Non-Malignant Hematology: Coagulation and Beyond

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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

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

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

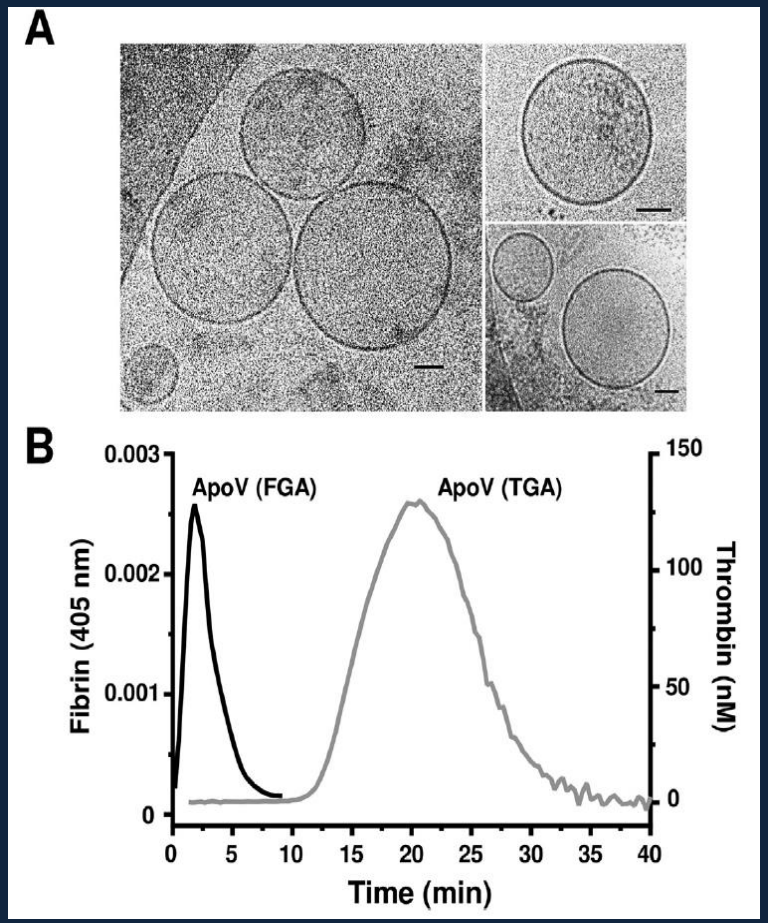
- More basic facts
  - Pancreatic Ca - 15-16 fold increased risk of VTE
  - Lung Ca – 7 fold increased risk of VTE
  - Primary brain Ca - 10 fold increased risk of VTE
  - Breast Ca- 2-3 fold increased risk of VTE
  - Prostate Ca – 2-3 fold increased risk of VTE
  - Stage IV Ca - 17 fold increased risk of VTE vs 2-3 fold increase in localized Ca

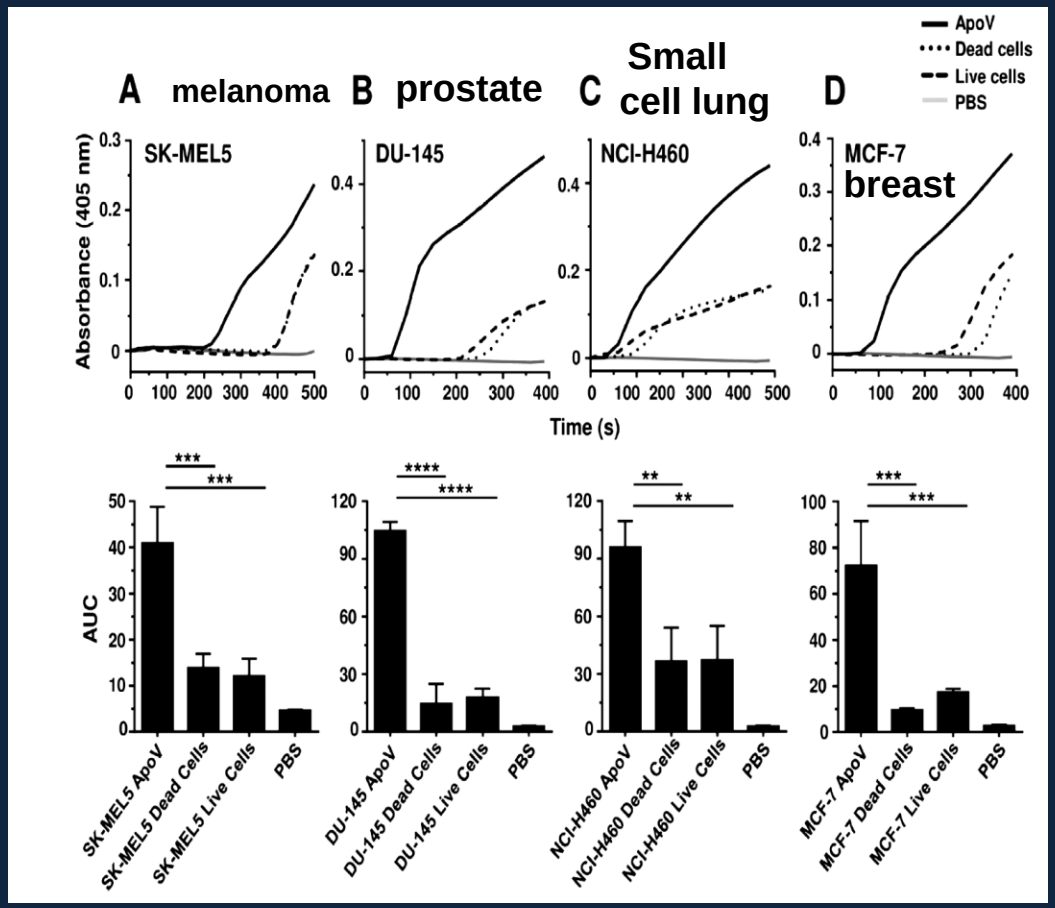
What factors make thrombosis more likely to develop in patients with cancer?

- Surgery and chemotherapy double VTE risk
- Hormonal therapy, such as tamoxifen, increase VTE within the first 3 months and diminishes over time
- Erythropoietin increases VTE risk
- IMIDs - thalidomide, lenalidomide , and pomalidomide - increase VTE risk when used with high dose dexa or in combination with chemotherapy
- Underlying thrombophilias synergistic with chemotherpapy to increase VTE risk- 12 fold for FVL
- CVADs increase VTE risk-are all CVADs equal?

Mechanistic insight into the procoagulant activity of tumor-derived apoptotic vesicles

Muhsin-Sharafaldine MR et al. Biochimica et Biophysica Acta 1861:286, 2017



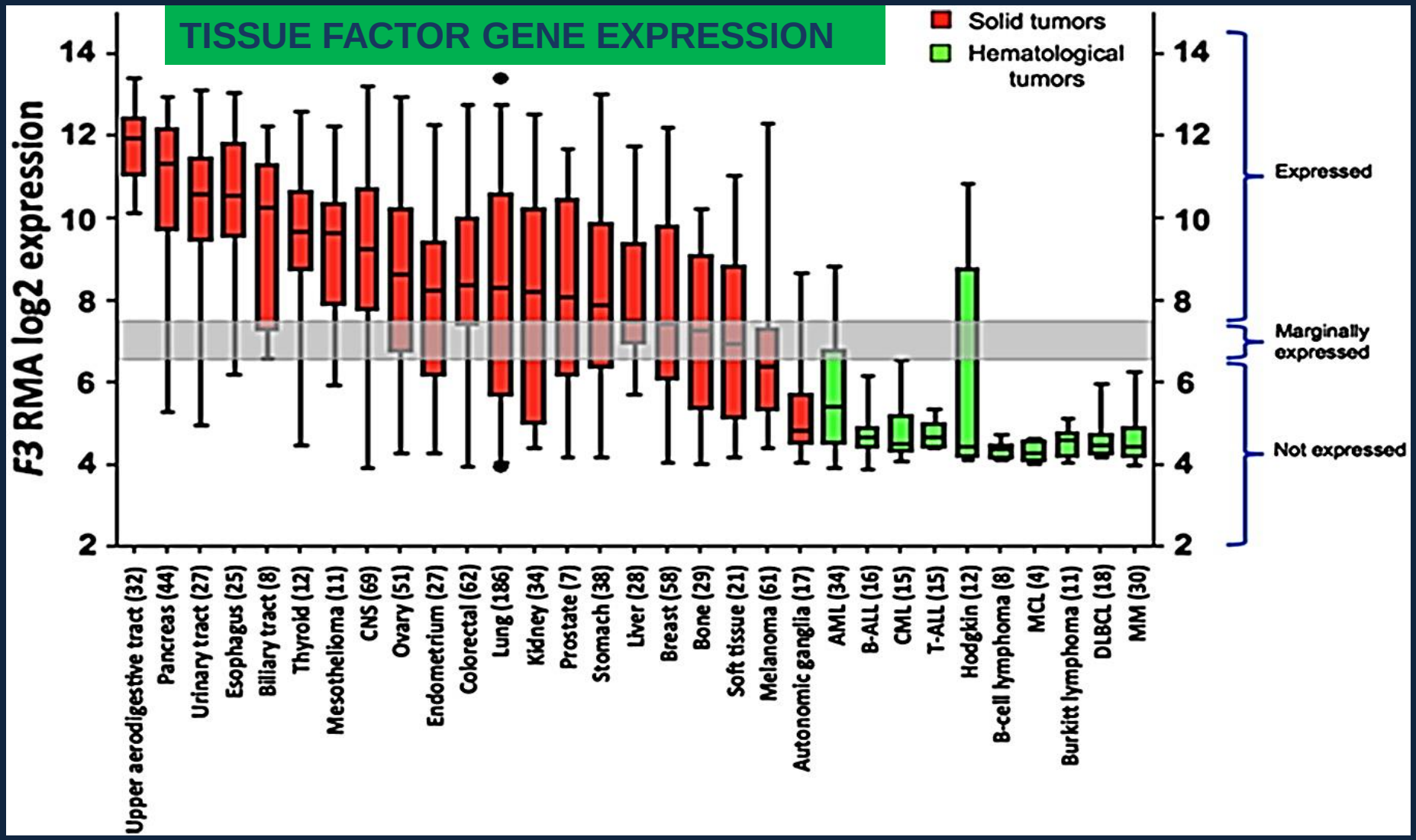


Doxo-treated Ca cells generate ApoV; added to PPP to enhance coagulation

Different human tumors + Doxo have variable ApoV potential to enhance coagulation - TF content dependent

Absence of tissue factor is characteristic of lymphoid malignancies of both T- and B-cell origin

Cesarman-Maus, G et al. Thromb. Res. 133 (2014) 606–609.



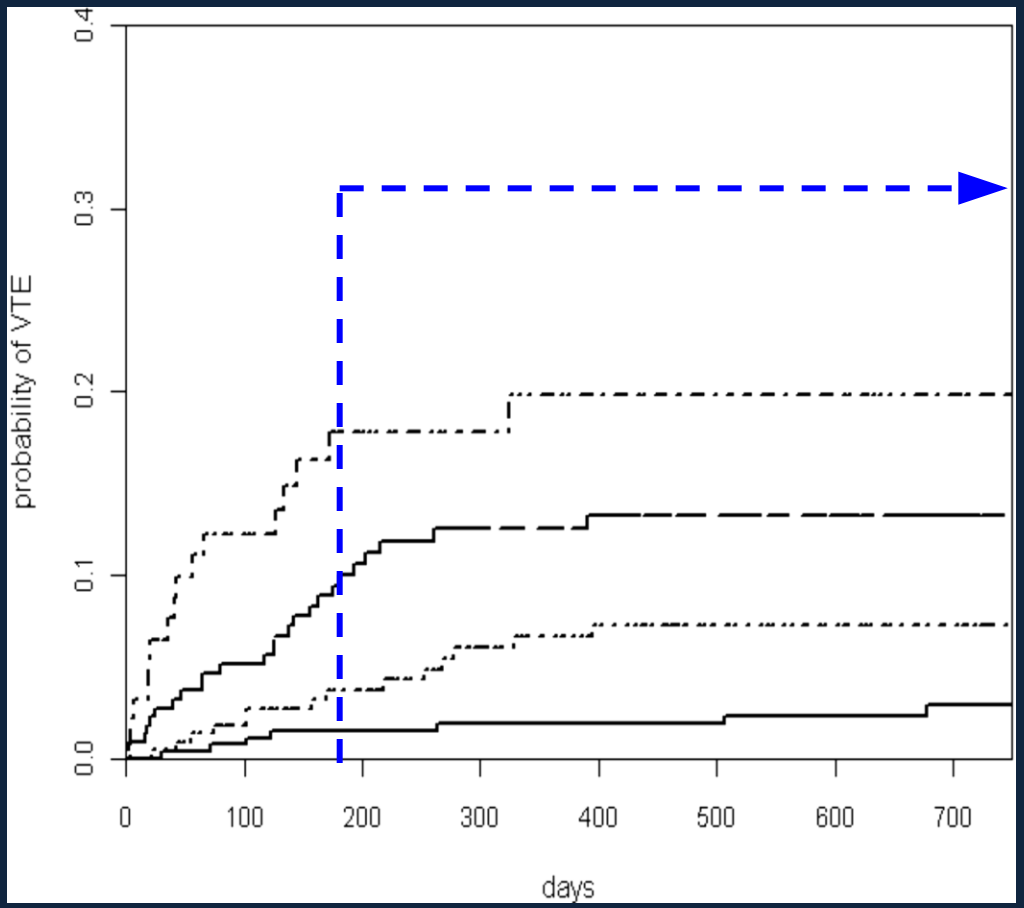
Khorana Model for Outpatients

Patient Characteristic	Score
Site of Cancer Very high risk (stomach, pancreas) High risk (lung, lymphoma, gynecologic, GU excluding prostate)	 2 1
Pre-chemotherapy platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Prechemotherapy leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

Khorana et al. Blood 2008.

