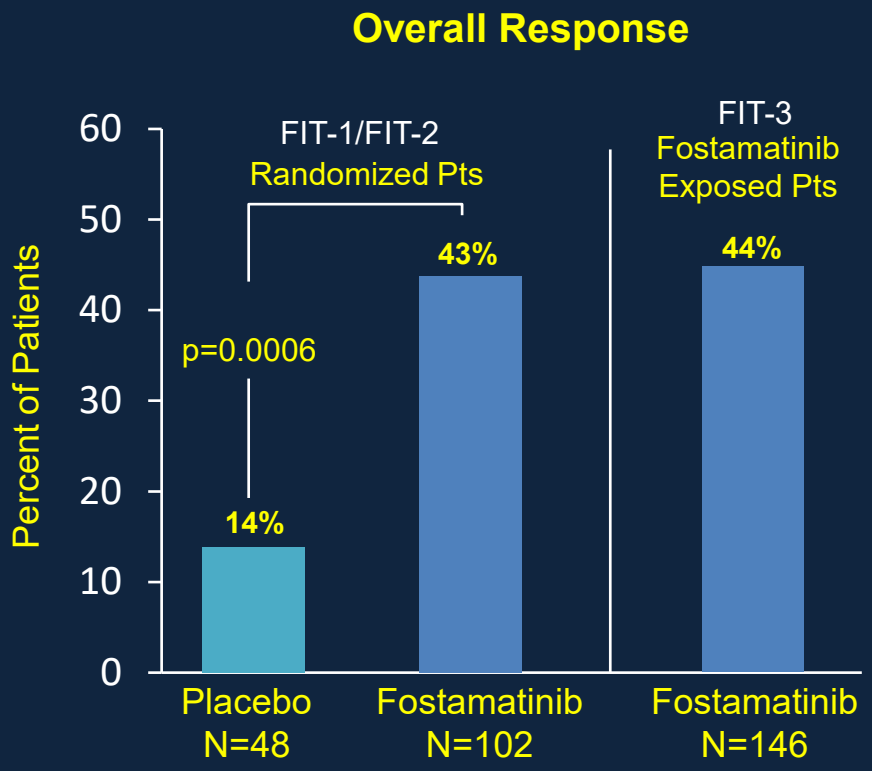
↑ Platelet Destruction



Macrophage Containing One Platelet (white arrow) and Engulfing Another (black arrow)

Overall Response (OR) in chronic ITP

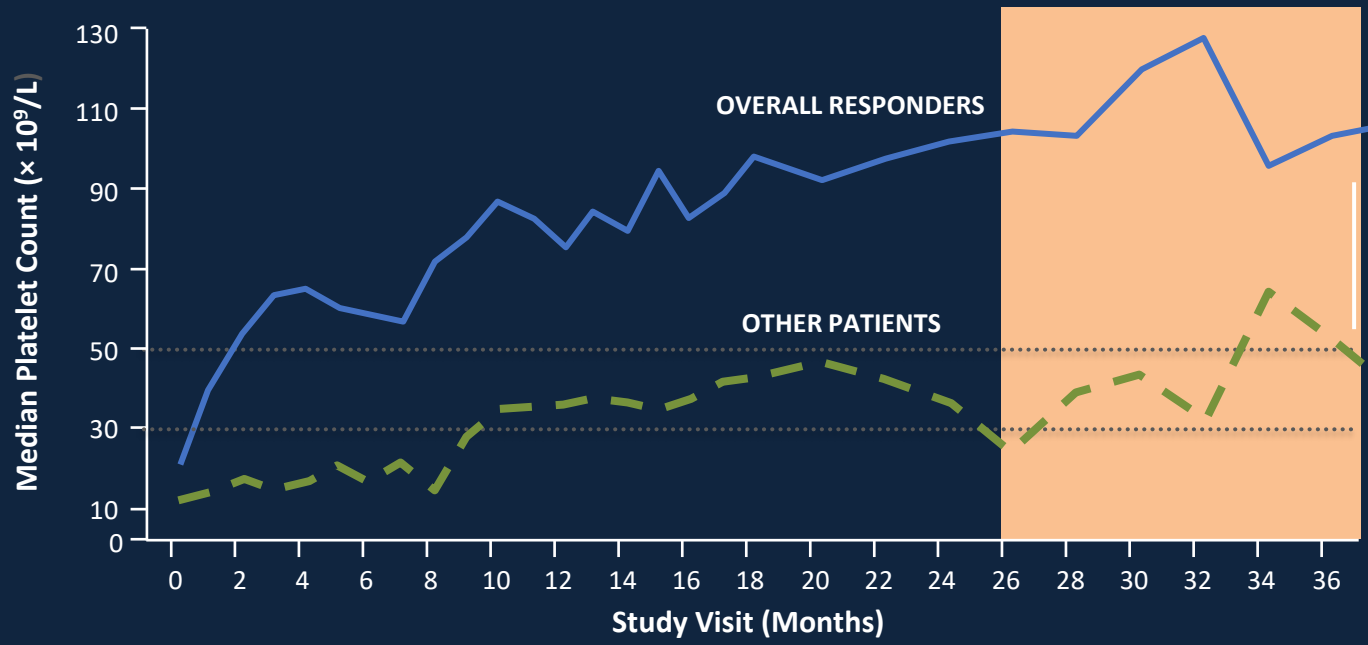
- Overall Response defined as ≥1 platelet count ≥50,000/µL in the first 12 weeks of fostamatinib treatment unrelated to rescue therapy
- Overall Response occurred in 64 of 146 (44%) patients in the fostamatinib studies



Interim analysis. Data cutoff April 14, 2017.
Bussel JB, et al. *Am J Hematol*. 2019;94(5):546-553.

36-month Follow-up Shows Continued Response

Overall responders: patients who had ≥1 platelet count ≥50,000/μL in the first 12 weeks of Fostamatinib treatment unrelated to rescue therapy



Overall Responder:	53	63	62	56	53	47	46	47	40	37	40	35	35	37	31	33	36	34	33	34	35	32	28	24	21	17	13	9
Other Responder:	66	67	57	59	52	46	43	35	18	18	16	14	15	16	15	16	15	15	15	15	15	13	9	8	7	4	4	2

*Data cutoff March 8, 2018 (FEP).
Shaded area includes data points with <10 patients.

1. Duliege AM, et al. *Blood Supplement*. 2018;132:736. 2. Data on file, Rigel Pharmaceuticals, Inc. April 2018.

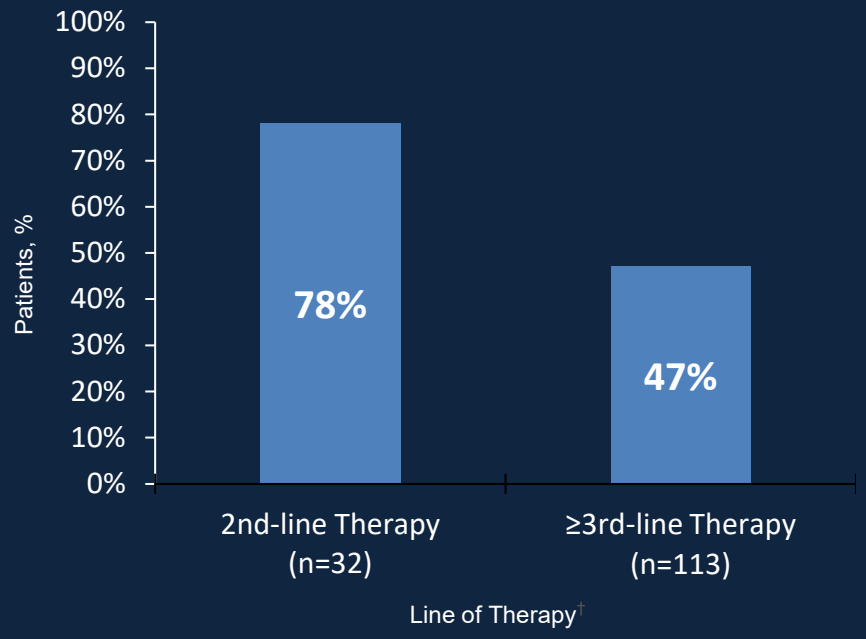
Other Patients:
Patients may have experienced clinical benefit including

- platelet counts ≥50,000/μL **after** the initial 12-week period
- platelet counts ≥30,000/μL
- decreases in bleeding or rescue.

This group also includes patients who did not respond.

Platelet Response at Anytime in Earlier Lines of Treatment

More patients responded to fostamatinib as 2nd line therapy

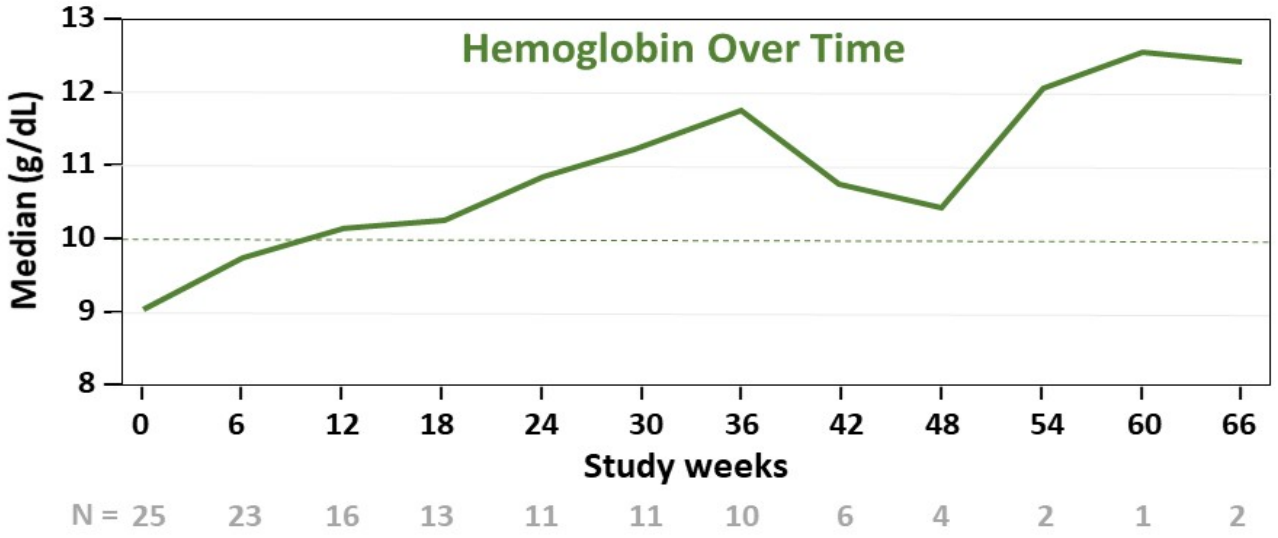


*A platelet response was defined as achieving ≥1 platelet count of ≥50,000/μL (without rescue therapy) at any visit.
†1st line: any combination of steroids, IVIg, and/or anti-D.
ASH 2019 Abstract.

