Benign Hematology and Coagulopathy

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Topics

- Cancer and thrombosis- fine tuning anticoagulation with biomarkers
- MPNs and thrombosis
- COVID-19 and thrombosis
- Advances in ITP- first line treatment strategies
- ITP- new drugs
- Rebalancing hemostasis
- Sickle cell therapies
- Hemophilia and Gene therapy

Background

- Cancer is associated with increased risk of venous thromboembolism (VTE)[1]
- Pathogenesis of cancer-associated thrombosis (CAT) is multifactorial and risk of cancer-associated VTE is highly variable
- Khorana score is currently the most widely validated predictive model for VTE in cancer[2,3]
- CASSINI examined the effect of rivaroxaban versus placebo on VTE incidence in ambulatory cancer patients at higher risk for VTE (Khorana score ≥ 2)[4]
  - Rivaroxaban 10 mg once daily reduced the risk of VTE compared with placebo

1. Liebman HA. *Thromb Res.* 2018;164(suppl 1):S19-S22;
2. Hisada Y, Mackman N. *Blood.* 2017;130(13):1499-1506;
3. Khorana AA, Connolly GC. *J Clin Oncol.* 2009;27(29):4839-4847;
4. Khorana AA, et al. *N Engl J Med.* 2019;380(8):720-728.

Biomarker Signatures in Cancer Patients With or Without Venous Thromboembolism Events: A Substudy of CASSINI

Alok A. Khorana,[1,*] John Barnard,[2] Ted Wun,[3] Ujjwala Vijapurkar,[4] CV Damaraju,[4] Kenneth Todd Moore,[4] Peter Wildgoose,[4] Keith R. McCrae[1]

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*Presenting author.

SCIENTIFIC WORKSHOP ON THE INTERPLAY BETWEEN COAGULATION AND MALIGNANCY

ASH 2021 Late Breaking Abstracts

Methods

- Case-control study design
- Blood samples from all 62 patients who developed VTE were compared with 62 patients without VTE
  - Matched by age, sex, cancer type, tumor stage, and Khorana score
- Baseline blood samples were analyzed for 280 biomarkers (Myriad Human DiscoveryMAP®, v3.3)