Khorana Model Validation

- Prospective follow up of 819 patients
- Median observation time/follow-up: 656 days



6-mo cumulative VTE rates:

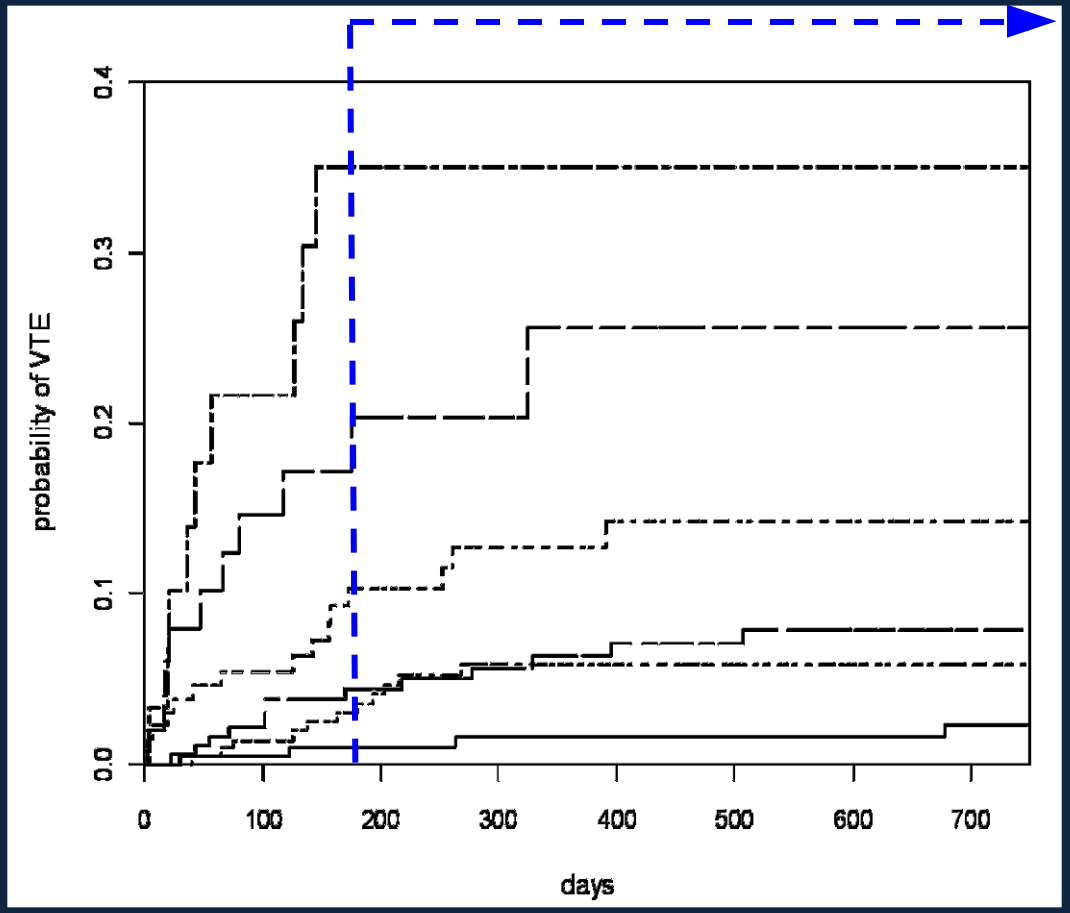
	Patients n	Events %
Score ≥3	93	17.7%
Score 2	221	9.6%
Score 1	229	3.8%
Score 0	276	1.5%

CANCERANDTHROMBOSISSTUDY

Ay et al Blood 2010.

Ay Model for Outpatients

- Addition of D-dimer and soluble P-selectin to Khorana model:



6-mo cumulative VTE rates:

	Patients, n	Events, %
Score ≥5	30	35%
Score 4	51	20.3%
Score 3	130	10.3%
Score 2	218	3.5%
Score 1	190	4.4%
Score 0	200	1.0%

CANCERANDTHROMBOSISSTUDY

Ay et al Blood 2010.

Biomarkers for predicting recurrent venous thromboembolism (VTE) in cancer: Validation from the CATCH (Comparison of acute treatments in cancer hemostasis) study

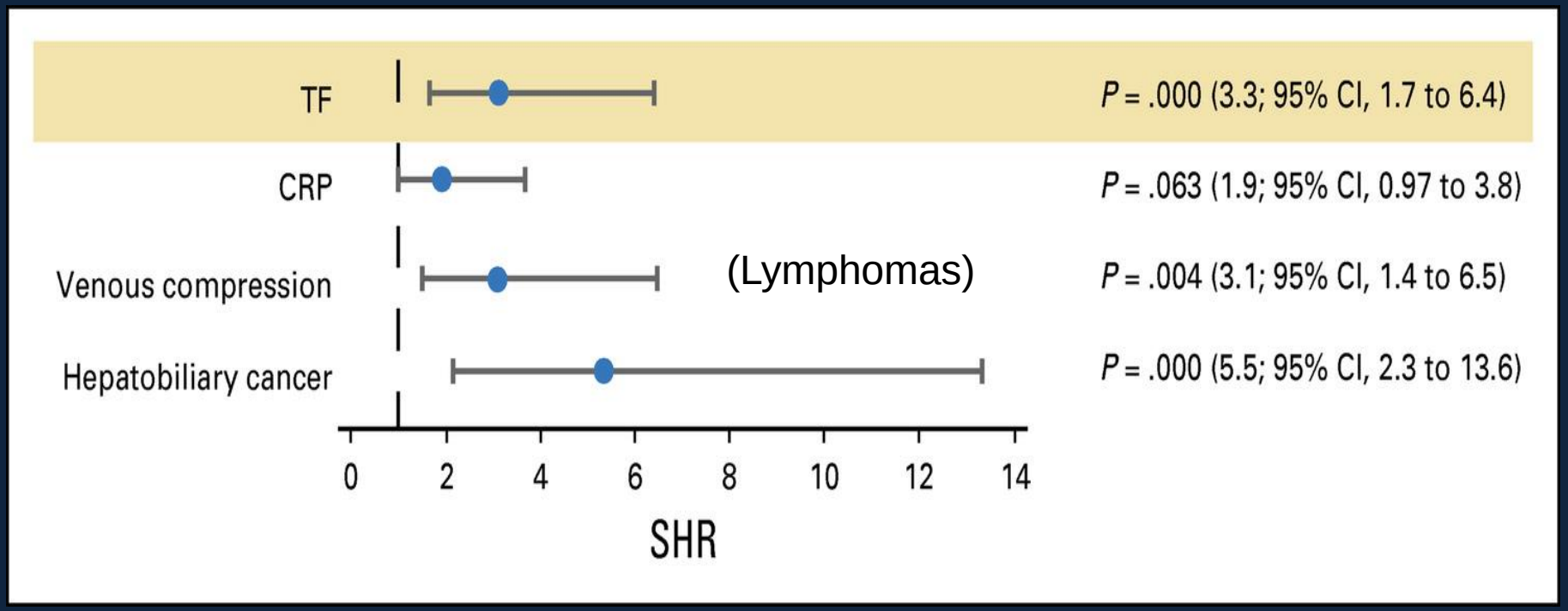


Fig 2. Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model. Competing risk regression analysis of time to recurrent VTE that accounts for study design variables and significant predictors identified in individual analyses. CRP, C-reactive protein; TF, tissue factor.

Published in: Alok A. Khorana; Pieter W. Kamphuisen; Guy Meyer; Rupert Bauersachs; Mette S. Janas; Mikala F. Jarner; Agnes Y.Y. Lee; *JCO* **2017,** 35, 1078-1085. DOI: 10.1200/JCO.2016.67.4564

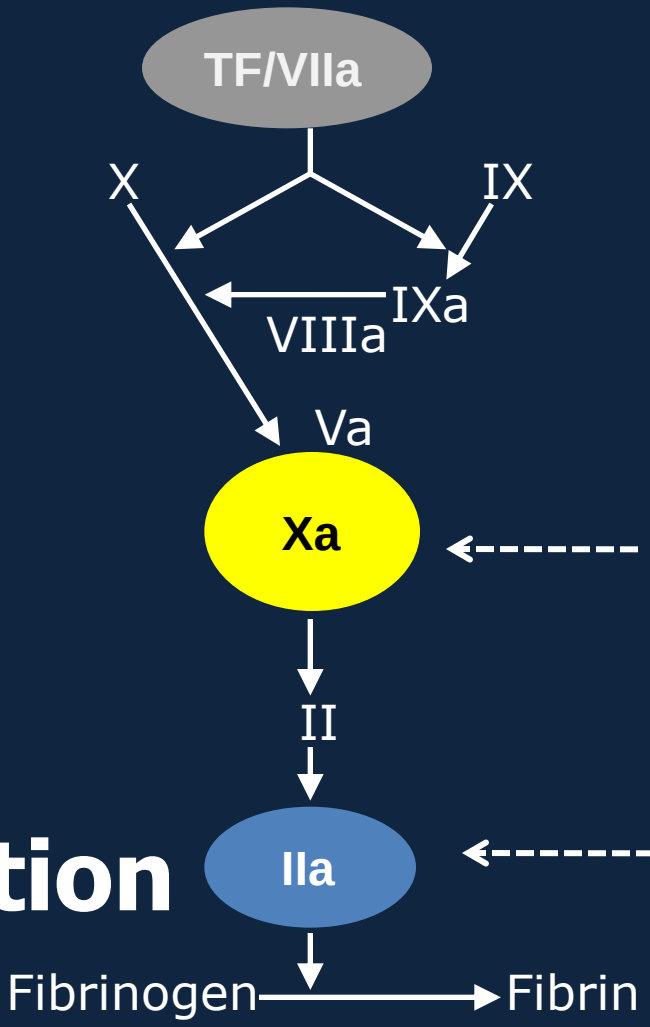
SITES OF ACTION

Steps in Coagulation **Pathway** **Drugs**

Initiation

Propagation

Fibrin formation



Rivaroxaban
Apixaban
Edoxaban
Betrixaban

Dabigatran

(Hankey GJ and Eikelboom JW. Circulation 2011;123:1436-1450)

Clinical Comparisons of the Novel Oral Anti-Xa Anticoagulants

Comparative pharmacology of non-vitamin K antagonist oral anticoagulants

	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)

Abbreviations: T_{max}, time to reach peak concentration in plasma after oral dose; h, hours; CYP450, cytochrome 450; $T_{1/2}$, terminal half-life of drug; PD $T_{1/2}$, pharmacodynamic half-life.

Vascular Health and Risk Management 2015:11

Betrixaban (Byvexxa)-FDA approved for extended VTE prophylaxis in acutely ill medical patients

RCTs evaluating extended thromboprophylaxis in acutely ill medical patient

Study (no of patient)	Population	Intervention	Control	All VTE rate (intervention vs control)	Major bleeding rate (intervention vs control)	Comments
EXCLAIM[27] (n=5,963)	Acutely ill medical patient	Extended duration enoxaparin	Enoxaparin	2.5% vs 4.0%	0.8% vs 0.3%	No net benefit
ADOPT[28] (n=6,528)	Acutely ill medical patient	Extended duration apixaban	Enoxaparin	2.7% vs 3.1%	0.5% vs 0.2%	No net benefit
MAGELLAN[29] (n=8,101)	Acutely ill medical patient	Extended duration rivaroxaban	Enoxaparin	4.4% vs 5.7%	1.1% vs 0.4%	No net benefit
APEX[14](n=6,850) (N Engl J Med 2016; 375:534-544)	Acutely ill medical patient	Extended duration betrixaban	Enoxaparin	**Cohort 1 (D-dimer ≥2X NL): 6.9 vs 8.5 (P-0.054)** **Cohort 2 (cohort 1 + ≥75y/o 5.6 vs 7.1% (P-0.03)** **Overall 5.3 vs 7% (P-0.006)**	**0.7% vs 0.6**	Enrichment design. Enrolling only patients at high VTE risk. Expected all VTE rate in control arm =7.5%

Abbreviations: VTE, venous thromboembolism; RCTs, randomized controlled trials.

Vascular Health and Risk Management 2015:11

Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

The Oncologist 2014;19:82

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Antimetabolites						
Antifolates						
Methotrexate				●		
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Immune-modulating agents						
Cyclosporine	**+++**		**++**	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	**+++**	**+++**		●	●	●
Prednisone	**+**	**++**				

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Abiraterone	+++		++			●
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			

The Oncologist 2014;19:82

Table. Results of Major Trials Comparing Low-Molecular-Weight Heparin vs Oral Anticoagulants for the Treatment of Cancer-Associated Venous Thromboembolism

Clinical Advances in Hematology & Oncology Volume 16, February 2018

	CLOT, 2003	CATCH, 2015	Hokusai VTE Cancer, 2017	Select-D, 2017
Patients, No.	676	900	1050	406
Age, y (SD)	Dalteparin: 62 (12) VKA: 63 (13)	Tinzaparin: 59.7 (12.7) Warfarin: 58.8 (12.5)	Edoxaban: 64.3 (11.0) Dalteparin: 63.7 (11.7)	67 (range, 22-87)
Metastatic disease, No. (%)	455 (67.3%)	492 (54.7%)	554 (53%)	240 (59%)
Recurrent VTE, No. (%)	Dalteparin: 27 (8%) VKA: 53 (15.8%) HR, 0.48 (95% CI, 0.30-0.77)	Tinzaparin: 31 (6.9%) Warfarin: 45 (10%) HR, 0.65 (95% CI, 0.41-1.03)	Edoxaban: 41 (7.9%) Dalteparin: 59 (11.3%) HR, 0.71 (95% CI, 0.48-1.06)	Dalteparin: 11% (95% CI, 7%-17%) Rivaroxaban: 4% (95% CI, 2%-9%)
Major bleeding, No. (%)	Dalteparin: 19 (5.6%) VKA: 12 (3.6%) *P*=.27	Tinzaparin: 12 (2.7%) Warfarin: 11 (2.4%) *P*=.77	Edoxaban: 36 (6.9%) Dalteparin: 21 (4.0%) HR, 1.37 (95% CI, 1.03-3.04)	Dalteparin: 6 (3%) (95% CI, 1%-6%) Rivaroxaban: 8 (4%) (95% CI, 2%-8%)
Clinically relevant non-major bleeding, No. (%)	NR	Tinzaparin: 49 (10.9%) Warfarin: 69 (15.3%) HR, 0.58 (95% CI, 0.40-0.84); *P*=.004	Edoxaban: 76 (14.6%) Dalteparin: 58 (11.1%) HR, 1.38 (95% CI, 0.98-1.94)	Dalteparin: 5 (2%) (95% CI, 1%-6%) Rivaroxaban: 27 (13%) (95% CI, 9%-19%)
Mortality at 6 mo, No. (%)	Dalteparin: 130 (39%) VKA: 136 (41%) *P*=.53	Tinzaparin: 150 (33.4%) Warfarin: 138 (24.4%) HR, 1.08 (95% CI, 0.85-1.36); *P*=.54	Edoxaban: 206 (39.5%) Dalteparin: 192 (36.6%) HR, 1.12 (95% CI, 0.92-1.37)	Dalteparin: 30% Rivaroxaban: 26%

HR, hazard ratio; mo, months; NR, not reported; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism; y, years.