ABS 3518: Fostamatinib, a Spleen Tyrosine Kinase (SYK) Inhibitor, for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia (wAIHA): Final Results of the Phase 2, Multicenter, Open-Label Study

Adult patients with primary or secondary wAIHA, documented by IgG positive DAT; failed ≥1 prior treatment for wAIHA

Efficacy endpoint: achieving Hgb >10 g/dL with an increase of ≥2 g/dL from baseline by Week 24 without rescue therapy or RBC transfusion



Rogers KA et al. ASH 2019

Evolving ITP/AIHA therapies of the future

ABS 897: Rozanolixizumab, an Anti-FcRn Antibody: Final Results from a Phase II, Multiple-Dose Study in Patients with Primary Immune Thrombocytopenia Robak T et al. ASH 2019

- Rozanolixizumab: targets the human neonatal Fc receptor (FcRn). By blocking IgG recycling, this SC monoclonal antibody reduces pathogenic autoantibody levels

Table 3. Mean platelet count (PPS) and mean observed IgG concentration (PD-PPS) on Day 8, after one dose of rozanolixizumab

	Rozanolixizumab doses				
	20 mg/kg N=12	15 mg/kg N=12	10 mg/kg N=11	7 mg/kg N=15	4 mg/kg N=14
Platelet count (x10^9/L), mean (range)					
n	12	12	11	14	14
Baseline†	18.0 (4–37)	1.2 (6–38)	18.5 (6–53)	13.7 (5–24)	17.7 (5–36)
Day 8	144.5 (9–548)*	1 7.8 (8–486)	40.9 (3–166)	21.0 (6–57)	27.1 (3–105)
Observed IgG concentration (g/L), mean (range					
n	12	12	11	15	14
Baseline	9.9 (7.3–15.8)	0.2 (5.8–16.0)	11.3 (7.2–22.5)	11.1 (6.7–14.7)	9.6 (6.2–13.4)
Day 8	3.9 (2.7–6.2)	5.1 (2.0–10.2)	6.2 (3.7–16.6)	8.2 (4.9–11.1)	7.1 (4.5–10.5)

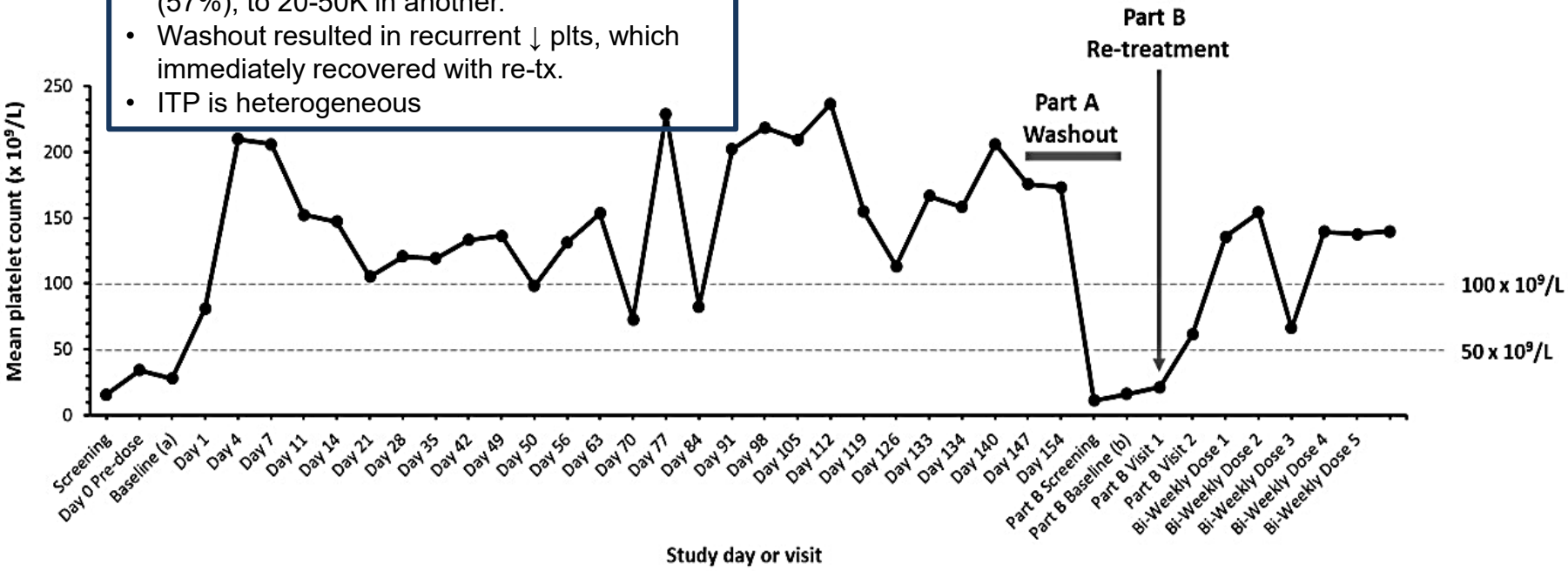
*In the 20 mg/kg dose cohort 12 patients had baseline values, which reduced to 11 by Day 8; †Central laboratory measurements

Evolving ITP/AIHA therapies of the future

ABS 898: Inhibition of the Classical Pathway of Complement with Sutimlimab in Chronic Immune Thrombocytopenic Purpura Patients without Adequate Response to Two or More Prior Therapies **Broome CA et al.**
ASH 2019

Figure. Mean Platelet Counts (x 10^9/L) Over Time in Patients Receiving Sutimlimab

- 7 refractory pts: unresponsive to >2 tx modes
- Platelets >50K in <24 hrs and sustained in 4 (57%); to 20-50K in another.
- Washout resulted in recurrent ↓ plts, which immediately recovered with re-tx.
- ITP is heterogeneous



(a) The value at Baseline is the average of all platelet counts during screening period including Day 0 pre-dose in Part A.
(b) The value at Part B Baseline is the average of all platelet counts during screening period in Part B.

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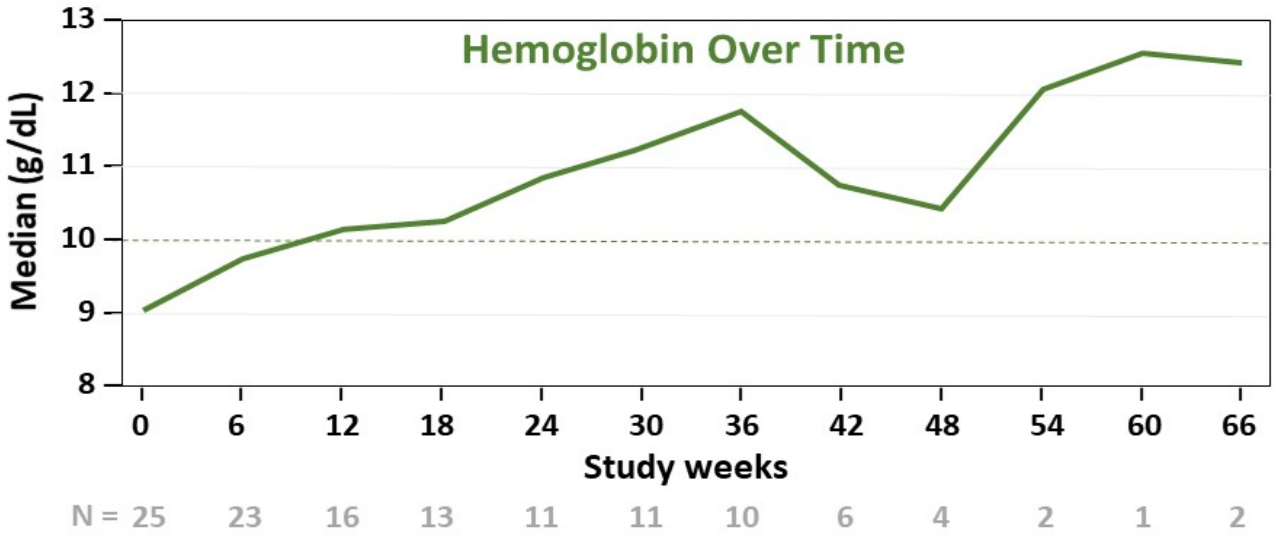
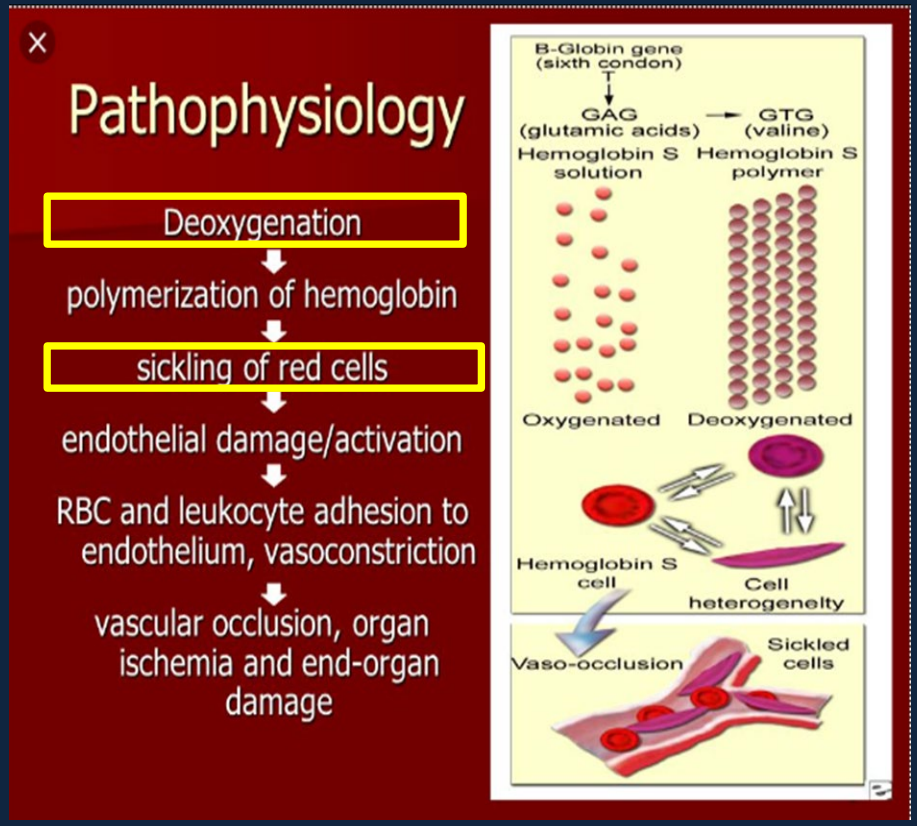