Khorana Score

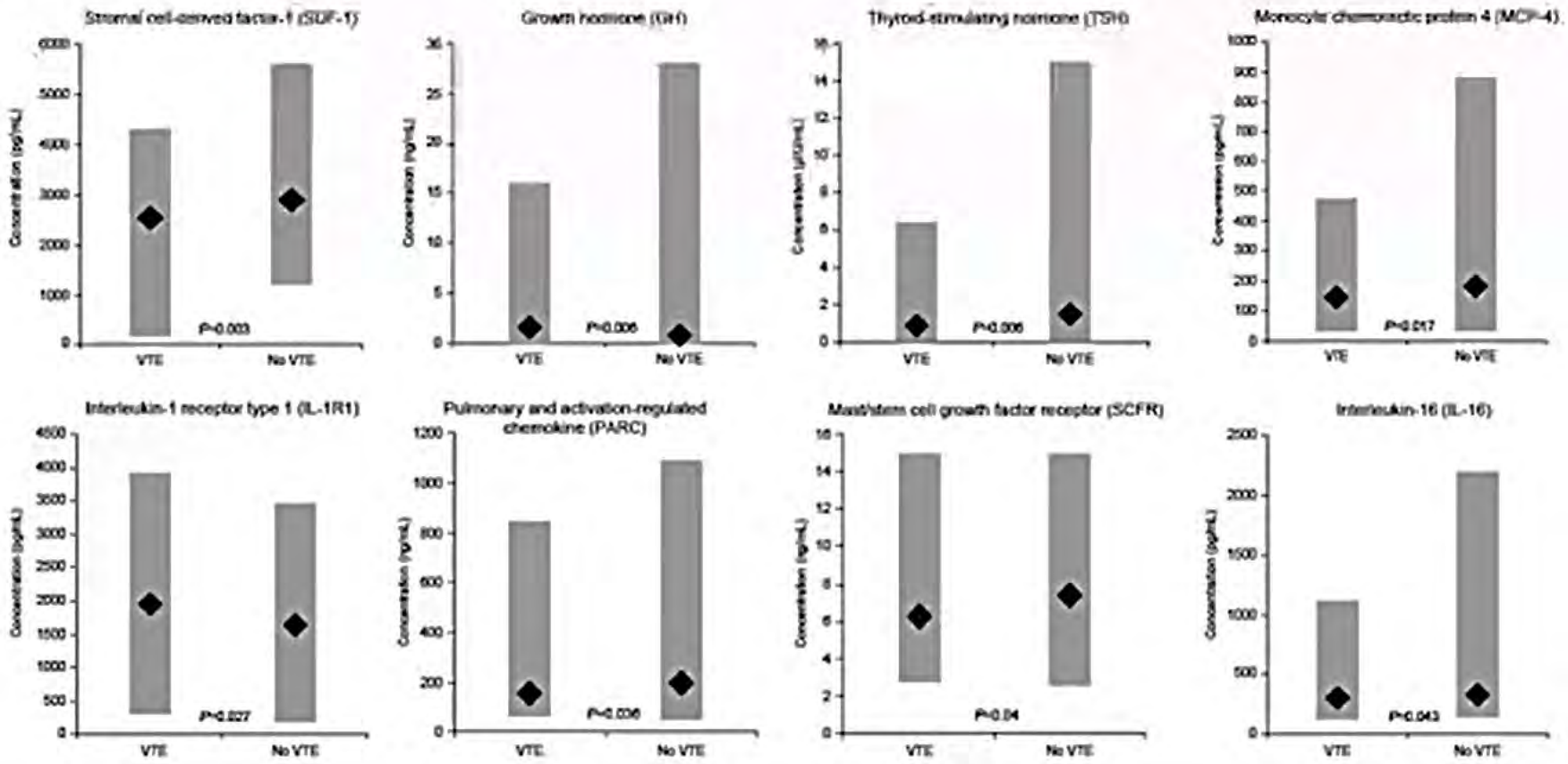
Patient Characteristic	Risk Score
Site of Primary Cancer ➢ Very High Risk (stomach, pancreas) ➢ High Risk (lung, lymphoma, gynecologic, bladder, testicular)	 2 1
Prechemotherapy platelet count ≥ 350 x 10^9/L	1
Hgb < 10 g/dL	1
Prechemotherapy leukocyte count ≥ 11 x 10^9/L	1
BMI 35 kg/m^2	1

Total Score	Risk of Symptomatic VTE
0	Low (0.8-3%)
1-2	Intermediate (1.8-8.4%)
3 or higher	High (7.1-41%)

- Pathway/gene set enrichment analysis of selected biomarkers was performed

Biomarker Distribution in Cancer Patients with and without VTE

- 11 statistically significantly different baseline biomarker distributions
- Biomarkers with the largest difference in median values include SDF-1, GH, TSH, MCP-4, IL-1R1, PARC, SCFR, and IL-16