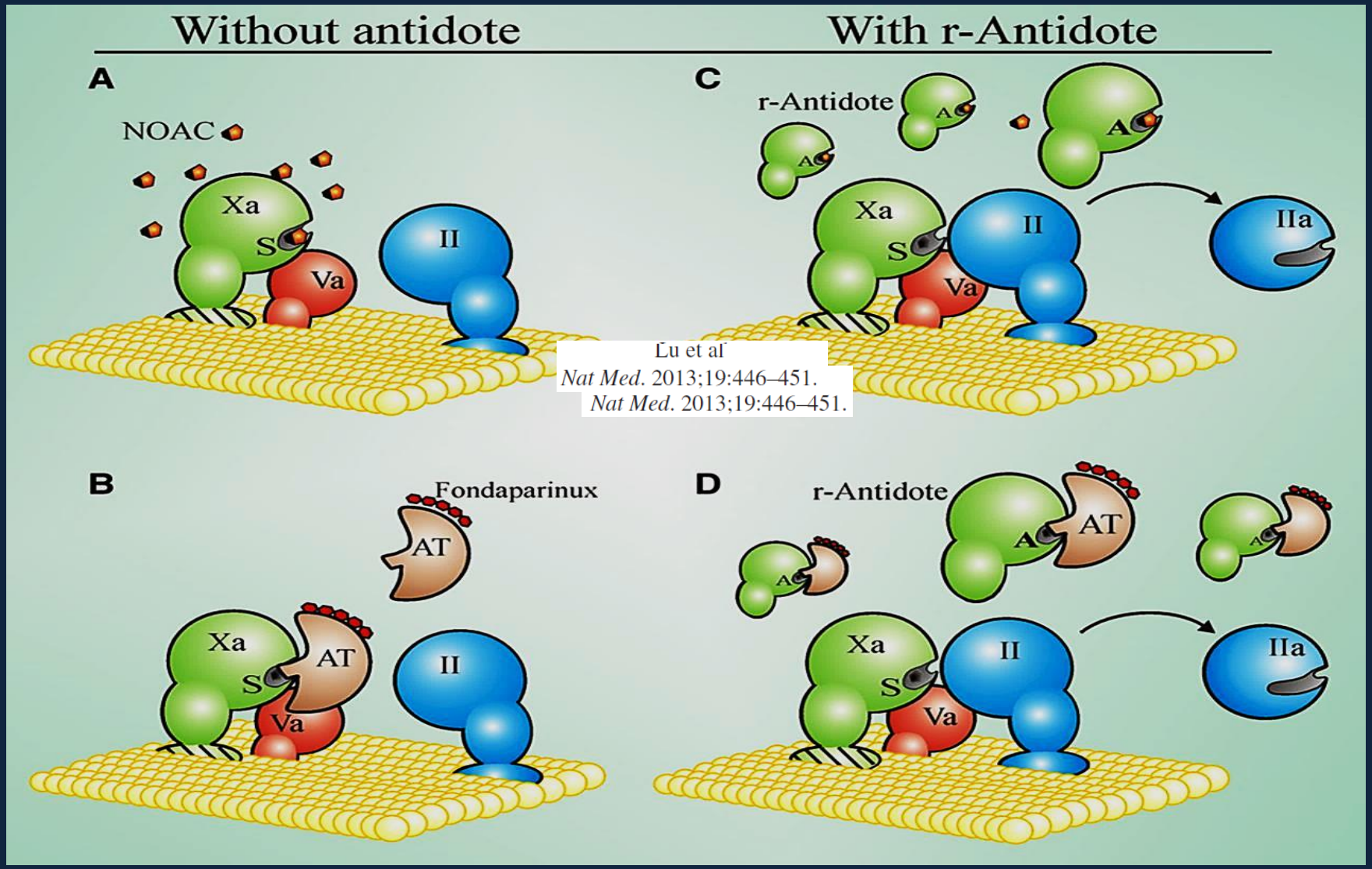
Sources: Lee AY et al. *N Engl J Med*. 2003;349(2):146-153; Lee AYY et al. *JAMA*. 2015;314(7):677-686; Raskob GE et al [published online December 12, 2017]. *N Engl J Med*; Young A et al [ASH abstract 625]. *Blood*. 2017;130(1)(suppl).

DOACs

New Reversal Agents

- Idarucizumab
  - Humanized antibody fragment directed against DTI dabigatran
- Andexanet alfa
  - Modified factor Xa molecule, direct reversal agent for Xa inhibitors
- Aripazine (PER977; ciraparantag)
  - Synthetic small molecule (D-arginine compound), broad activity against various anticoagulants:
    - Heparin, LMWH
    - NOACs
    - Mechanism of action not known

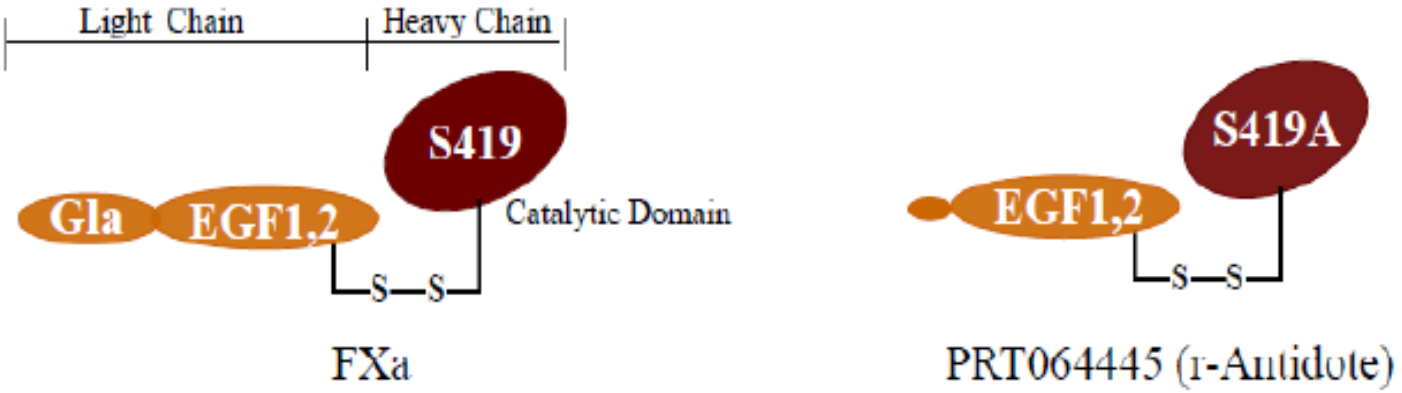
R-Antidote is a decoy for anti-Xa anticoagulation reversal



Nat Med. 2013;19:446–451.

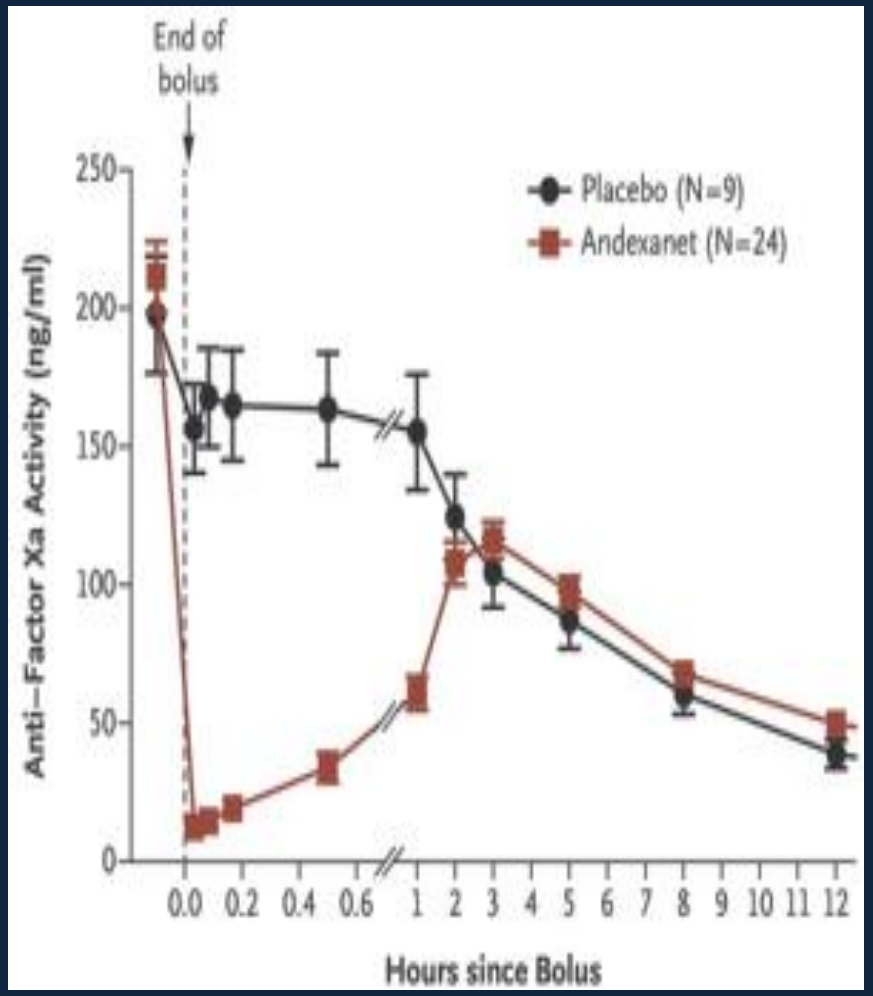
Lu et al, Nat Med, 2013

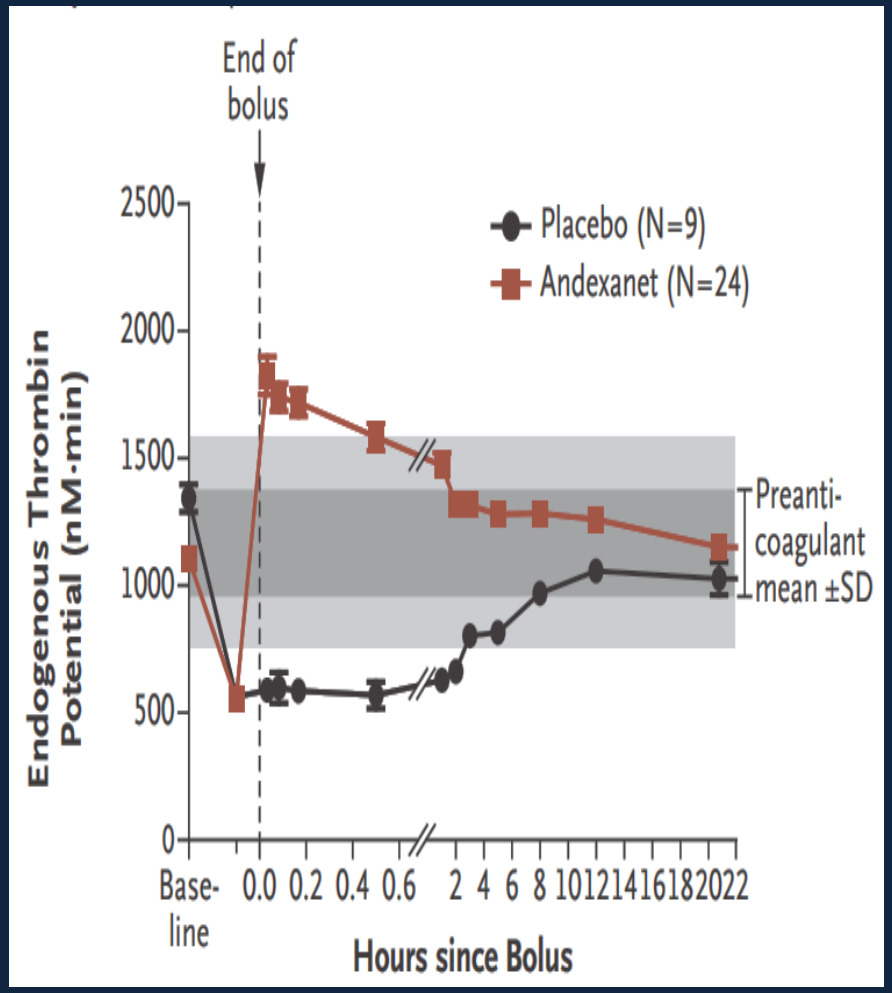
PRT064445 is a recombinant fXa variant with modifications in the Gla-domain and active site



- **Two modifications introduced to human fXa**
  - Removal of the Gla-domain
  - Mutation at the active site (S419A)
- **PRT064445 (r-Antidote)**
  - No pro- or anti-coagulant activity
  - Retains binding ability for fXa inhibitors