Rogers KA et al. ASH 2019

Pathophysiology of Sickle Cell disease

- Genetics : HOMOZYGOSITY for sickle cell *HbS gene m*issense mutation (Glu6Val) in the β-globulin gene



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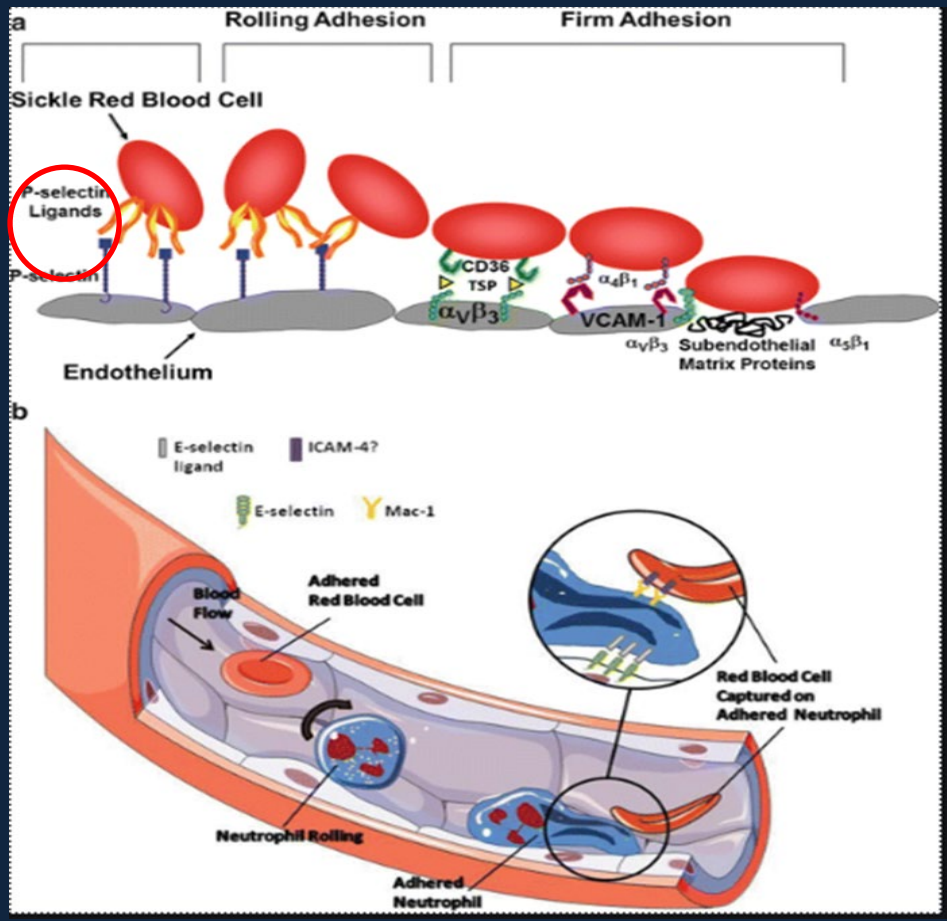


https://media.springernature.com/original/springer-static/image/chp:10.1007/978-3-319-06713-1_3/MediaObjects/324557_1_En_3_Fig4_HTML.gif

ORIGINAL ARTICLE

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

July 19, 2018; N Engl J Med 2018; 379:226-235

Rationale:

Sickle cells have LOWER redox ratio (NADH: NAD^+ +NADH) and thus increased oxidative stress

L-glutamine is an essential amino acid required to synthesize NAD^+

Uptake of L-glutamine is HIGHER in sickled cells →↑ NADH and ↓ Oxidative stress; decreased sickling

Supplementation of L-glutamine shown to increase intracellular NAD^+

Hypothesis: higher L-glutamine consumption by sickled cells may be facilitated by PO L-glutamine

Results

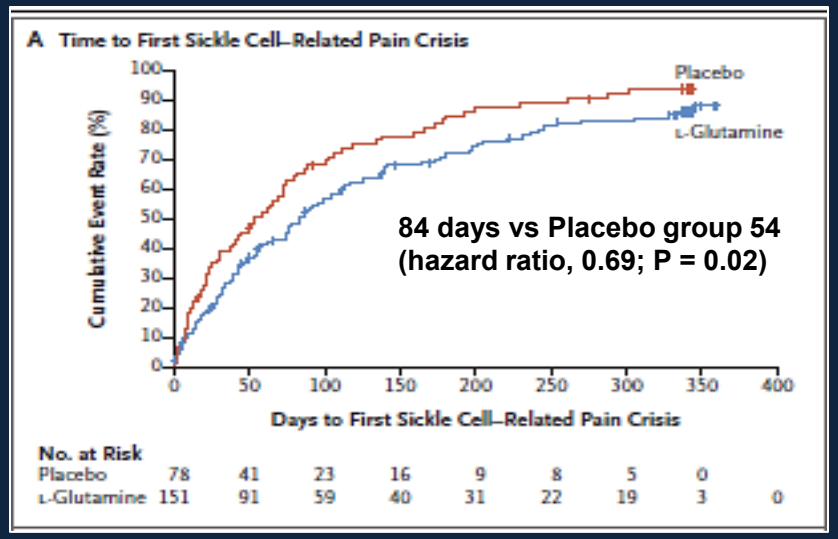
- **Primary End Point: Pain Crises over 1 yr**

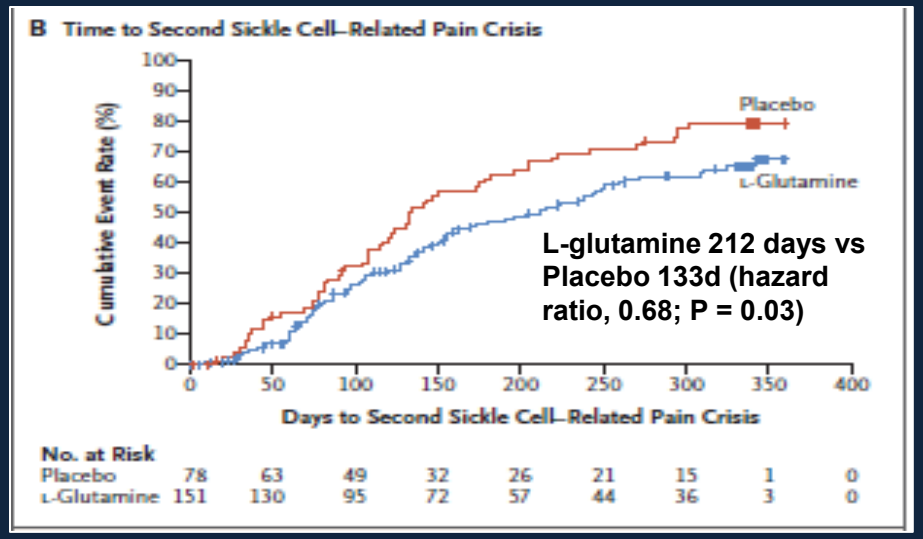
  median: L-glutamine 3.0 vs Placebo group 4.0 (P = 0.005); 25 % reduction