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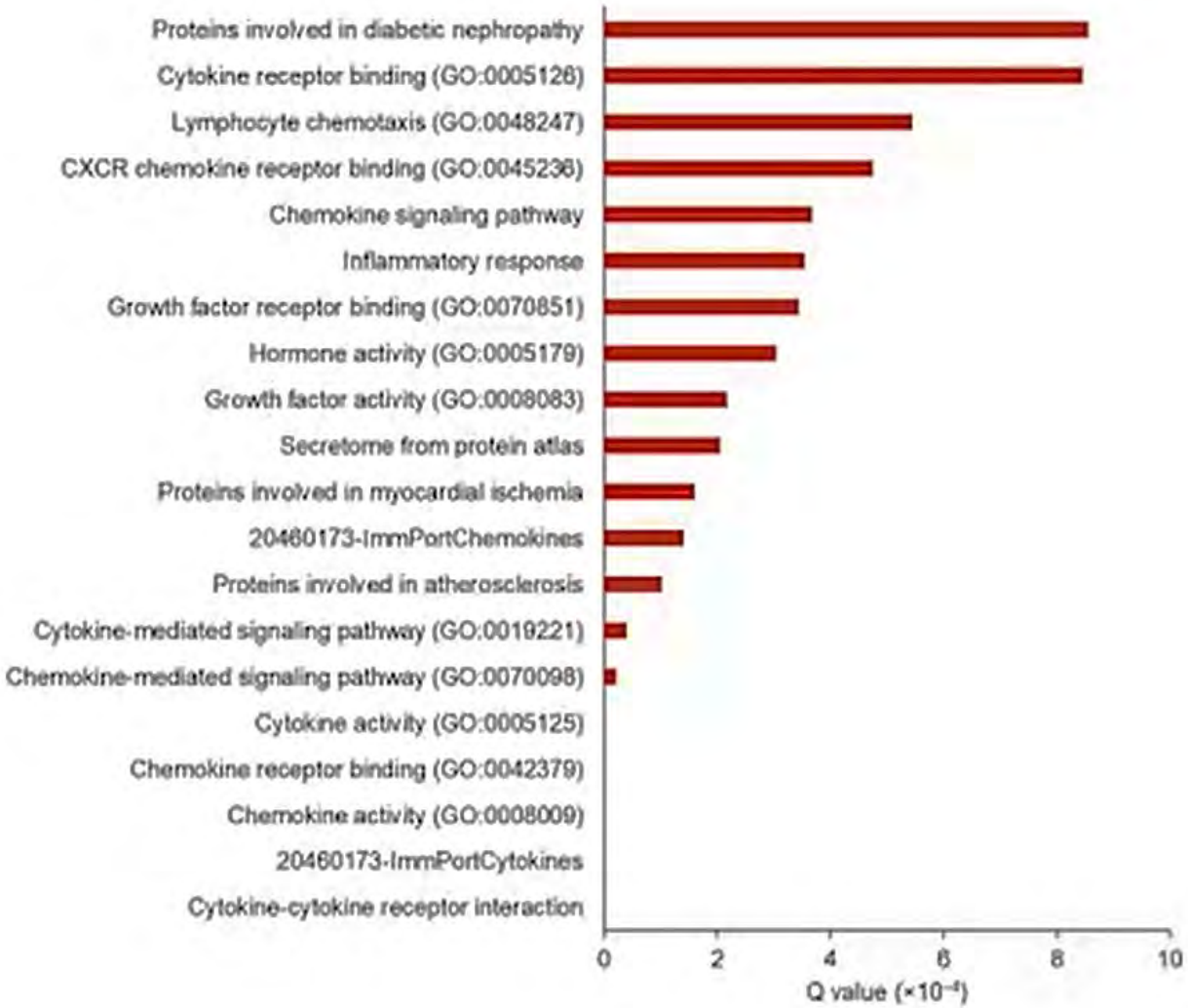
Enrichment of Multiple Genes Sets/Pathways



Pathway analysis indicated enrichment of multiple gene sets/pathways, including cytokine–cytokine receptor interaction, cytokine activity, and chemokine activity

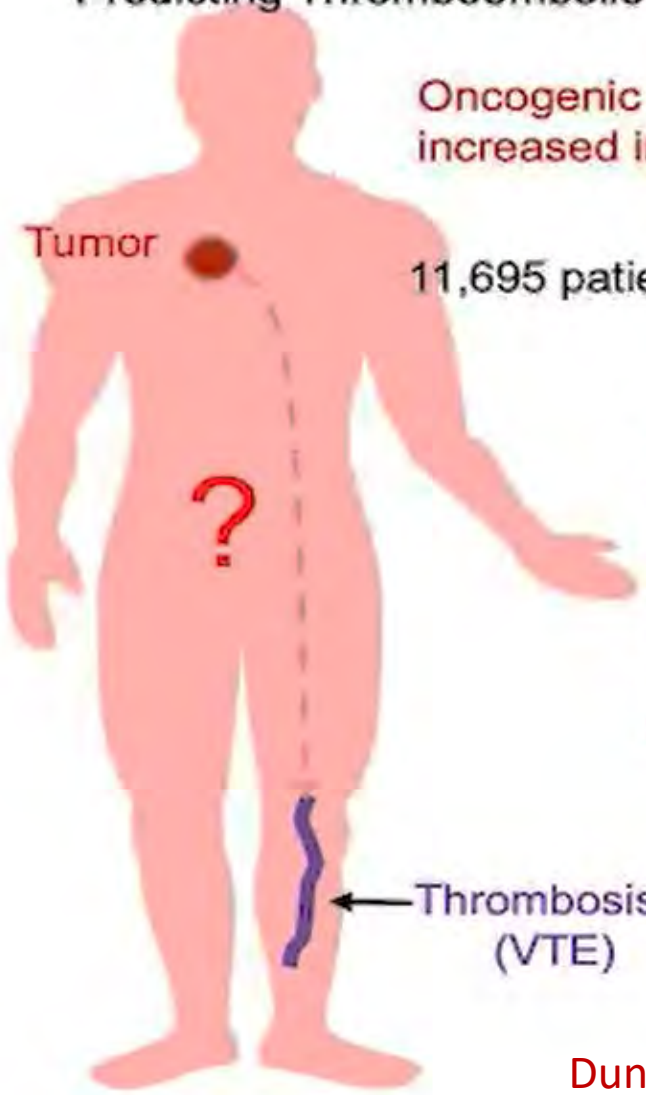
Predictions from the model were 86% correct for those predicted to not develop VTE (54/63) and 87% correct for those predicted to develop VTE (53/61)