Adexanet reverses anti-Xa DOACs immediately but with rebound effect



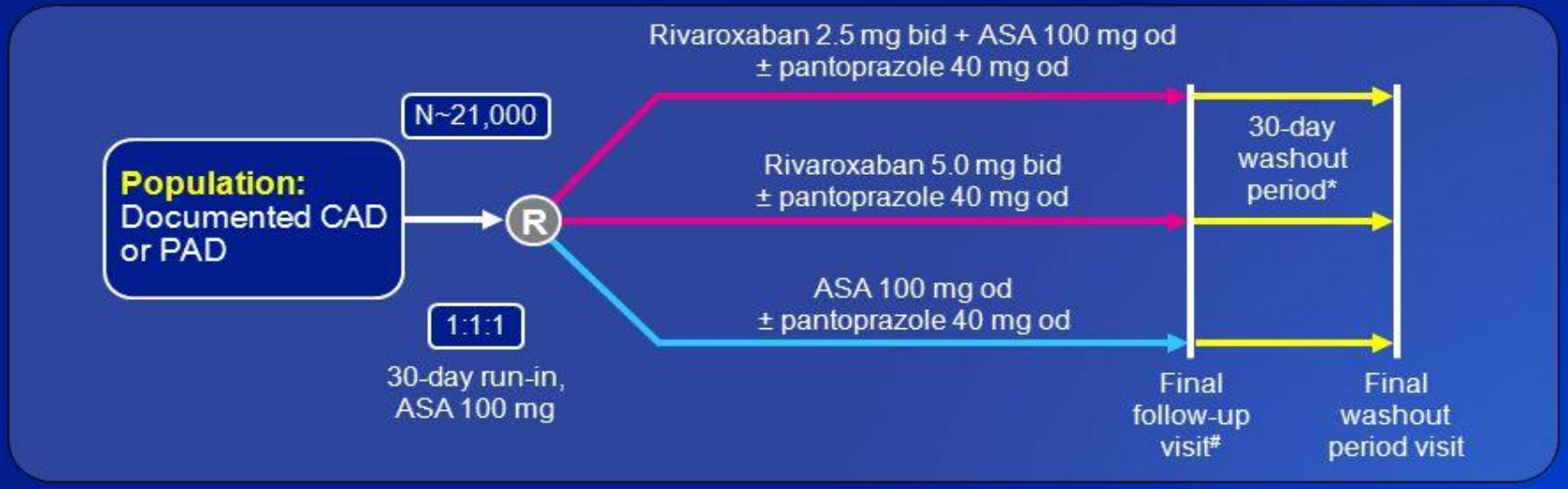


Siegal DM et al. NEJM 2015:373, 2413

COMPASS
CAD/PAD Study

Official study title: A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease (COMPASS - Cardiovascular OutcoMes for People Using Anticoagulation StrategieS)

Objective: efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or cardiovascular death in CAD or PAD



Short design: Randomized, double-blind, controlled trial

Indication: CAD/PAD

Start: Q2-13
LPLV: Q1-18

*Patients treated according to local standard of care; #≤30 days of the required pre-specified number of events having occurred

www.clinicaltrials.gov/show/NCT01776424

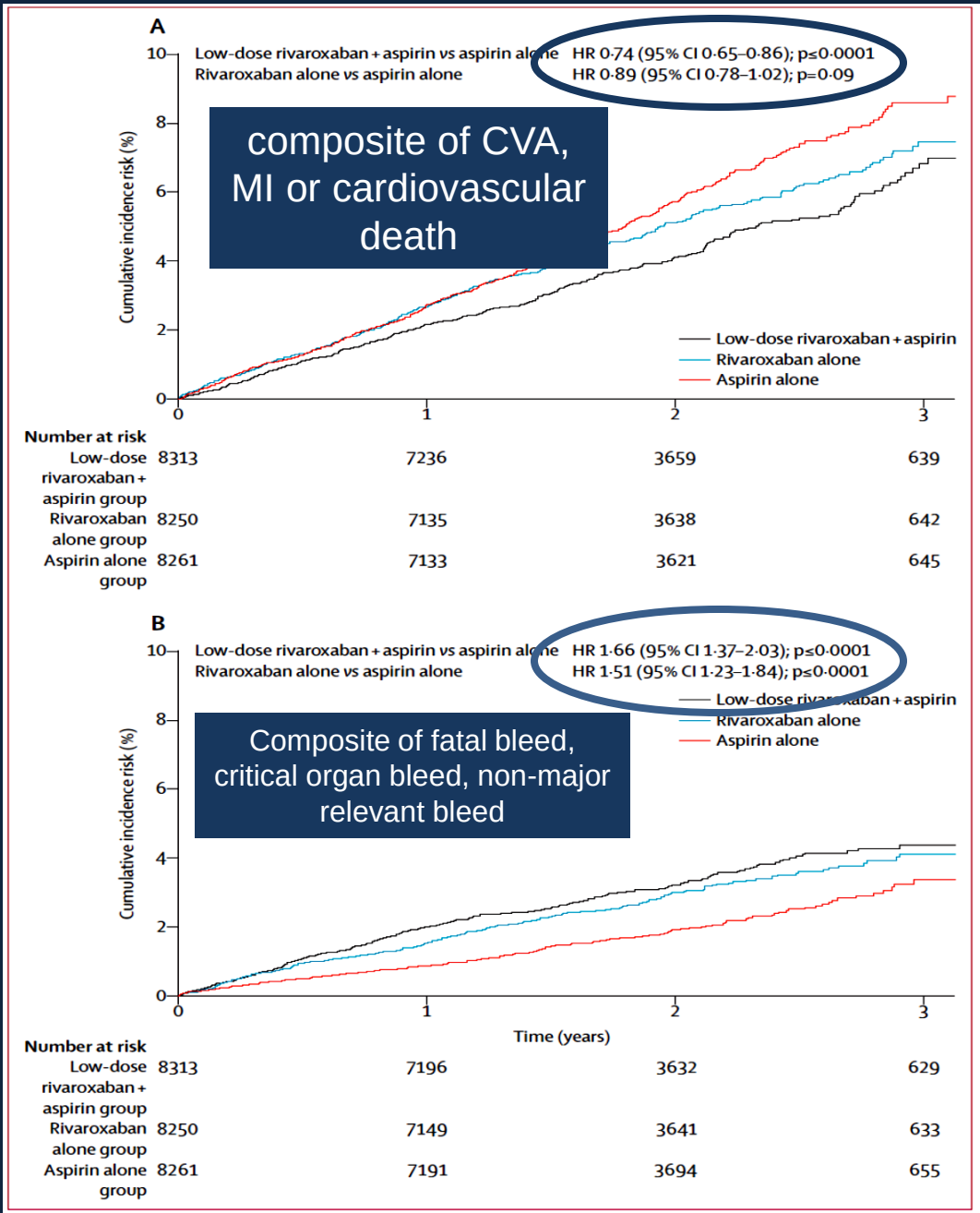
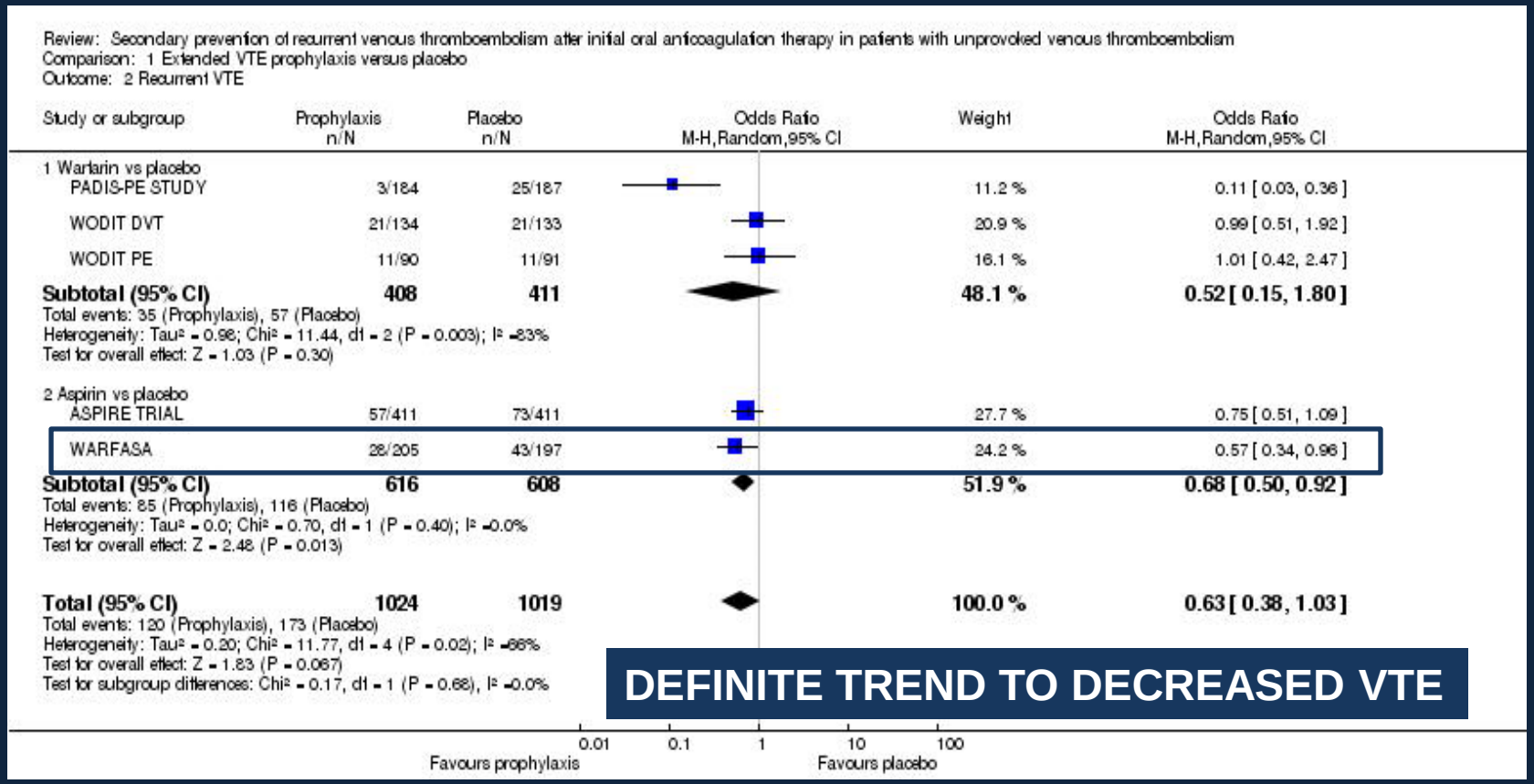


Figure 2: **Primary efficacy and safety outcomes**
Graphs represent (A) primary efficacy outcomes and (B) safety outcomes. HR=hazard ratio.

- **Early termination by DSMB**
- **Trend toward benefit for PAD with low dose riva + ASA**
- **Trend toward Lower CV and CAD related deaths**
- **Major bleeds more common with riva + ASA (p<0.001) and riva alone (p<001) vs. ASA**
- **Excess bleeding events were GI in location**
- **Intraorgan bleed ↓ with riva+ASA vs ASA (4.7% vs 5.9% , p<0.001)**
- **Does advantage convey to all DOACs? APIX + ASA→↑ bleeds but no ↓ ischemic events**

"At present, evidence is insufficient to show whether oral therapeutic options such as aspirin, warfarin, and DOACs provide effective and safe extended thromboprophylaxis for individuals with a first unprovoked venous thromboembolism (VTE) who have completed at least three months of initial oral anticoagulation." Cochrane Database of Systematic Reviews, 12:2017



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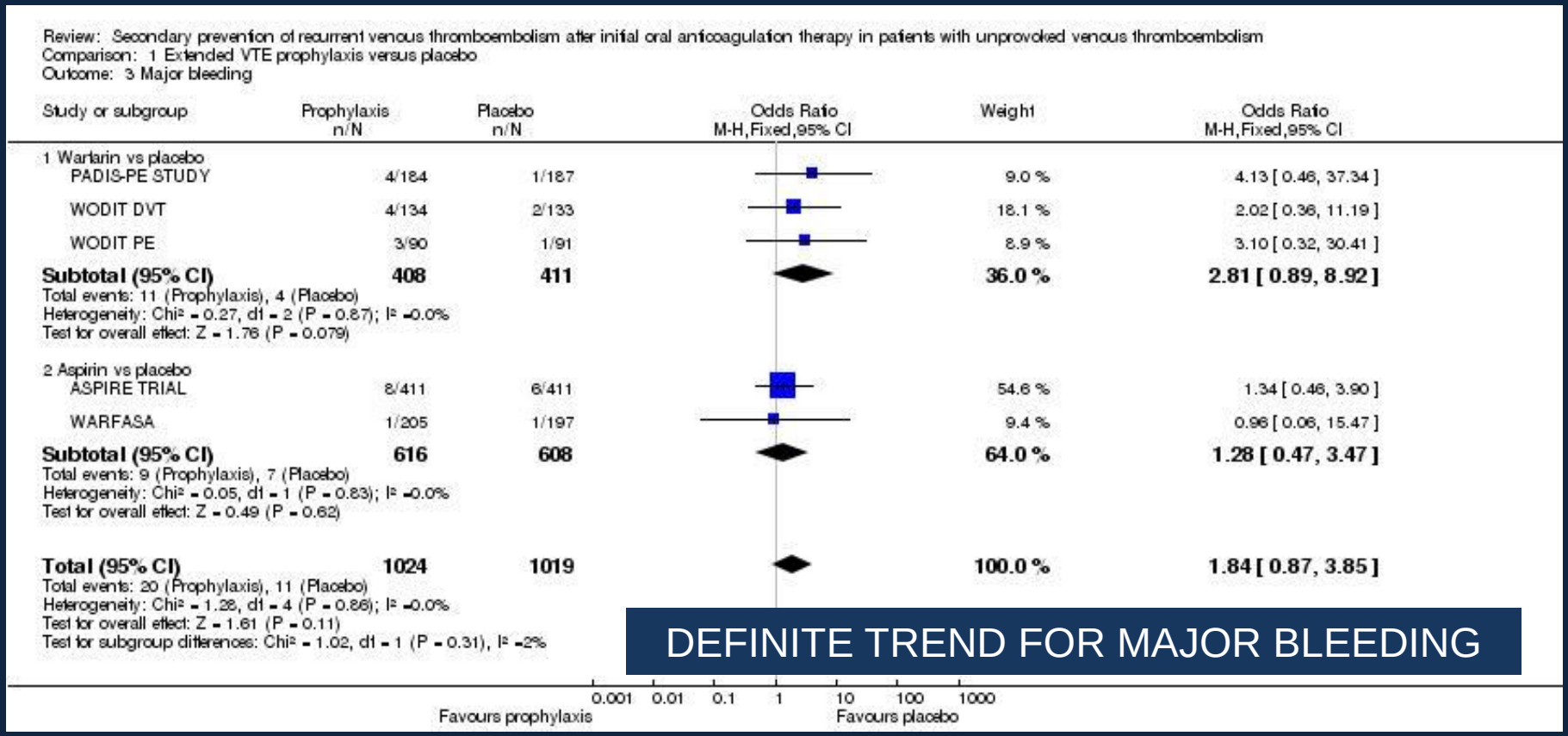