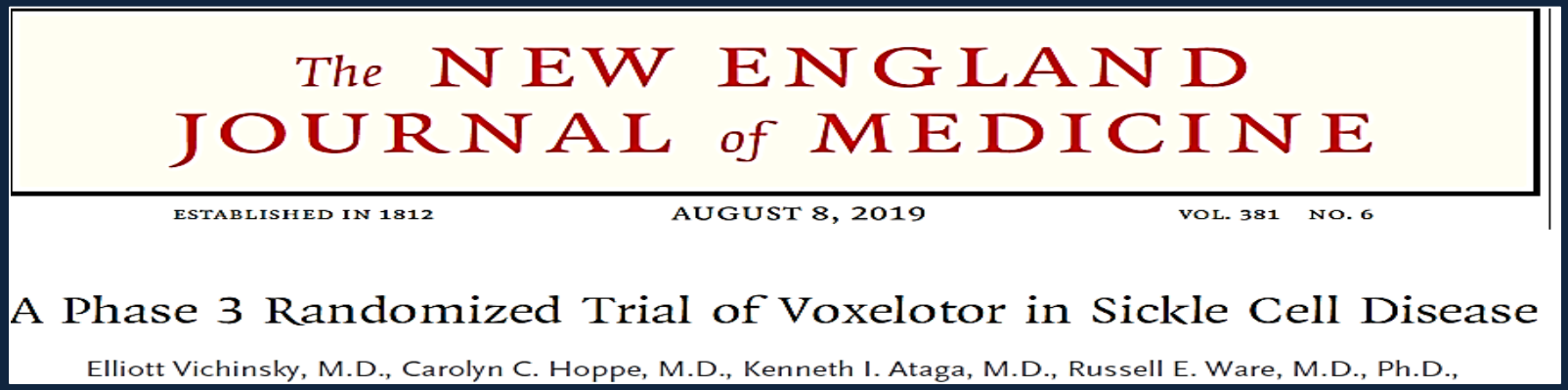
- **Secondary endpoint: Hospitalizations**
  - median: L-glutamine 2.0 vs Placebo group 3.0 (P = 0.005); 33% reduction

- **No change in H/H or hemolytic markers**

- **2 Cardiac deaths in L-glutamine cohort**







The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 8, 2019 VOL. 381 NO. 6

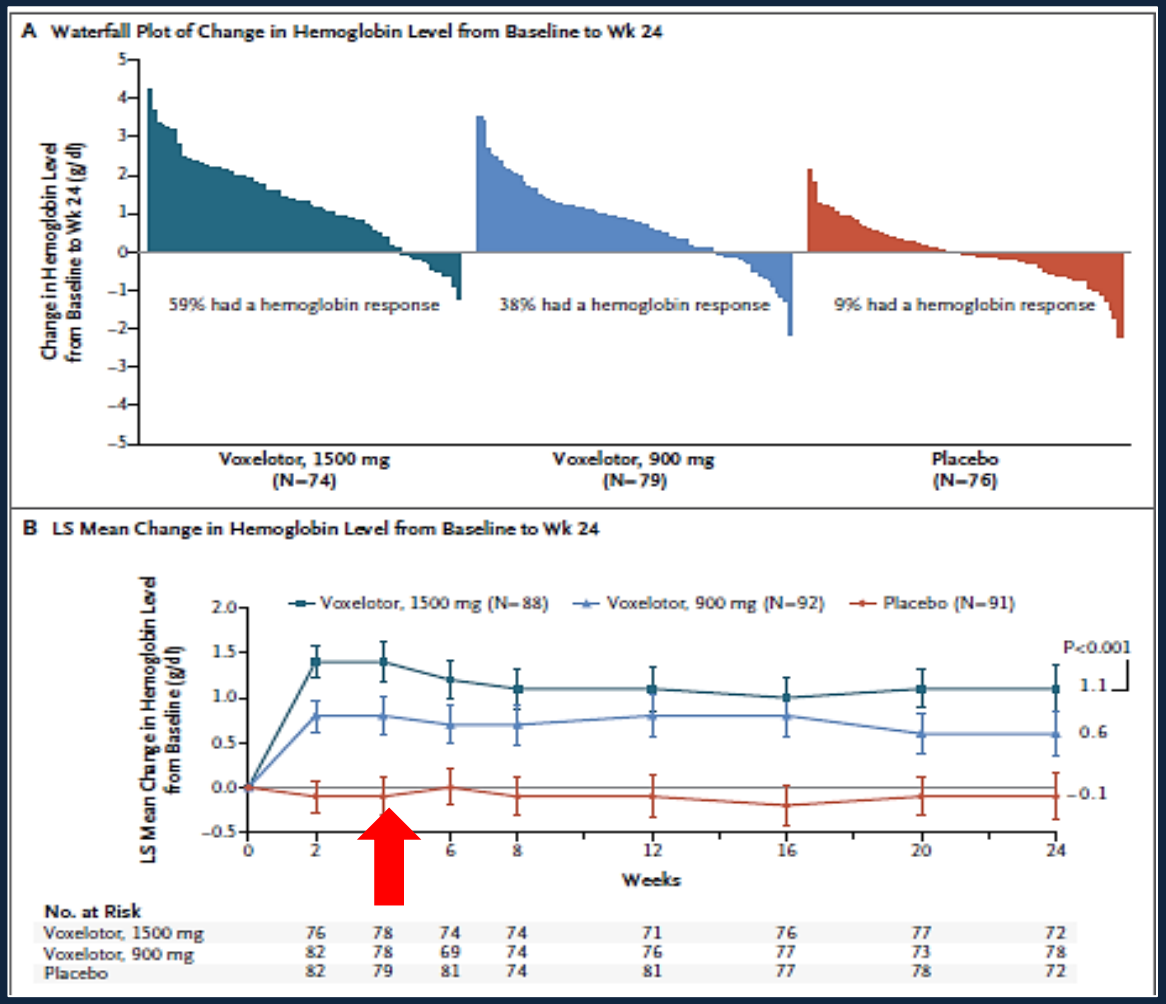
A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D.,

Rationale:

- Deoxygenated sickle cell hemoglobin POLYMERIZATION drives pathophysiology
- Direct inhibition of HgS polymerization has potential to favorably modify disease outcomes
- Voxelotor is a HgS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the Oxygenated Hemoglobin state
- Hypothesis: voxelotor can improve markers of hemolysis (HgB, bilirubin, LDH, reticulocyte)

Voxelotor mediated significant increases in Hgb levels in a dose response manner



- No significant differences in absolute retic counts or LDH
- Secondary endpoint: Annualized Rate of Vaso-occlusive Crisis:
- ITT: Voxelator 1500mg **2.7** vs Voxelator 900mg **2.7** vs Placebo **3.1**
- The incidence of vaso-occlusive crisis DID NOT DIFFER SIGNIFICANTLY

ORIGINAL ARTICLE

N Engl J Med 2017; 376:429-439

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie,

Rationale:

- Upregulation of P-SELECTIN on endothelial cells/platelets involved in Vaso-occlusion
- Crizanlizumab is a humanized monoclonal antibody that binds P-selectin and blocks interaction with P selectin glycoprotein ligand 1
- Hypothesis: Crizanlizumab can decrease rate of sickle cell crisis at 1 year

Crizanlizumab reduced number of pain crises in SCD

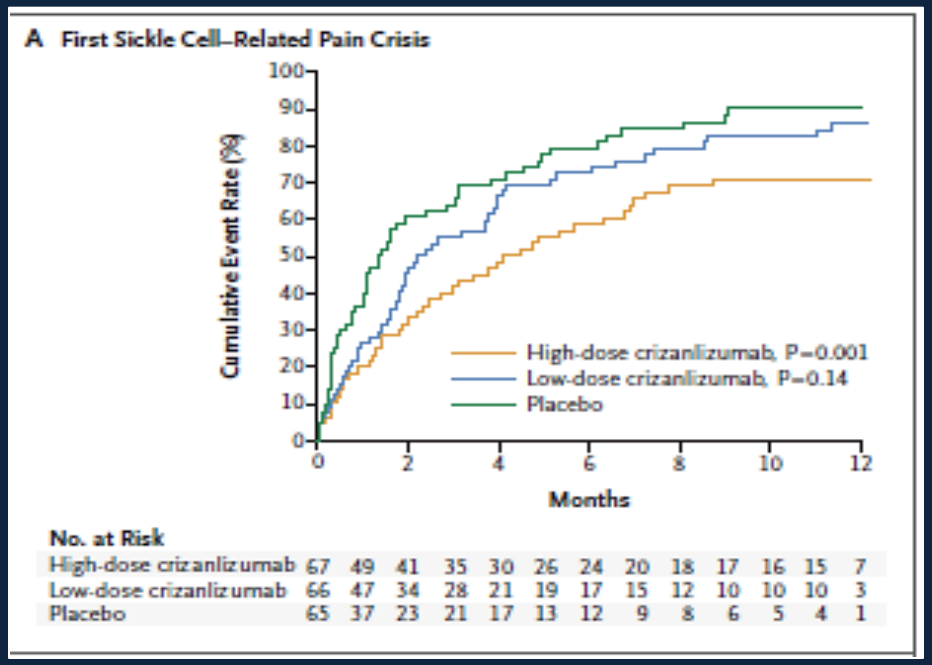
Crizanlizumab 5.0mg/kg 1.63 vs
Crizanlizumab 2.5mg/kg 2.01 vs
Placebo 2.98

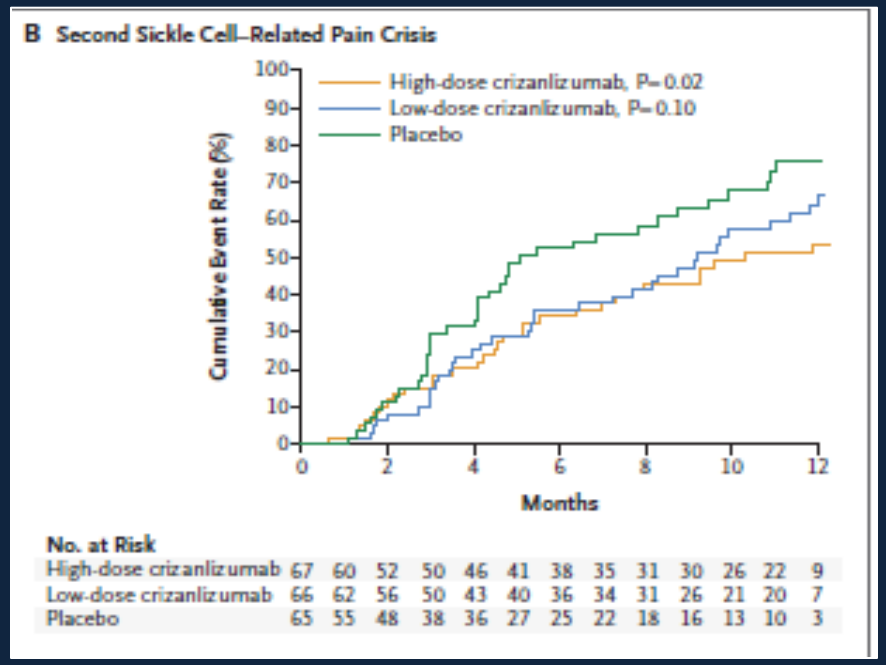
N Engl J Med 2017; 376:429-439

Crizanlizumab 5.0mg/kg vs Placebo (P<0.001)