ASH 2021 Late Breaking Abstracts

Cancer Somatic Mutations Predict Thrombosis

Dunbar et al: Genomic Profiling Identifies Somatic Mutations Predicting Thromboembolic Risk in Patients with Solid Tumors, *Blood, 2021*

Oncogenic mutations associated with increased incidence of systemic thrombosis

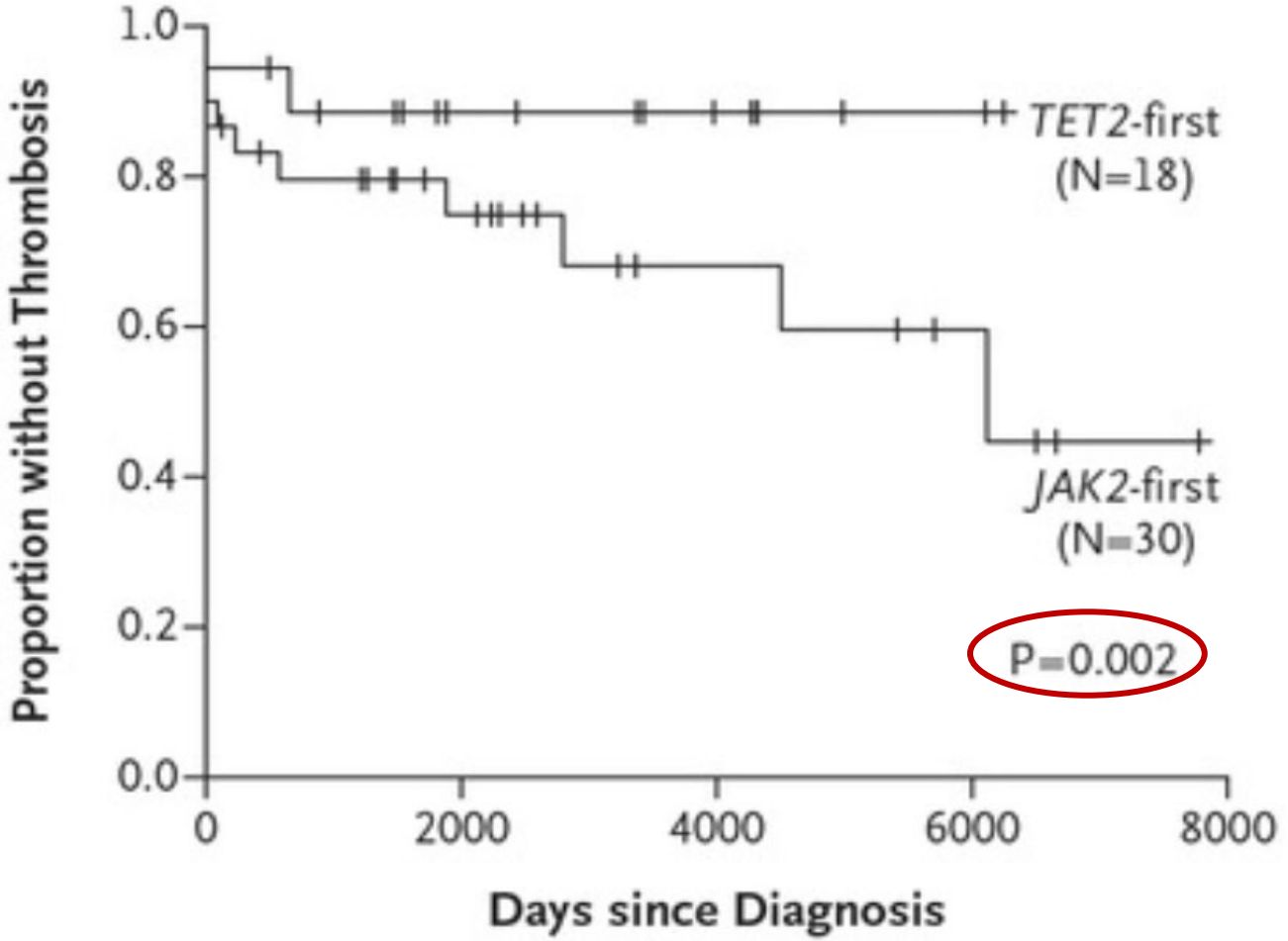


11,695 patients with >15 types of solid tumours