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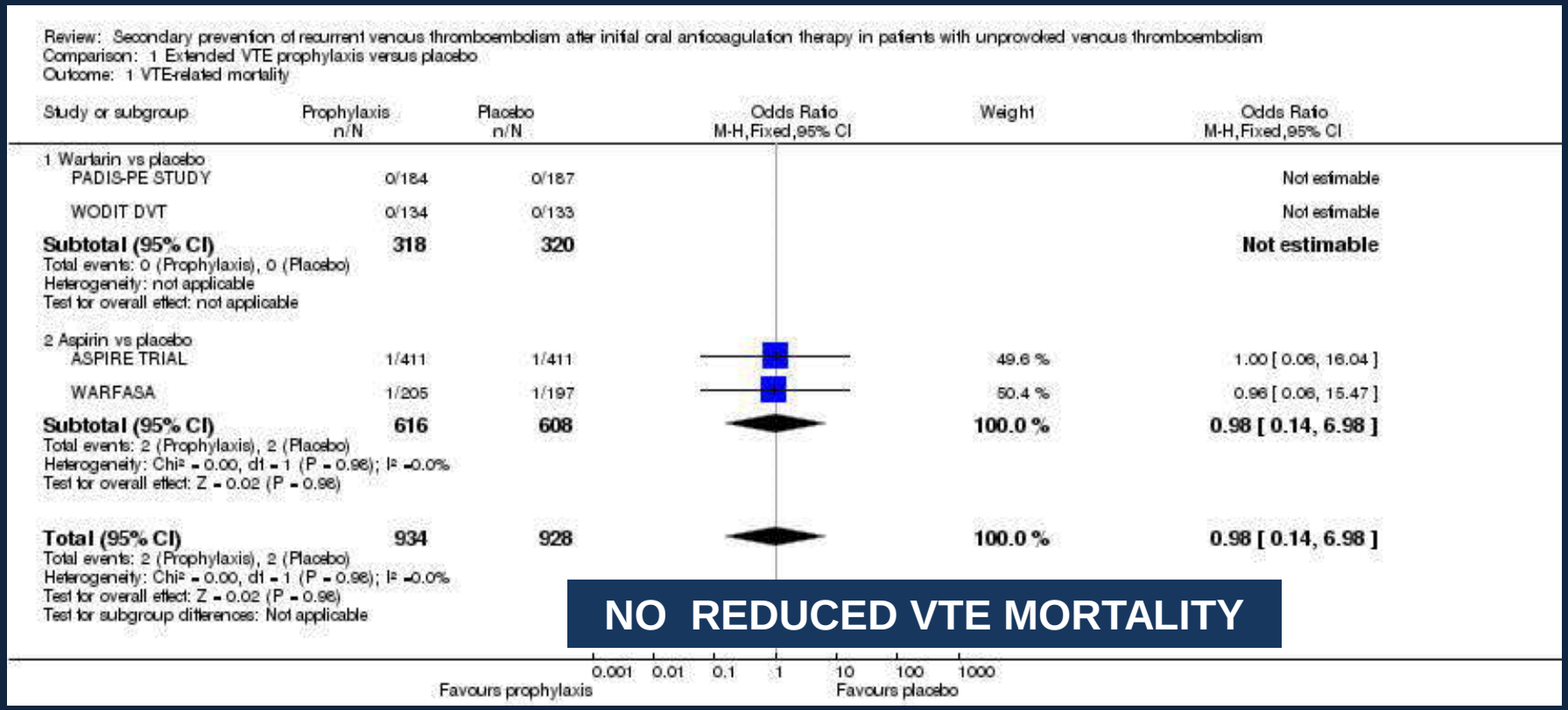
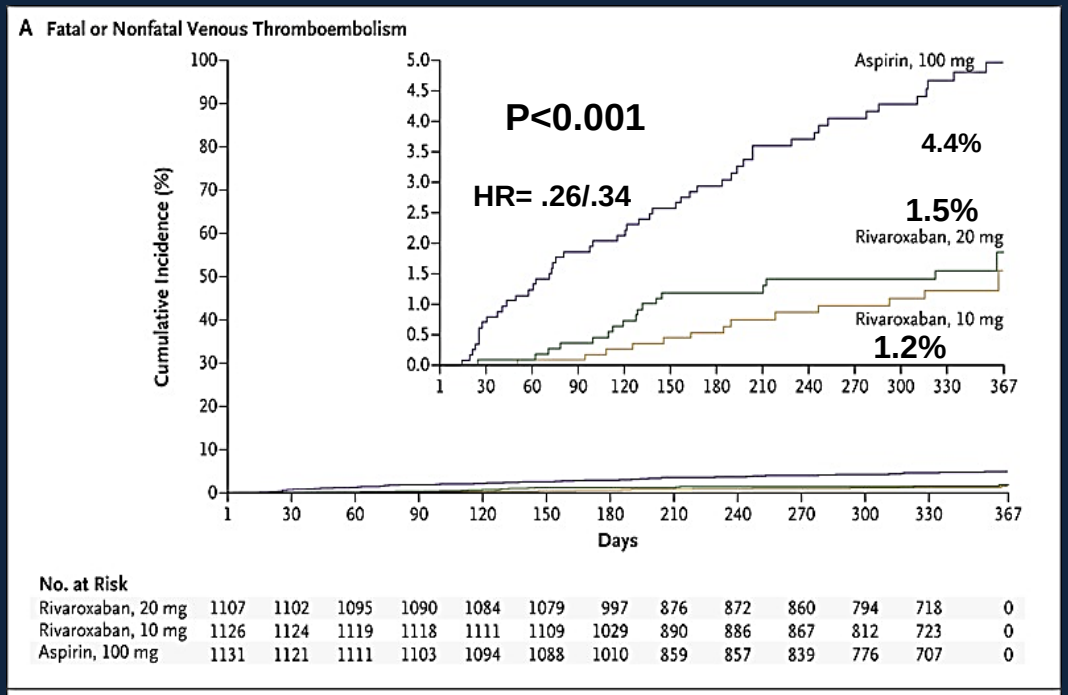
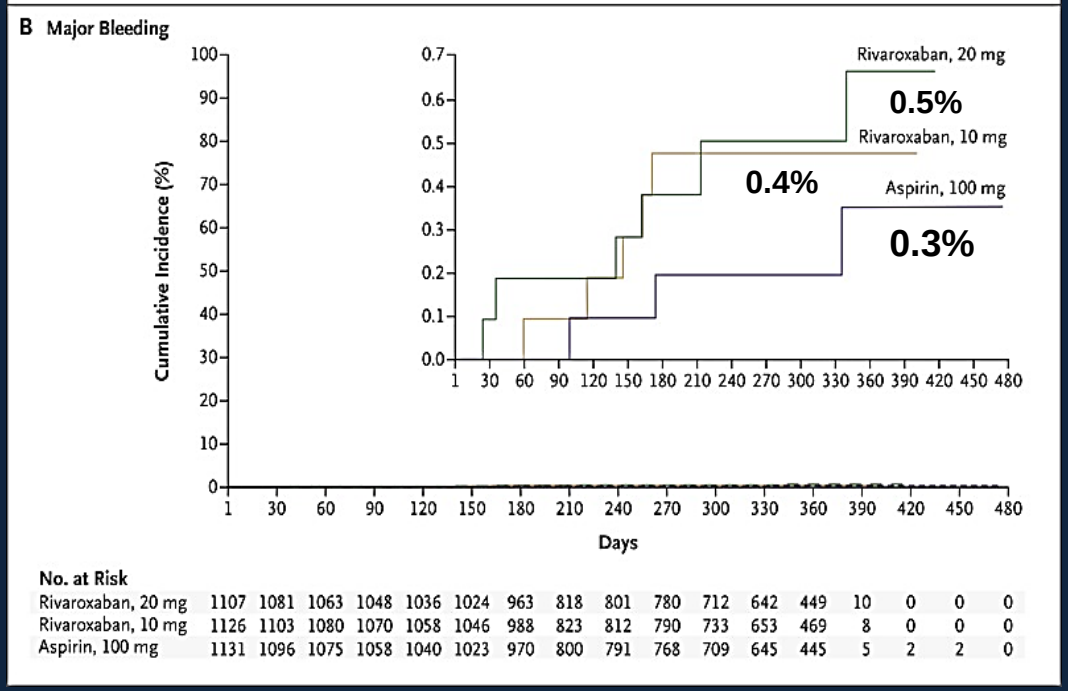


Einstein Choice: Riva vs ASA for extended VTE prophylaxis

Weitz JL et al. NEJM 2017; 376:1211-1222





Post 6-12 mos for VTE (new or recurrent) double blinded and randomized to Riva 10/20 or ASA 100 mg/d

Provoked/unprovoked: 60/40
3365 patients randomized

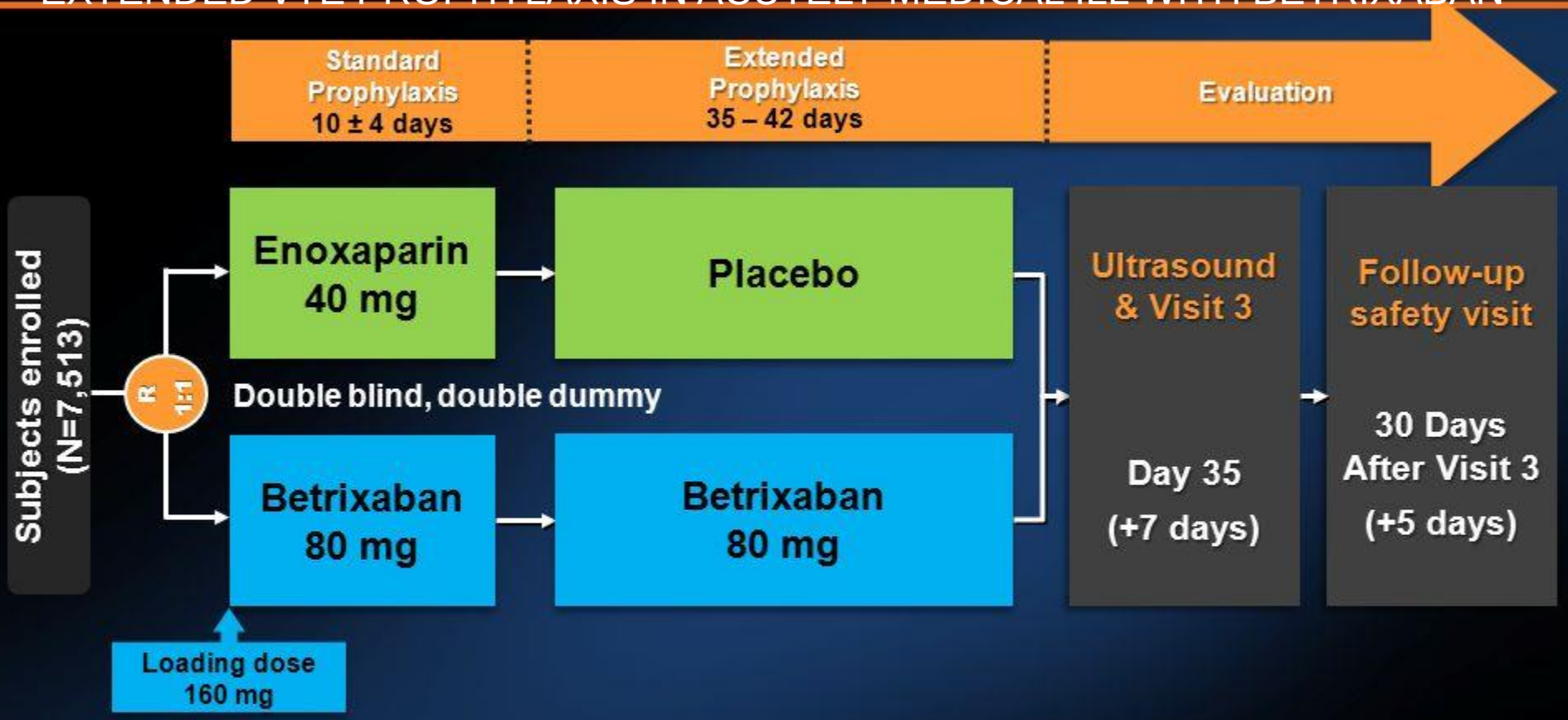
Extended TX >12 mos

No differences in unprovoked vs provoked cohorts

Riva was more effective than ASA for prevention of recurrent VTE; associated with a similar risk of bleeding