Regardless of concurrent hydroxyurea use subgroup analysis
Regardless of prior crises (2-4, 5-10) subgroup analysis

Did not improve markers of hemolysis or reduce rate of hospitalization

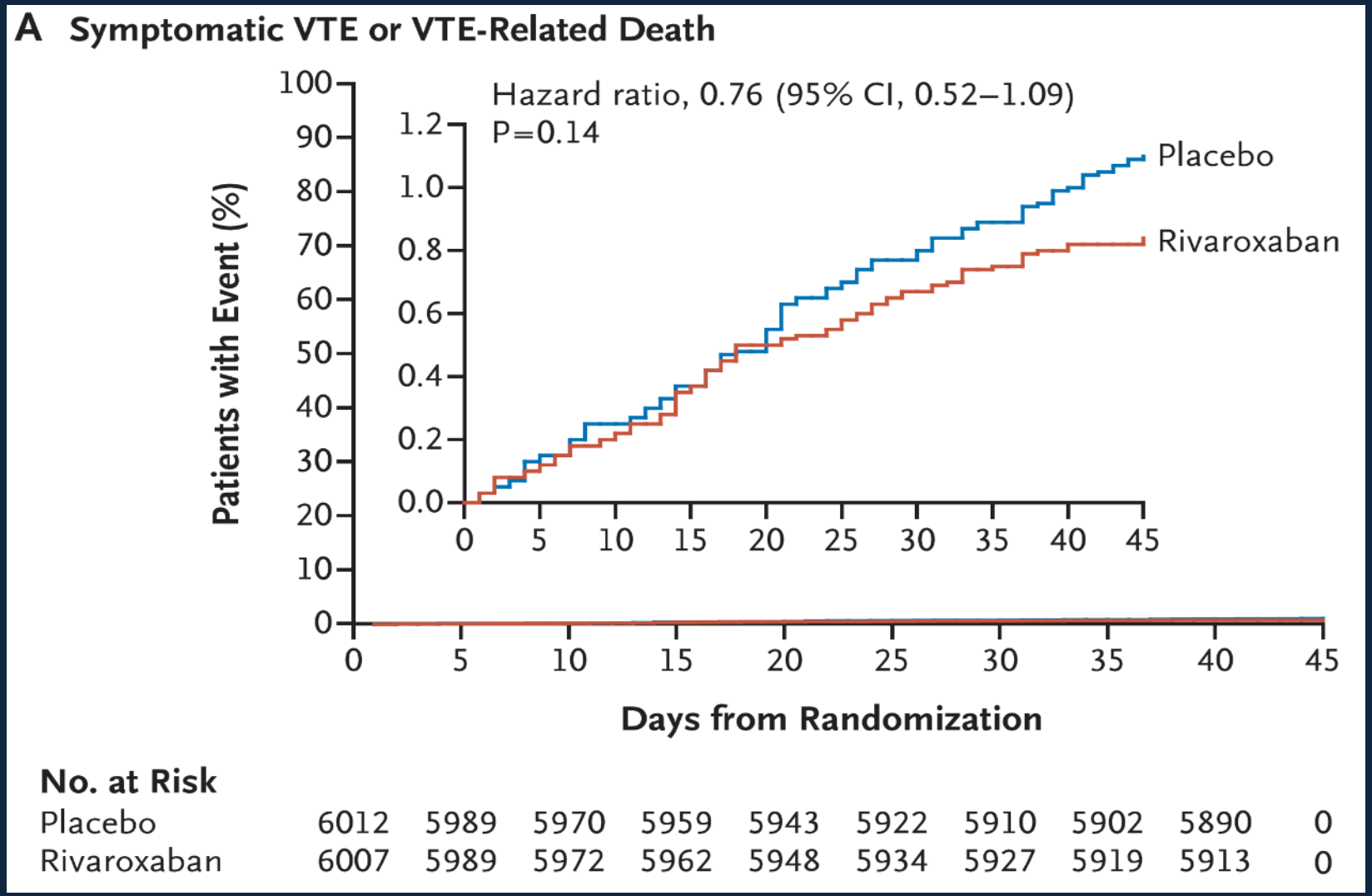




	Crisis Reduction	Hemolysis Marker Reduction	Prolong Time to Crisis	Cost
L-Glutamine	Yes	No	Yes	$65/yr
Voxelotor (HbB polym inh)	No	Yes	n/a	$120,000/yr
Crizanlizumab (P-selectin)	Yes	No	Yes	$1,2000,000/yr