STK11/LKB1 (HR=2.12 [1.55- 2.89])
KEAP1 (HR=1.84 [1.21-2.79])
MET (HR=1.83 [1.15-2.92])
CTNNB1 (HR=1.73 [1.15-2.60])
CDKN2B (HR= 1.45 [1.13-1.85])
KRAS (HR=1.34 [1.09-1.64])

Dunbar A et al. *Blood* (2021) 137 (15): 2103–2113
Rak J. Blood. 2021 Apr 15;137(15):1996-1997

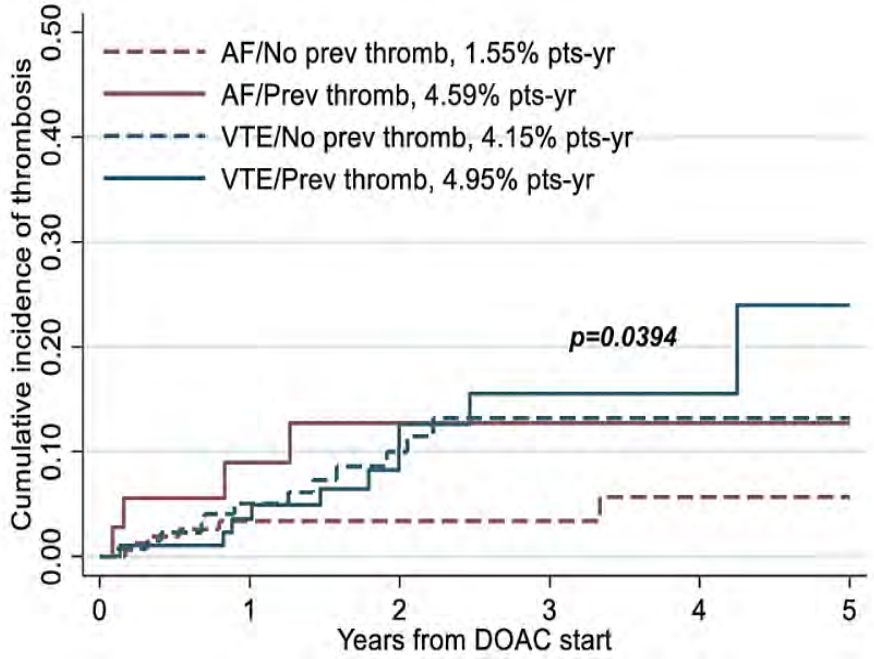
Mutational order may influence thrombotic potential in MPNs: "JAK2 first" is an independent risk factor