APEX Study Design

EXTENDED VTE PROPHYLAXIS IN ACUTELY MEDICAL ILL WITH BETRIXABAN



Primary Efficacy Endpoint: Composite of asymptomatic proximal DVT (detected on ultrasound), symptomatic DVT (proximal or distal), non-fatal PE, and VTE-related death through Visit 3

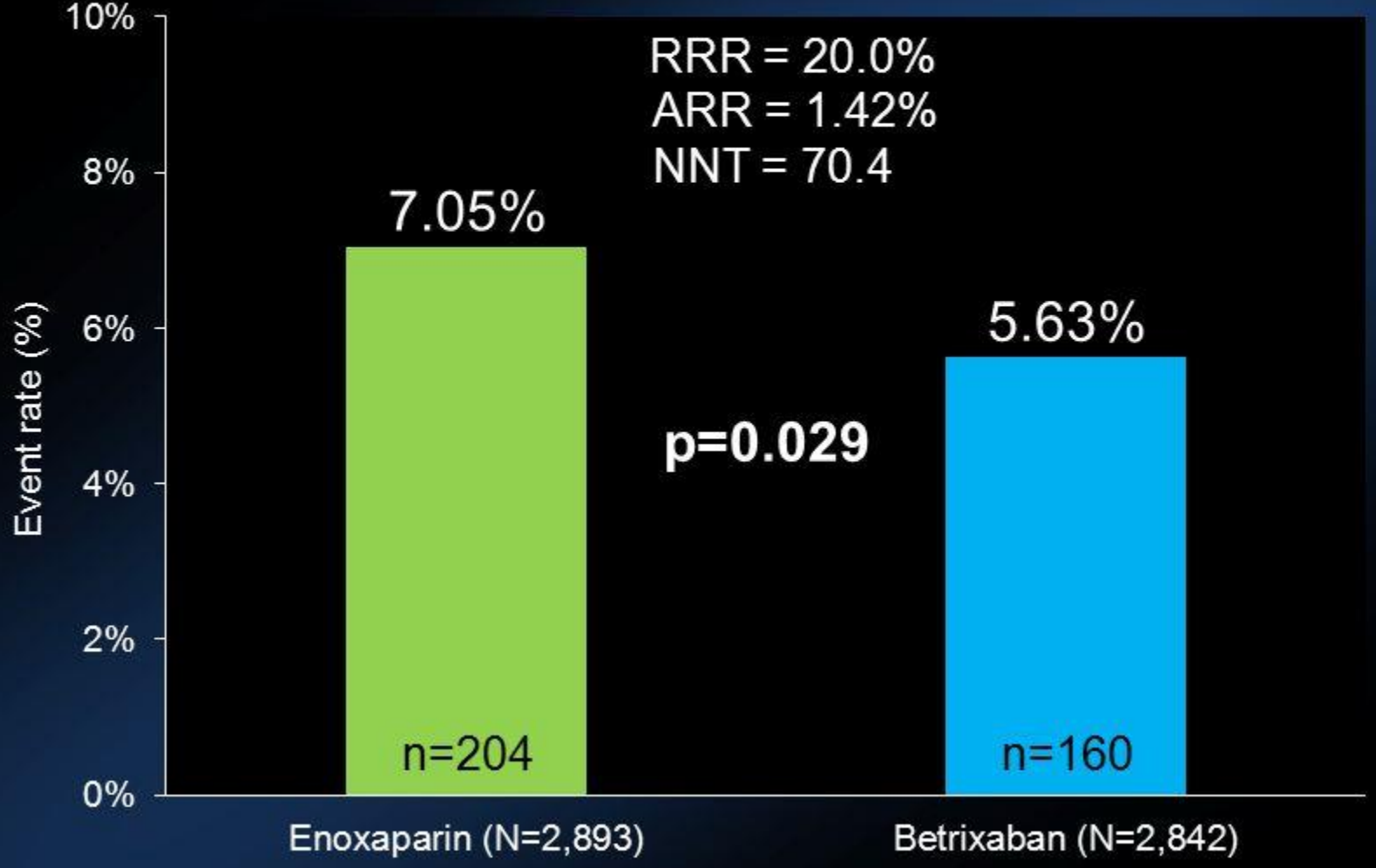
Primary Safety Endpoint: ISTH Major bleeding through 7 days after drug discontinuation

Net Clinical Benefit: Composite of primary efficacy and primary safety endpoints

Dose adjustments in severe renal insufficiency (CrCl < 30 mL/min): Betrixaban 40 mg PO qd and Enoxaparin 20 mg SC qd

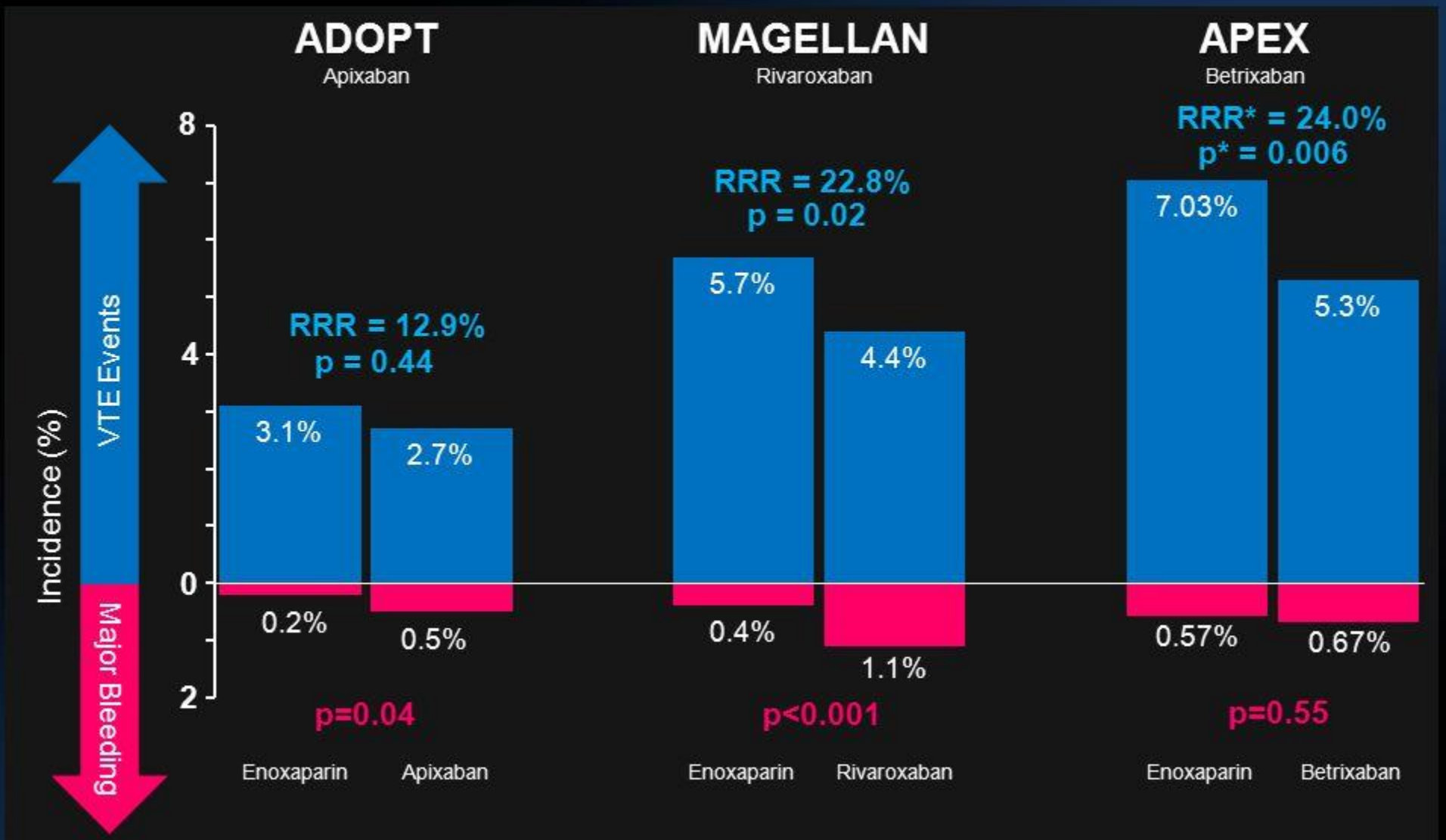
Primary Efficacy Endpoint
Cohort 2: D-Dimer ≥ 2 x ULN OR Age ≥75

Composite of Adjudicated Asymptomatic Proximal DVT, Symptomatic Proximal or Distal DVT, non-fatal PE, or VTE-related Death



P-values reported using the Mantel-Haenszel test stratified for dosing and entry criteria (ie. No adjustment, renal insufficiency, or P-gp inhibitor / DD > 2x ULN or DD < 2x ULN). Symptomatic events from Day 1 till Day 42 or the date of Visit 3, if Visit 3 occurred before Day 42; Asymptomatic DVT between Day 32 and 47.

Comparison to Previous Novel Oral Anticoagulant Trials of Extended Thromboprophylaxis in Acute Medically Ill Patients



* Overall efficacy population analysis used for comparison purposes

Abs 13: Recombinant Human Thrombopoietin (rhTPO) and High-Dose Dexamethasone (HD-DXM) Versus High-Dose Dexamethasone Monotherapy As Frontline Treatment in Newly Diagnosed Adult Immune Thrombocytopenia (ITP) : a Prospective, Multicentre, Randomised, Controlled Trial
Wang M et al

WILL THIS BE THE NEW NORM?

Table 1 Responses and outcomes in the HD-DXM + rhTPO and HD-DXM groups

	HD-DXM + rhTPO	HD-DXM	P
Day 14			
OR, n (%)	89 (89.00)	64 (66.67)	<0.001
CR, n (%)	75 (75.00)	41 (42.71)	<0.001
Month 6			
SR, n (%)	51 (51.00)	35 (36.46)	0.022
Sustained CR, n (%)	46 (46.00)	31 (32.29)	0.043
Median TTR, d (range)	4 (2–14)	4 (2–29)	0.124

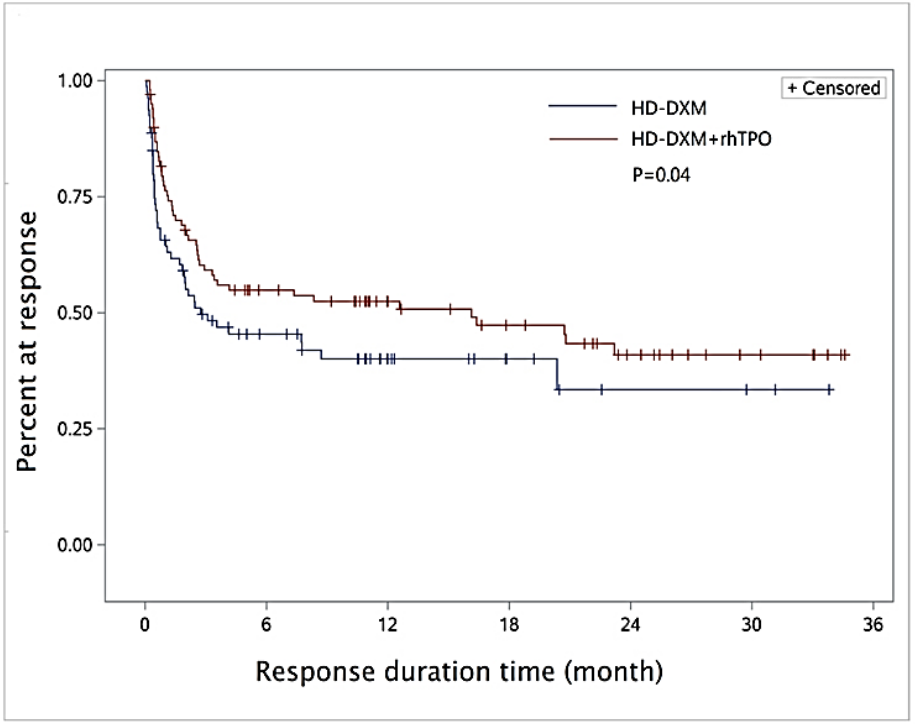


Figure 1: Kaplan–Meier estimates of the duration of response

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

Abs. 1119: Final Result of a Pilot Study Using Eculizumab to Overcome Platelet Transfusion Refractoriness in Allo-Immunized Patients Receiving HLA Mismatched Platelets

Vo P et al

	Platelet Response after Eculizumab	No response to Eculizumab
Number of eculizumab infusions	n=5 (45.5%)	n=6 (54.5%)
Number of patients treated	n=4 (40%)	n=6 (60%)
Median age (years) (range)	34 (24-57)	43 (20-71)
Gender Male Female	 0 4	 3 3
Diagnoses/ Disease status at enrollment • SAA • High risk MDS • Relapsed/Refractory AML • Relapsed ALL	 2 (25%) 1 (25%) 0 2 (50%)	 2 (33.3%) 0 3 (66.7%) 0
Anti HLA-class I antibodies detected pre-treatment	4 (100%)	6 (100%)

Table 1: Patient characteristics and Treatment results. SAA, Severe Aplastic Anemia; MDS, Myelodysplastic syndrome; AML, Acute myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia.