MARINER Trial

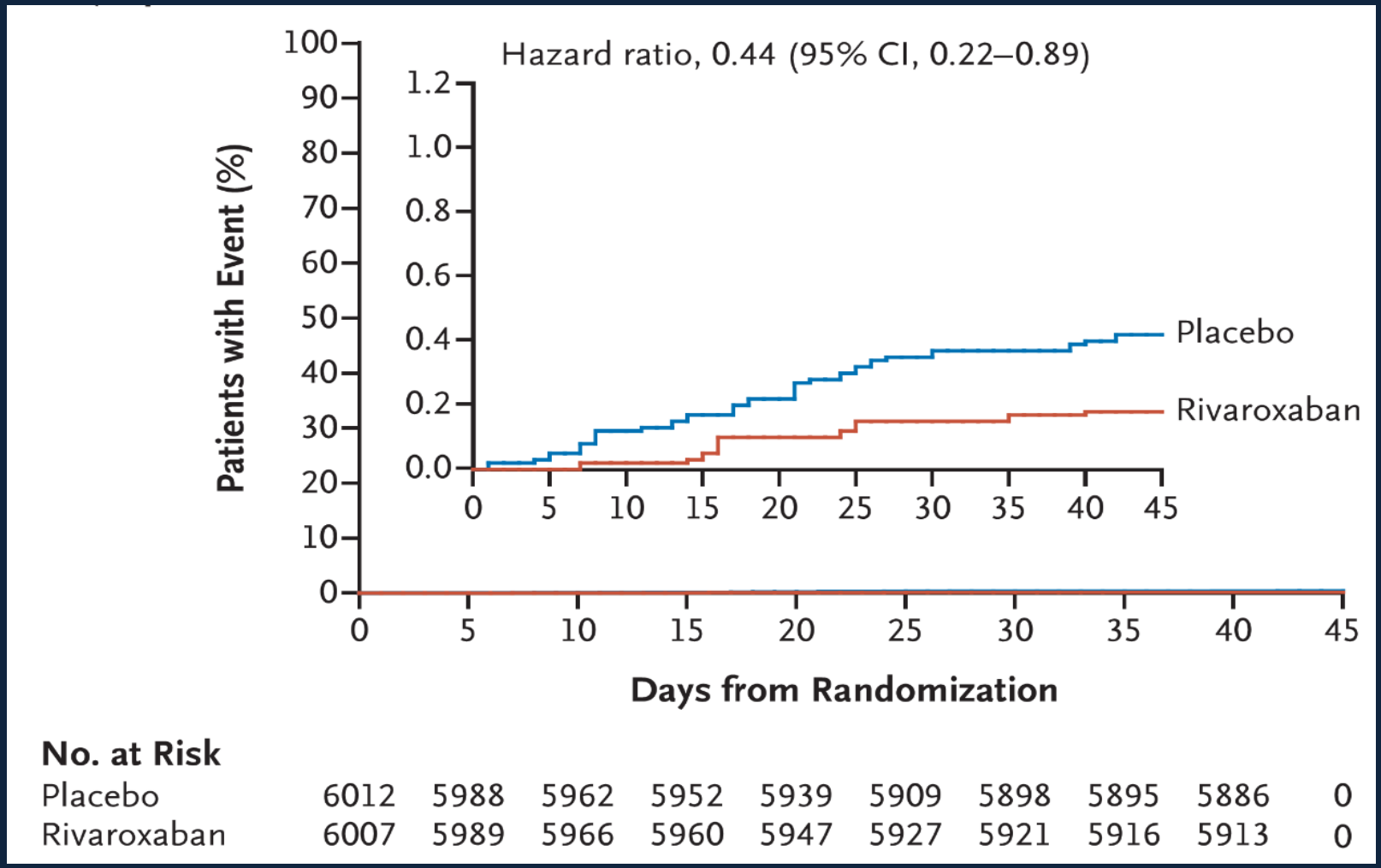
Primary Efficacy Endpoint



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

MARINER Trial

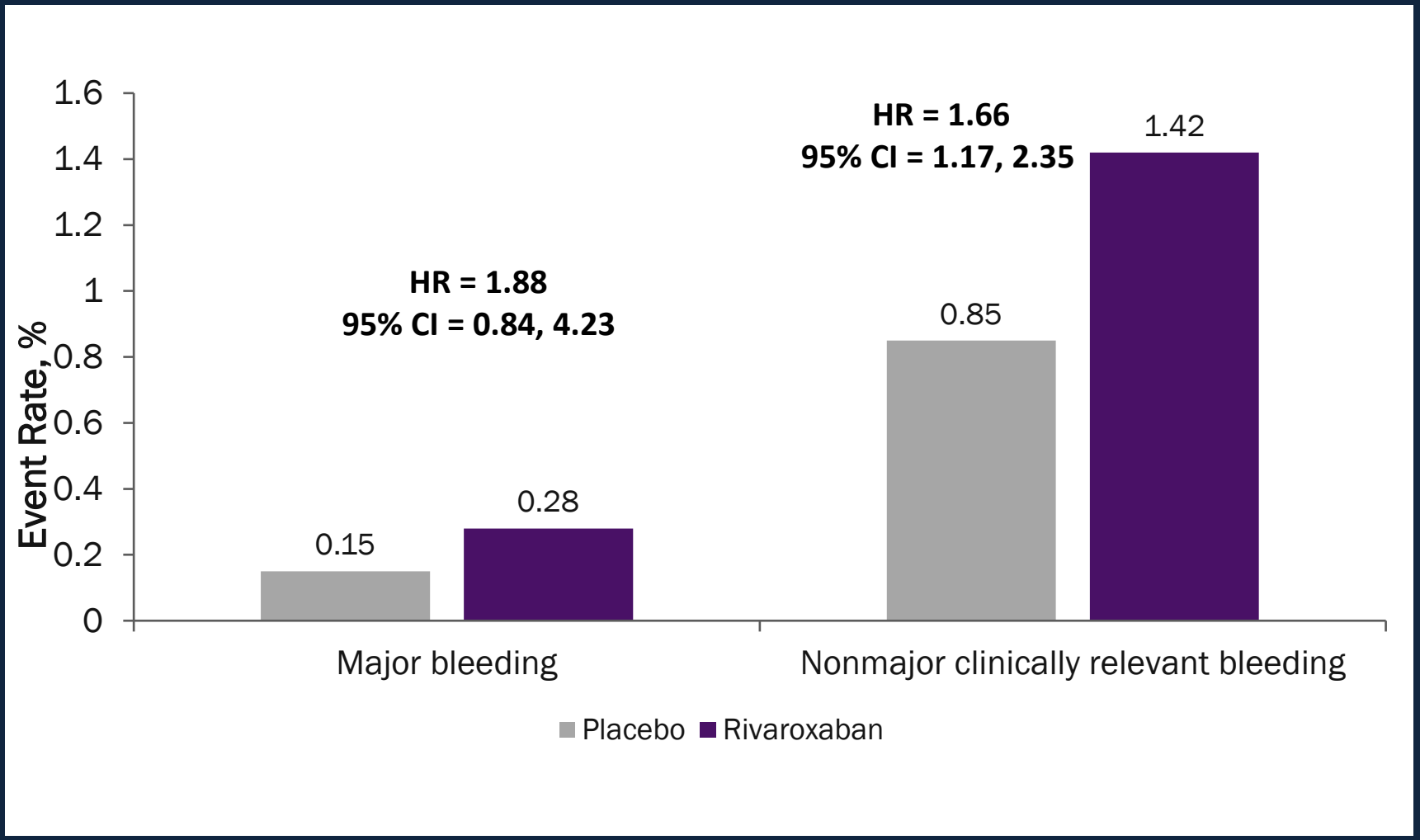
Symptomatic VTE



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

MARINER Trial

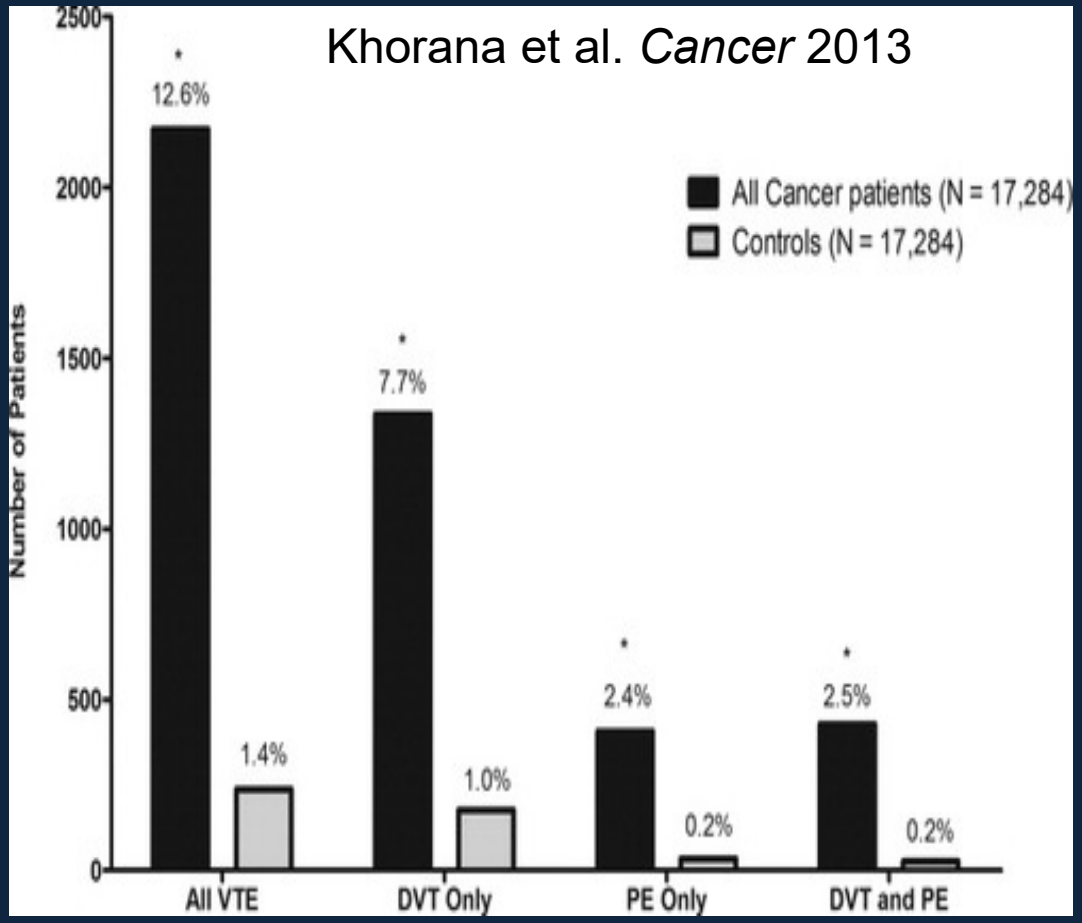
Major *Bleeding Complications*



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

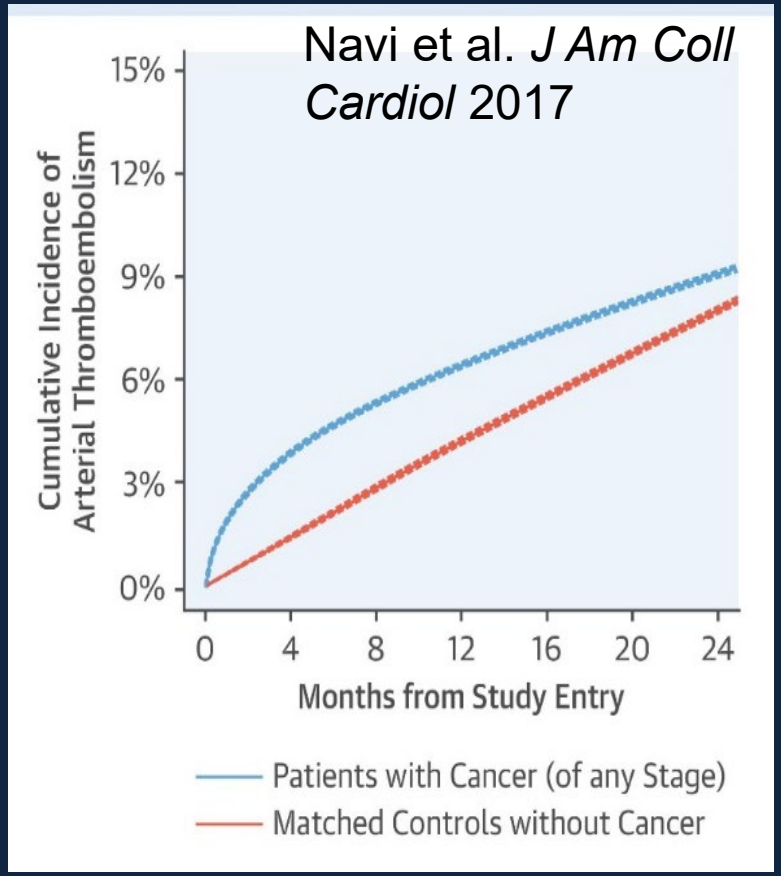
Cancer-associated Thrombosis (CAT)
Scope of the Problem

Khorana et al. *Cancer* 2013



12.6% rate of VTE 3-12 mos from diagnosis in US ambulatory patients with bladder, colorectal, lung, ovary, pancreas, or gastric cancers