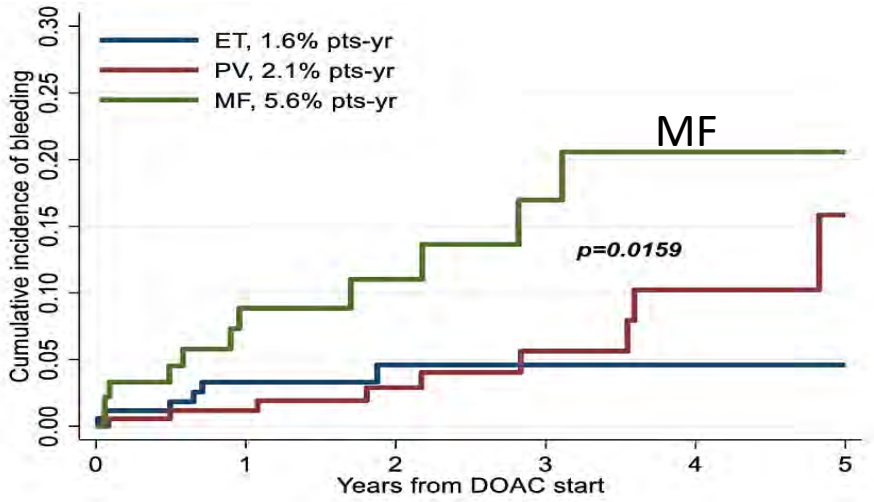


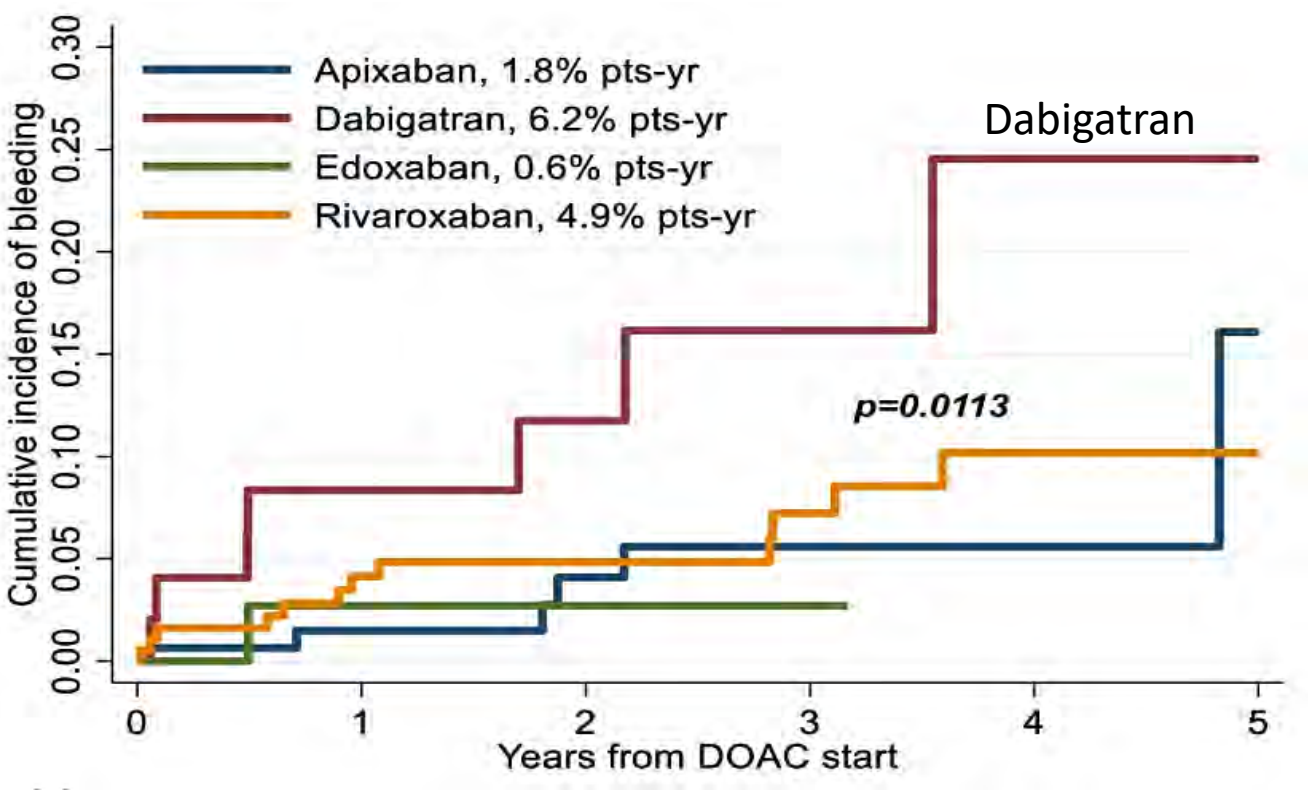
- Younger age at dx of ET or PV
- Higher probability of PV
- Larger homozygous subclones
- Elevated risk of thrombosis

Ortmann CA et al N Engl J Med. 2015 Feb 12;372(7):601-612. doi: 10.1056/NEJMoa1412098.