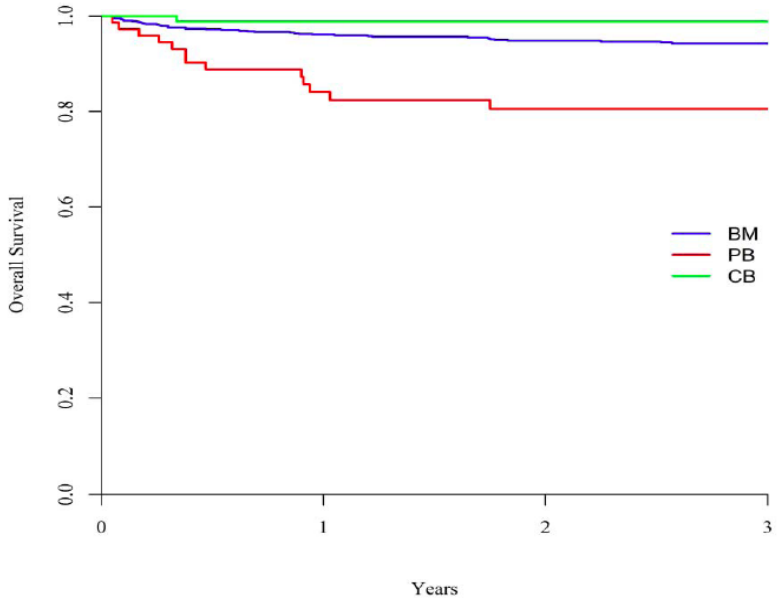
All pts received meningiococcal vaccine

1200 mg Eculizumab , followed immediately with platelets

The path to achieving a cure for SCD?

Stem Cell Transplantation

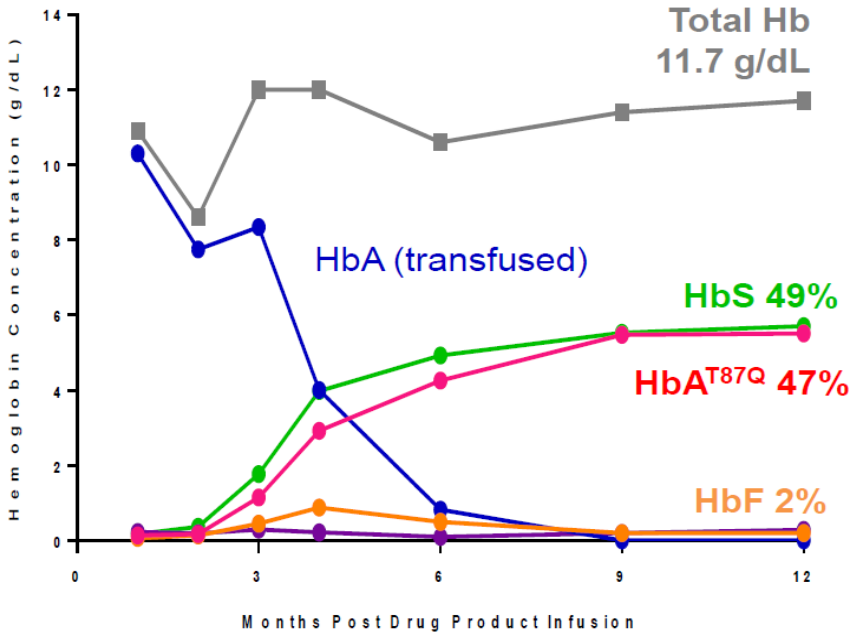
- Data from 1000 children with SCD from Europe, Brazil, United States, Africa and the Middle East who underwent stem cell transplants from matched, sibling donors



94% Overall Survival @3Y

Gene Therapy

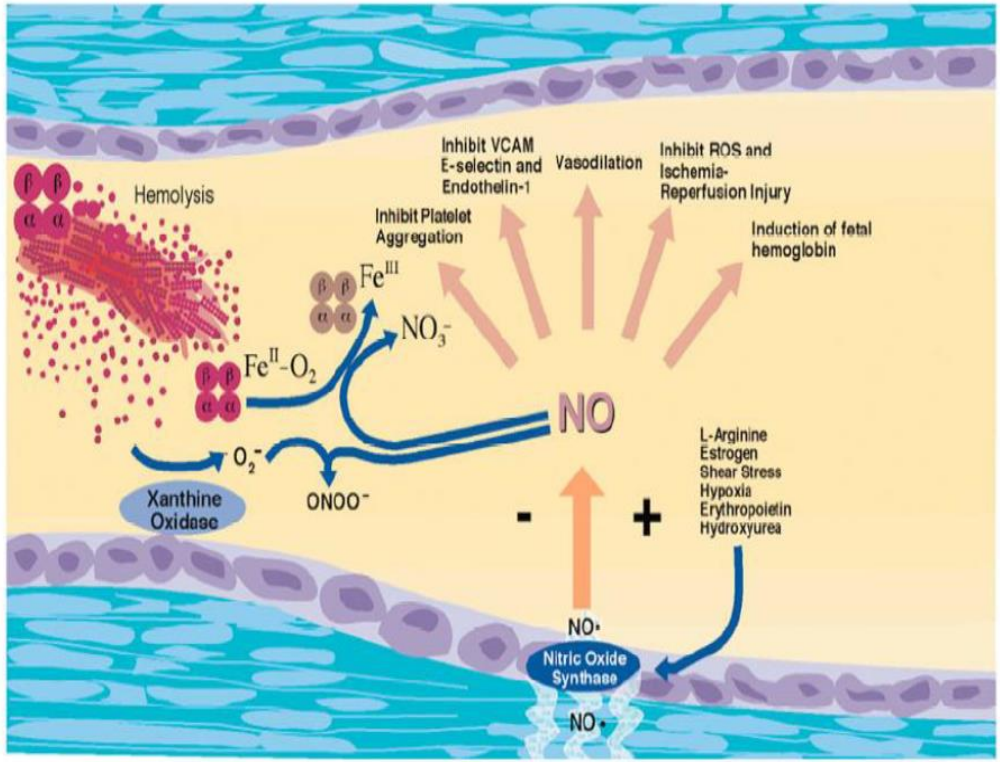
- Patient serves as own donor
- Engineered viral vector used to insert normal copy of single gene that is defective in SCD



Thompson A, 2016

Druggable Targets in SCD?

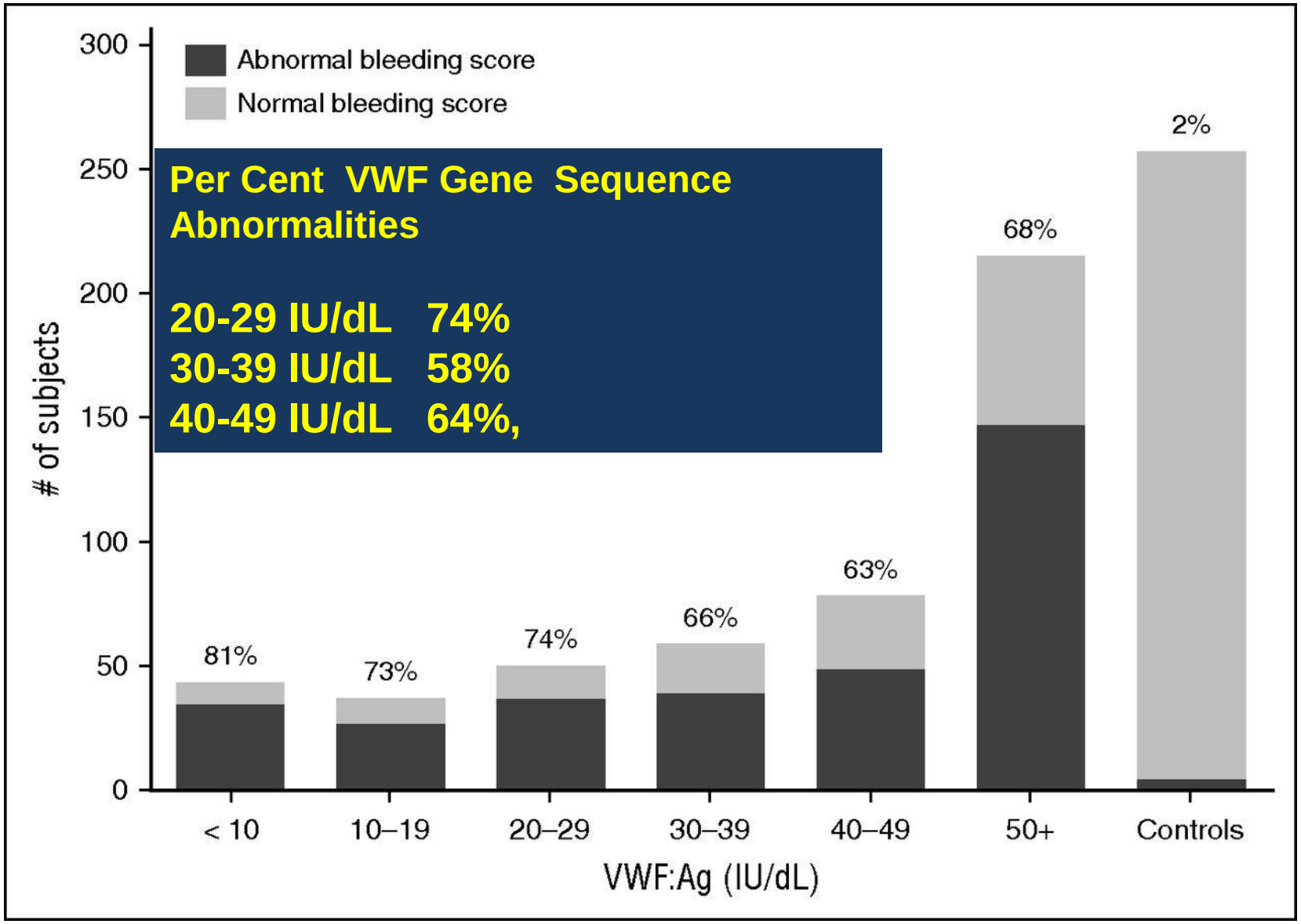
- Polymerization of sickle hemoglobin
- Alterations in RBC membrane
- Reduced nitric oxide bioavailability
- Endothelial dysfunction
- Platelet activation
- Pro-inflammatory cytokine production
- Activation of adhesion molecules on leukocytes, endothelial cells and platelets