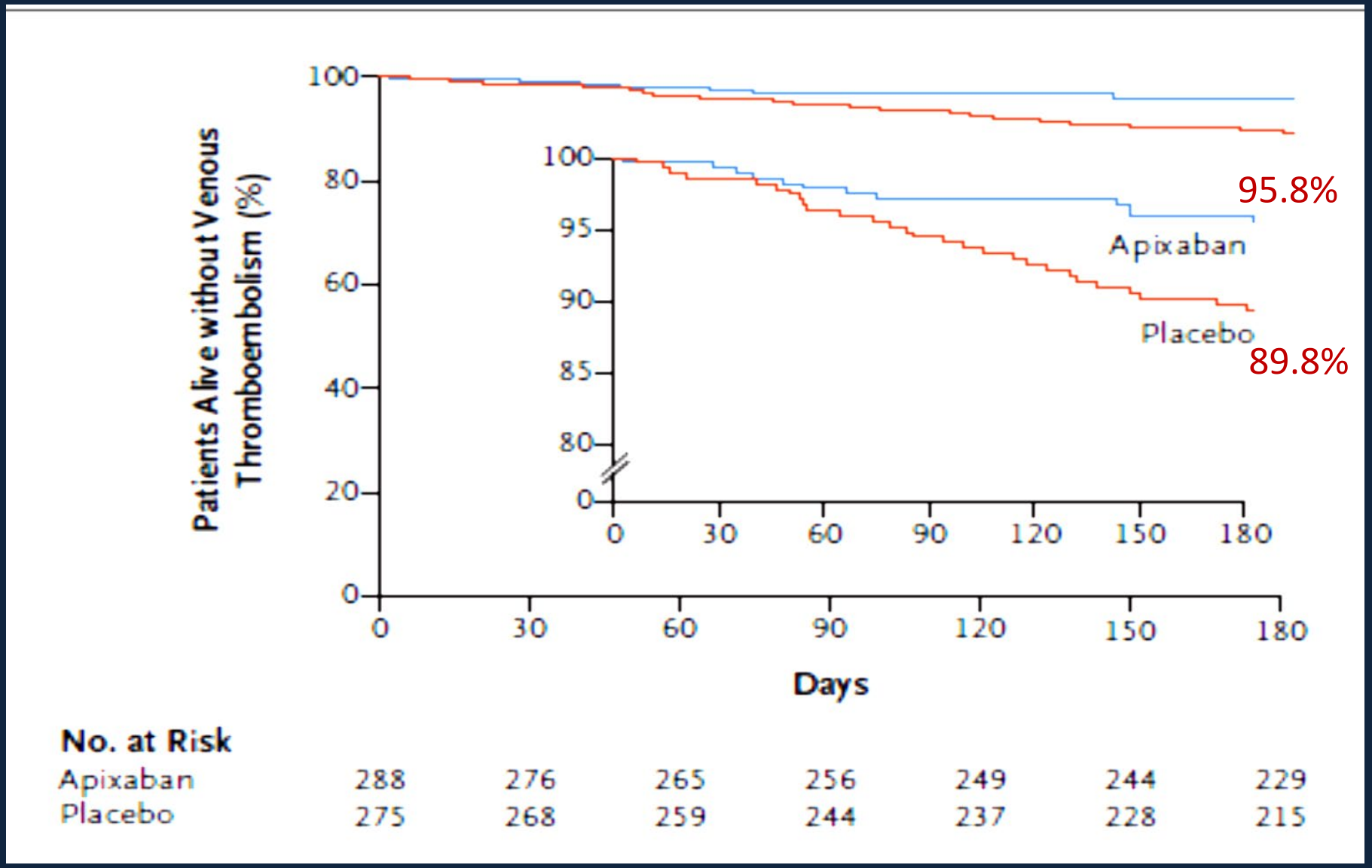
Navi et al. *J Am Coll Cardiol* 2017



6-month cumulative incidence of arterial thromboembolism 4.7% (2% MI, 3% stroke) with cancer v 2.2% in controls (HR: 2.2)

What evidence do we have for use of DOACs in primary prevention of VTE in CA patients?

AVERT: Results



Carrier M, et al. *N Engl J Med*. 2019;380:711-719.

NNT=17

AVERT: Results

	Apixaban (n=288)	Placebo (n=275)	HR (95% CI)	P Value
VTE DVT PE	4.2% 2.4% 1.7%	10.2% 4.4% 5.8%	0.41 (0.26-0.43)	<0.01
Secondary Death from any cause	12.2%	9.8%	1.29 (0.98-1.71)	

NNT=17

Carrier M, et al. *N Engl J Med*. 2019;380:711-719.

AVERT: Safety Outcomes

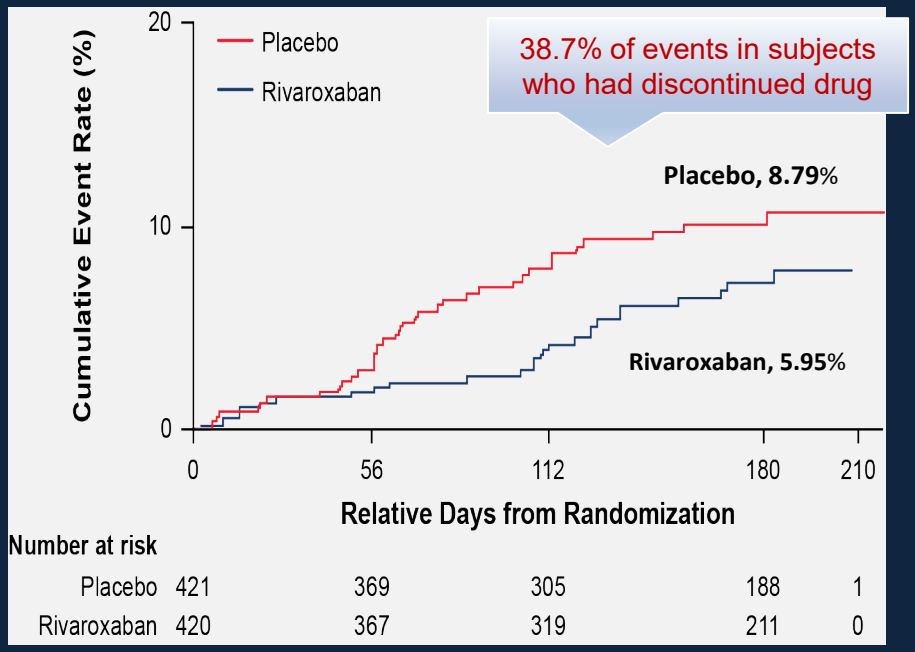
	Apixaban (n=288)	Placebo (n=275)	HR (95% CI)	P Value
Primary Major bleeding	3.5%	1.8%	2.0 (1.01-2.395)	0.046
Secondary CRNM bleeding	7.3%	5.5%	1.28 (0.89-1.84)	

On-treatment NNH = 100

Carrier et al, *NEJM* 2019

CASSINI Primary Outcome: *All Randomized Patients*

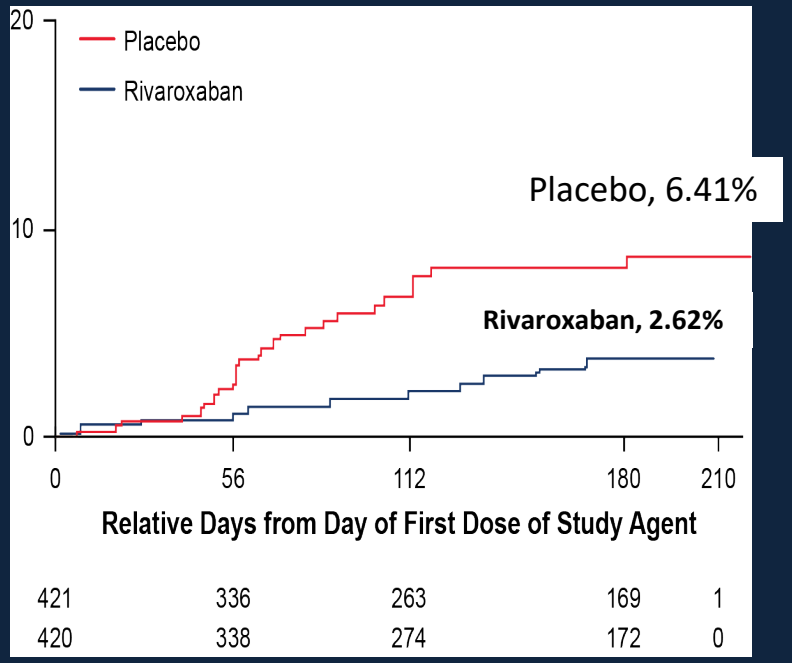
Up to Day 180 (primary)



HR, 0.66; 95% CI, 0.40-1.09; *P*=0.101

NNT=35

On-treatment



HR, 0.40; 95% CI, 0.20-0.80; *P*=0.007

NNT=26

Khorana et al, LBA-1, *ASH* 2018; *NEJM* 2019

CASSINI: Safety Outcomes

Table 3. Primary Safety End Points, According to Trial Group.*

End Point	Placebo (N=404)	Rivaroxaban (N=405)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary safety end point: major bleeding	4 (1.0)	8 (2.0)	1.96 (0.59–6.49)	0.26
Secondary safety end point: clinically relevant nonmajor bleeding	8 (2.0)	11 (2.7)	1.34 (0.54–3.32)	0.53
Major and clinically relevant nonmajor bleeding	12 (3.0)	19 (4.7)	1.54 (0.75–3.17)	0.24

* Data are for the 809 patients who took at least one dose of placebo or rivaroxaban (safety population) during the intervention period and as adjudicated by an independent committee whose members were unaware of the group assignments. Bleeding events were defined according to the International Society on Thrombosis and Hemostasis.[17]

Sites of major bleeding included gastrointestinal (n=8), intraocular (n=2), and intracranial (n=2). Fatal bleed (n=1, rivaroxaban arm).