DOACs in MPNs: Cumulative incidence of bleeding and thrombosis







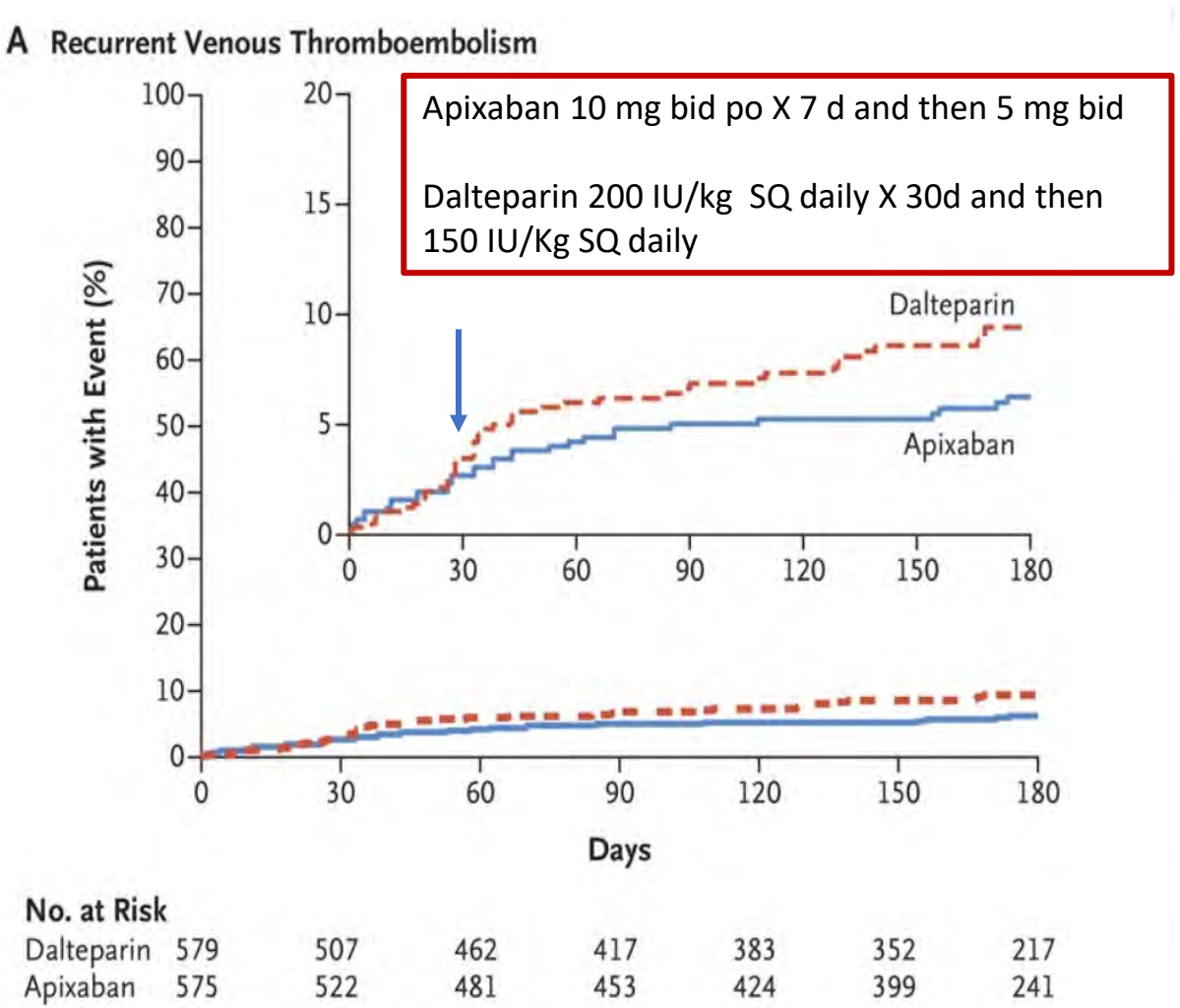
Observational, multicenter, international study in 442 consecutive patients on any DOAC for VTE or AF