Microcirculation 2004;11(2):179-93

Thompson A, 2016

Von Willebrand Disease Type I Diagnosis: Not So Simple



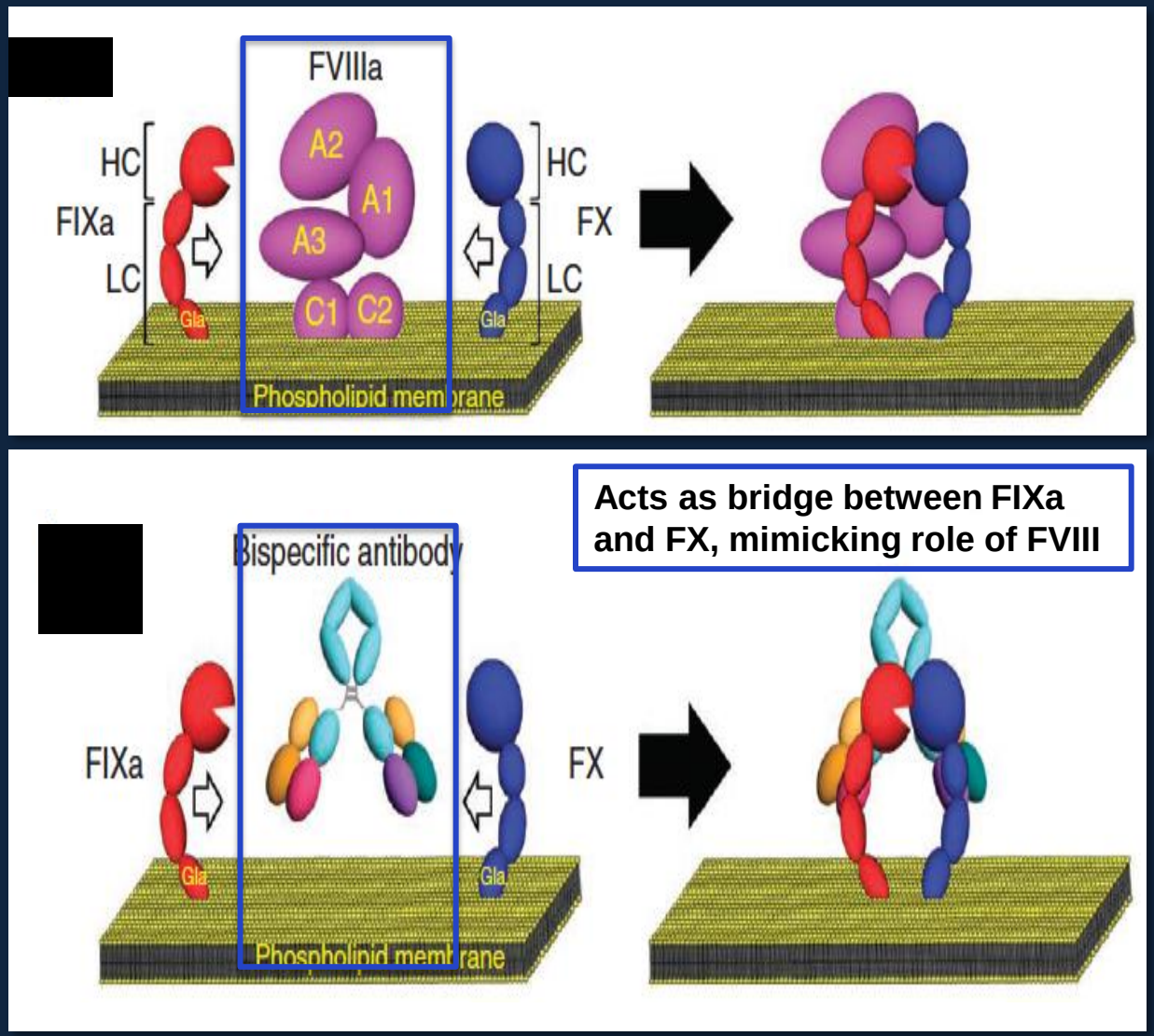
Flood VH et al. Blood 2016;127:2481

Mimetics: New Era in Hemophilia Management

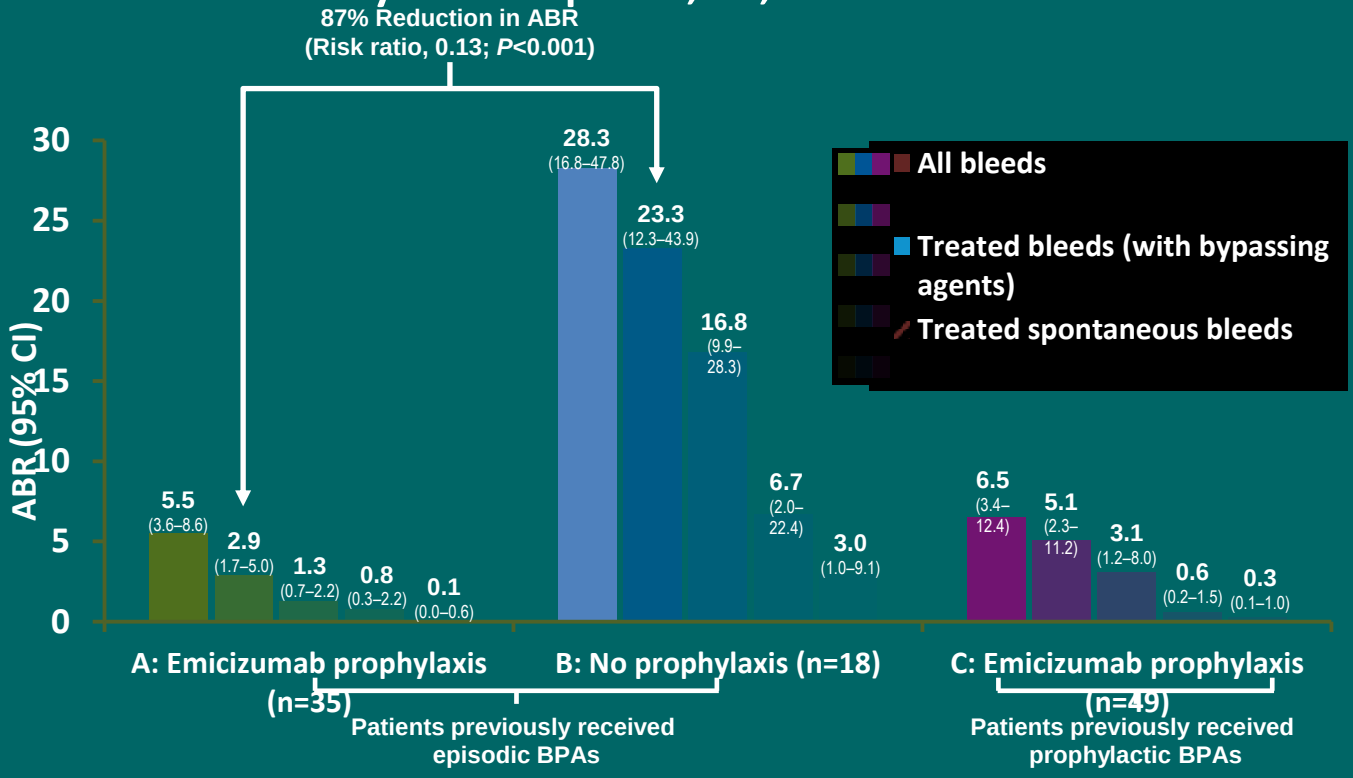
- For the first time, offers the potential to treat hemophilia A without factor replacement

- Emicizumab
  - First-in-class bi-specific monoclonal antibody (mAb)
  - Approved 2017 for prophylaxis in adults and children with inhibitors based on HAVEN 1 and 2 studies
  - Once weekly SQ administration
  - Use in patients without inhibitors (HAVEN 3) and as monthly dosing (HAVEN 4) also under investigation

Mimetics: Emicizumab



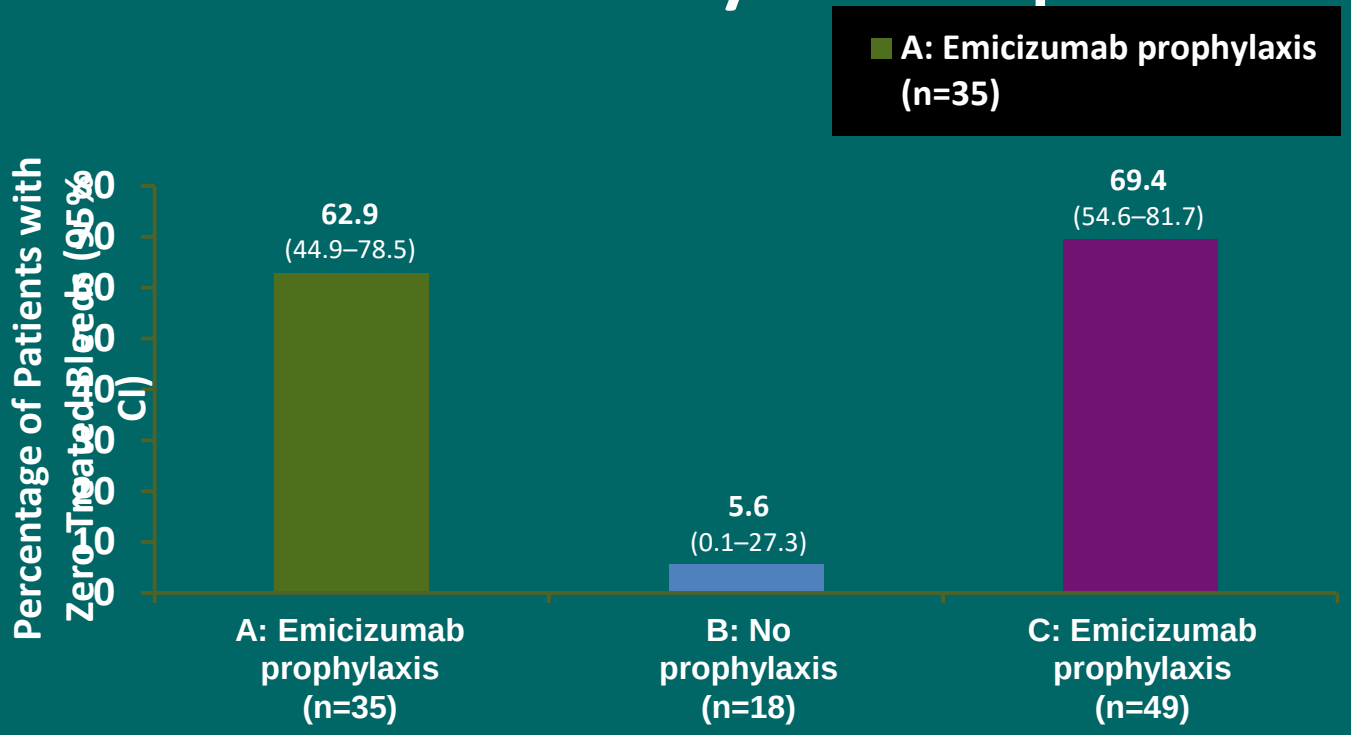
HAVEN 1: Annualized Bleeding Rate* for Study Groups A, B, and C



*Calculated using negative binomial regression model, and Group D was not included due to the short follow-up at the time of data cutoff (October 25, 2016). ABR=annualized bleeding rate; CI=confidence interval; BPA=bypassing agent.

Oldenburg J et al. *N Engl J Med*. 2017;377:809-818.

HAVEN 1: Patients with Zero Treated Bleeds Across Study Groups*



*Group D was not included due to the short follow-up at the time of data cutoff (October 25, 2016).
CI=confidence interval.
Oldenburg J et al. *N Engl J Med*. 2017;377(Suppl):S1-S28.

Overview of Thrombotic Safety Events Requiring Expedited Safety Reporting

Five thrombosis-related SAEs

3 TMAs and 2 TE occurred in patients enrolled in the emicizumab phase 3 inhibitor study (HAVEN 1)

All of these events occurred in patients

on **emicizumab prophy and who used multiple doses of aPCC** to treat a breakthrough bleed

Death occurred in one patient*

The SAEs have resolved or improved in 4 patients

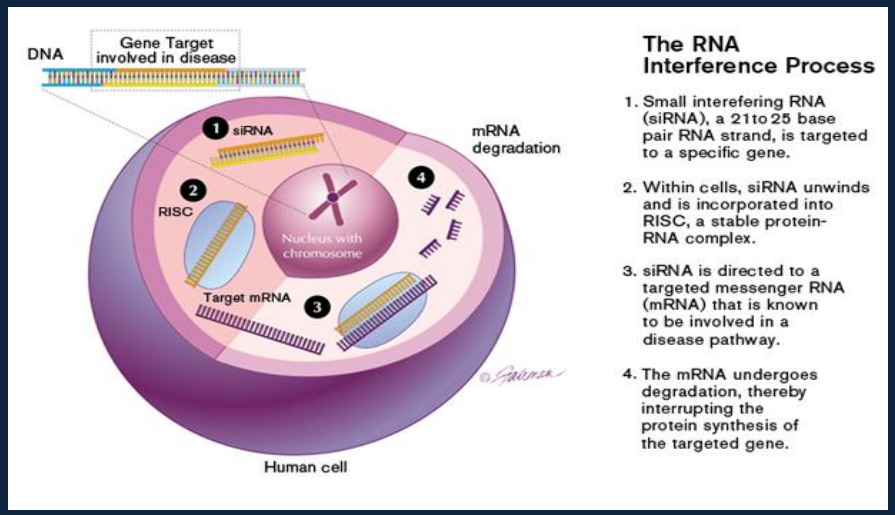
Two patients have resumed treatment with emicizumab

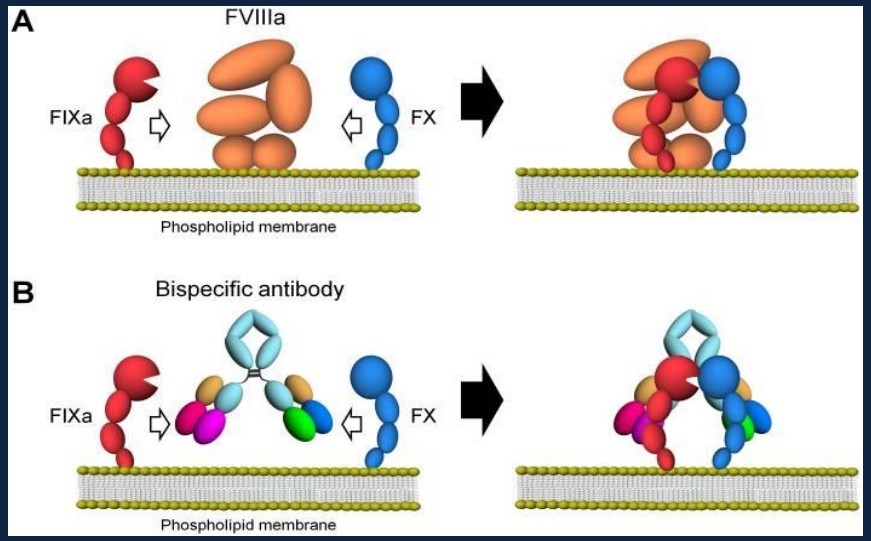
TMA=thrombotic microangiopathy; TE=thromboembolic event; aPCC=Activated prothrombin complex concentrate; SAE= serious adverse event.

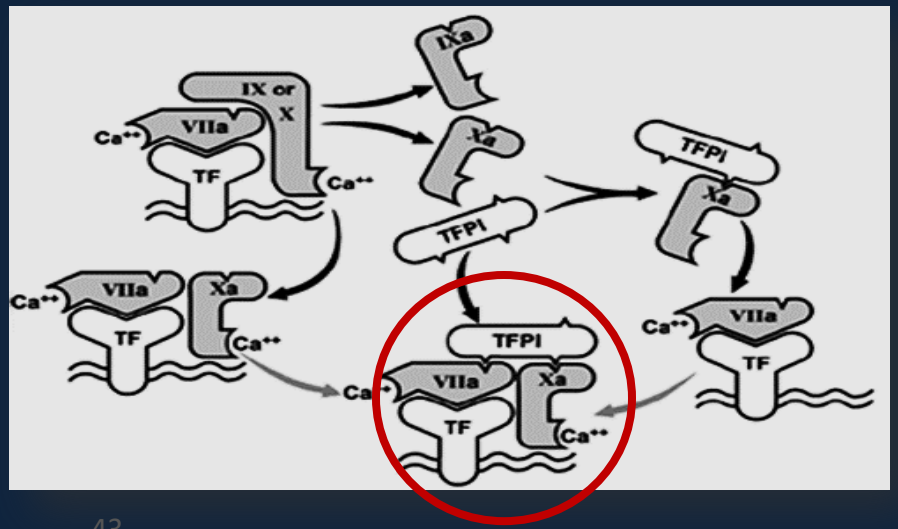
***The investigator's assessment is that the cause of death was due to rectal hemorrhage, which was not related to emicizumab**

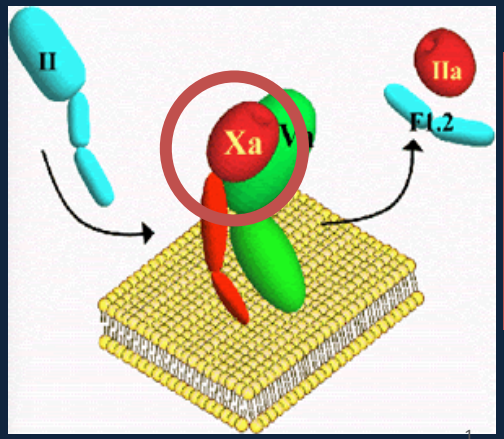
Genentech, data on file.

The promise of non-FVIII alternatives as adjunctive enhancers of coagulation









Zymogen FXa mutants (Camire *et al*)
Super V mutants (Griffin *et al*)

http://www.technologyreview.com/sites/default/files/legacy/rnai.secondary x616.png 2. Sampei Z. *et al. PLoS One.* 2013; 8 (2) [Epub ahead of print]. 3. http://hematology.im.wustl.edu/people/faculty/Broze/tfpi.gif 4. http://stokes.chop.edu/programs/thrombosis/camire/img/clotthingscheme.gif