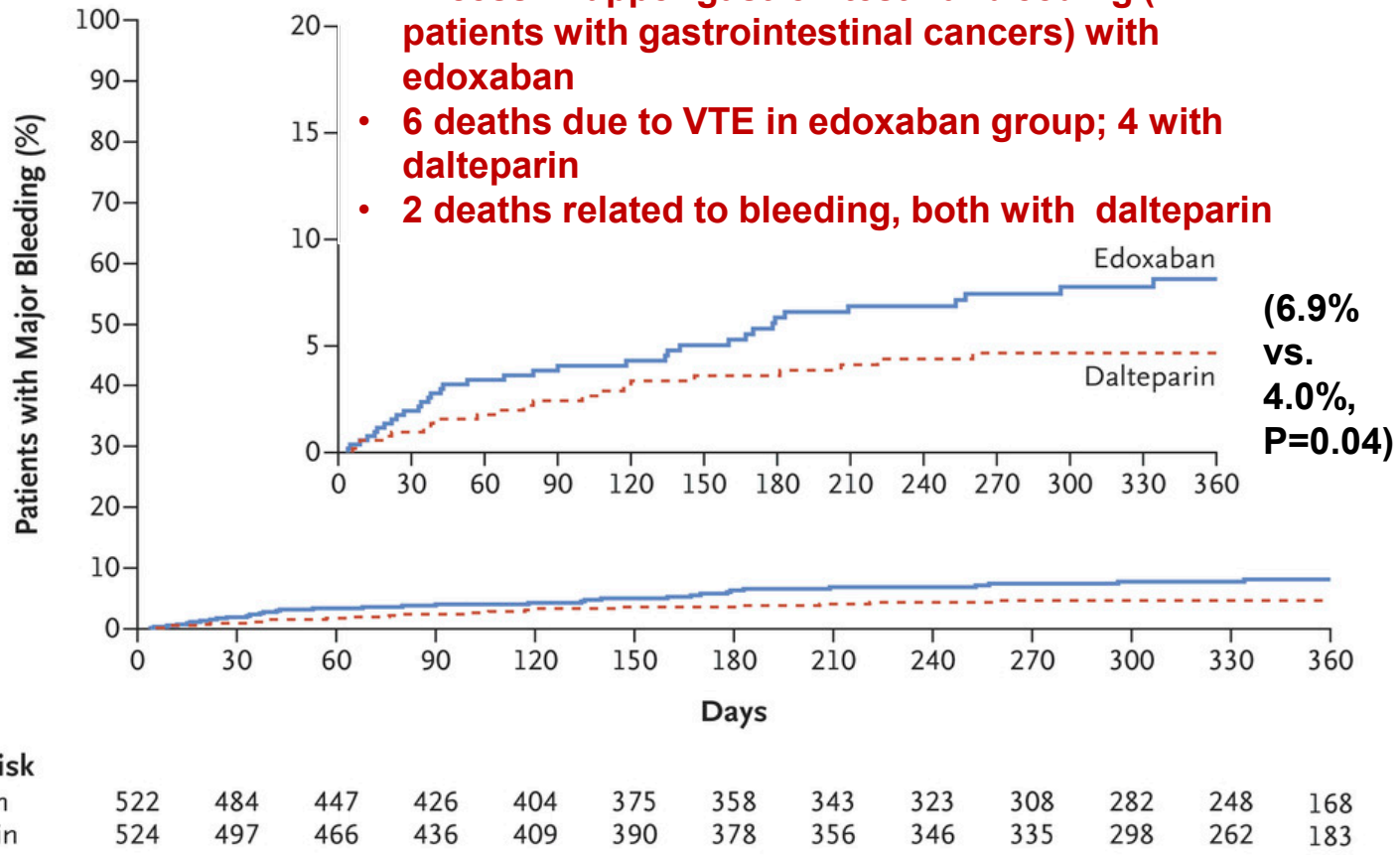
NNH=101 (MB), 135 (CRNMB)

Khorana et al, *NEJM* 2019

What evidence do we have for use of DOACs in secondary prevention of recurrent VTE in CA patients?

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

ASCO Guidelines for Cancer Associated Thrombosis-2019

1. LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over VKA

2. There is an increase in major bleeding risk with NOACs, particularly in GI and potentially GU cancer. Caution with NOACs also with high risk for mucosal bleeding. DDI should be checked prior.
   (Evidence high; Strength strong).

3. AC with LMWH, NOACs, or VKAs > 6 months should be offered to selected patients with active cancer, such as metastatic disease or chemotherapy.

AC > 6 months needs to be assessed intermittently for favorable risk-benefit profile (informal consensus; Evidence low; Strength weak to moderate).

[Caveat: Await RCT with Apixaban]

Key NS, et al J Clin Oncol. 2019 Aug 5:JCO1901461.2019/08/06.

Incidence of Thrombotic Manifestations of COVID-19

- Risk factors for thrombosis:
  - Advanced age
  - Sex (male)
  - Obesity
  - Active cancer
- Incidence of thrombosis in outpatients is unknown
  - Post hospital discharge
  - Non hospitalized patients

ICU or ward setting (n)	Thrombo-prophylaxis	Number of events, n (%)	Type of event (n)
Chinese ICU (81)[1]	None	20 (25)	DVT (20)
French ICU (26)[2]	LMWH or UFH	18 (69)	DVT (18)*
Dutch ICU (184)[3]	LMWH	31 (17)	PE (25), DVT (3), stroke (3)
French ICU (150)[4]	LMWH or UFH	64 (43)	PE (25), DVT (3), stroke (2), limb ischemia (1), CRRT filter (28/29), ECMO (2/12)
Dutch ICU (74)[5]	LMWH	29 (39)	PE (9), DVT (20)
French ICU (107)[6]	LMWH or UFH	22 (21)	PE (22)†
Dutch ward (124)[5]	LMWH	4 (3.2)	PE (2), DVT (2)
Italian ward (327)[7]	LMWH (in 75%)	20 (6.1)	PE (7), DVT (2), SVT (2), MI (3), stroke (6)

COVID-19, coronavirus disease of 2019; CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LMWH, low molecular-weight heparin; MI, myocardial infarction; PE, pulmonary embolism; SVT, superficial vein thrombosis; UFH, unfractionated heparin.
* Patients were screened for DVT. † Only reported PE.

1. Cui S, et al. J Thromb Haemost. 2020;18:1421-1424. 2. Llitjos J-F, et al. J Thromb Haemost. 2020 Apr 22. [Epub]. 3. Klok FA, et al. Thromb Res. 2020;191:145-147. 4. Helms J, et al. Intensive Care Med. 2020;46:1089-1098. 5. Middledorp S, et al. J Thromb Haemost. 2020 May 5. [Epub]. 6. Poissy J, et al. Circulation. 2020 Apr 24. [Epub]. 7. Lodigiani C, et al. Thromb Res. 2020;191:9-14.

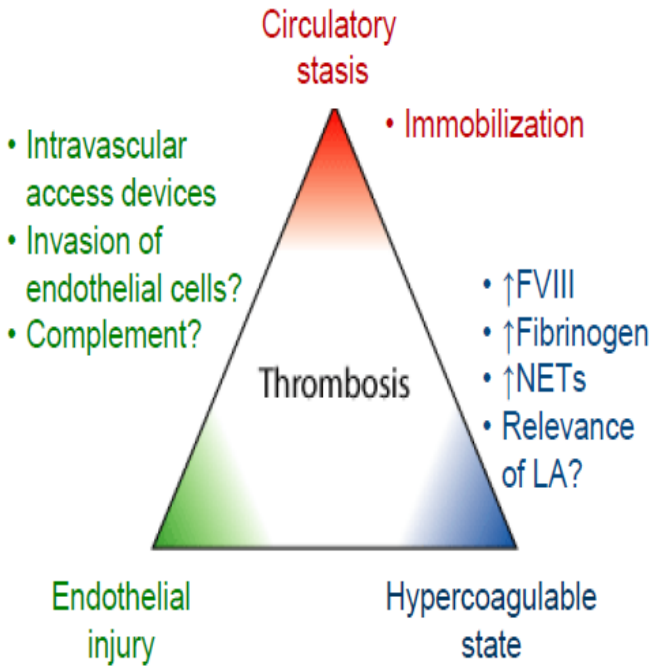
COVID-19: Real-World Experience

COVID-Associated Coagulopathy[1-6]

↑ D-Dimer
↑ Fibrinogen
↑ C reactive protein
↑ Factor VIII
↑ Von Willebrand factor
Lupus anticoagulant
TEG changes (↓R-time, ↓K-time, ↑MA, ↓LY30)

Minor or no effect on:
Platelet count
Prothrombin time
Antithrombin/Protein C/Protein S levels

Pathophysiology: Virchow's Triad



Treatment Intensity Recommendations[7-9]

	Non critically ill	Critically ill
ISTH	Prophylactic	Prophylactic
AC forum	Prophylactic	Intermediate
NIH	Prophylactic	Prophylactic

Prophylactic-intensity regimens: enoxaparin 40 mg daily, UFH 5000 U SC BID or TID.
Intermediate-intensity regimens: enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, UFH 7500 U SC TID

BID, twice daily; COVID-19, coronavirus disease of 2019; CRP, C-reactive protein; K-time, amplification time; LA, lupus anticoagulant; LY30, measure of clot stability; MA, maximum amplitude; NET, neutrophil extracellular traps; R-time, initiation time; SC, subcutaneously; TEG, thromboelastography; TID, 3 times daily; U, units; UFH, unfractionated heparin.

1. Magro C, et al. Transl Res. 2020; 220:1-13. 2. Panigada M, et al. J Thromb Haemost. 2020 Apr 17. [Epub]. 3. Ranucci M, et al. J Thromb Haemost. 2020 Apr 17. [Epub]. Tang N, et al. J Thromb Haemost 2020 Feb 19. [Epub]. 5. Bowles L, et al. N Engl J Med. 2020 May 5. [Epub]. 6. Levi et al. Br J Haematol. 2009;145:24-33. 7. Thachil J, et al. J Thromb Haemost. 2020 Mar 25. [Epub]. 8. Barnes GD, et al. J Thromb Thrombolysis. 2020;50:72-81. 9. https://www.covid19treatmentguidelines.nih.gov/

Take-home Points

- Thrombotic manifestations of COVID-19 include VTE, pulmonary microvascular thrombosis, and, less commonly, arterial thrombosis
- VTE is common in ICU patients (≈20%-40%) despite prophylactic-intensity anticoagulation
- Potential mechanisms include immobilization, hypercoagulability, and endothelial injury
- Clinical trials are needed to determine whether increasing the intensity of anticoagulation is effective and safe
- Current clinical guidance is mixed on whether patients in the ICU should receive increased-intensity anticoagulation