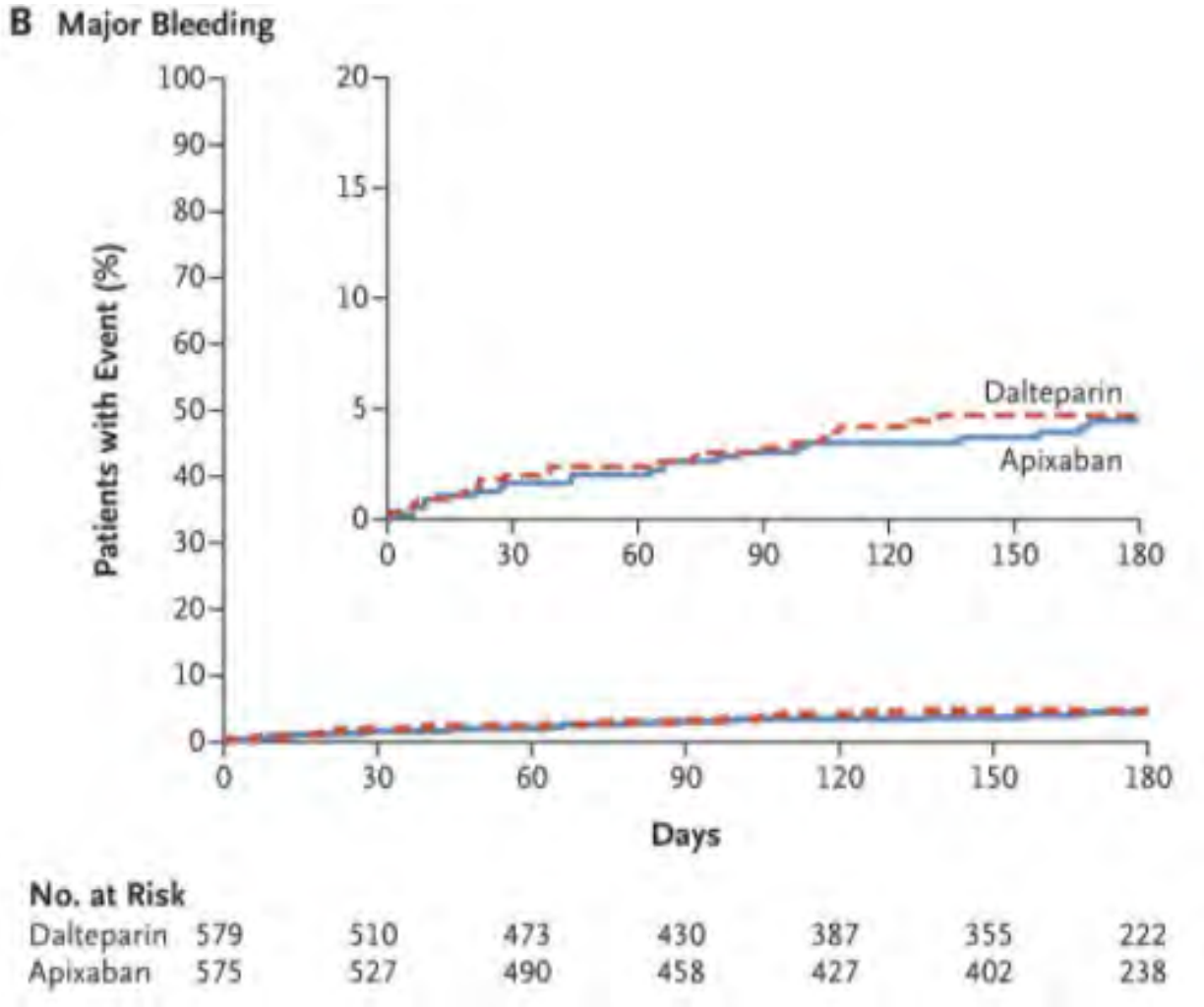
Barbui, T. et al. *Leukemia* **35,** 2989–2993 (2021). https://doi.org/10.1038/s41375-021-01279-1

Apixaban is noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding

Apixaban 10 mg bid po X 7 d and then 5 mg bid

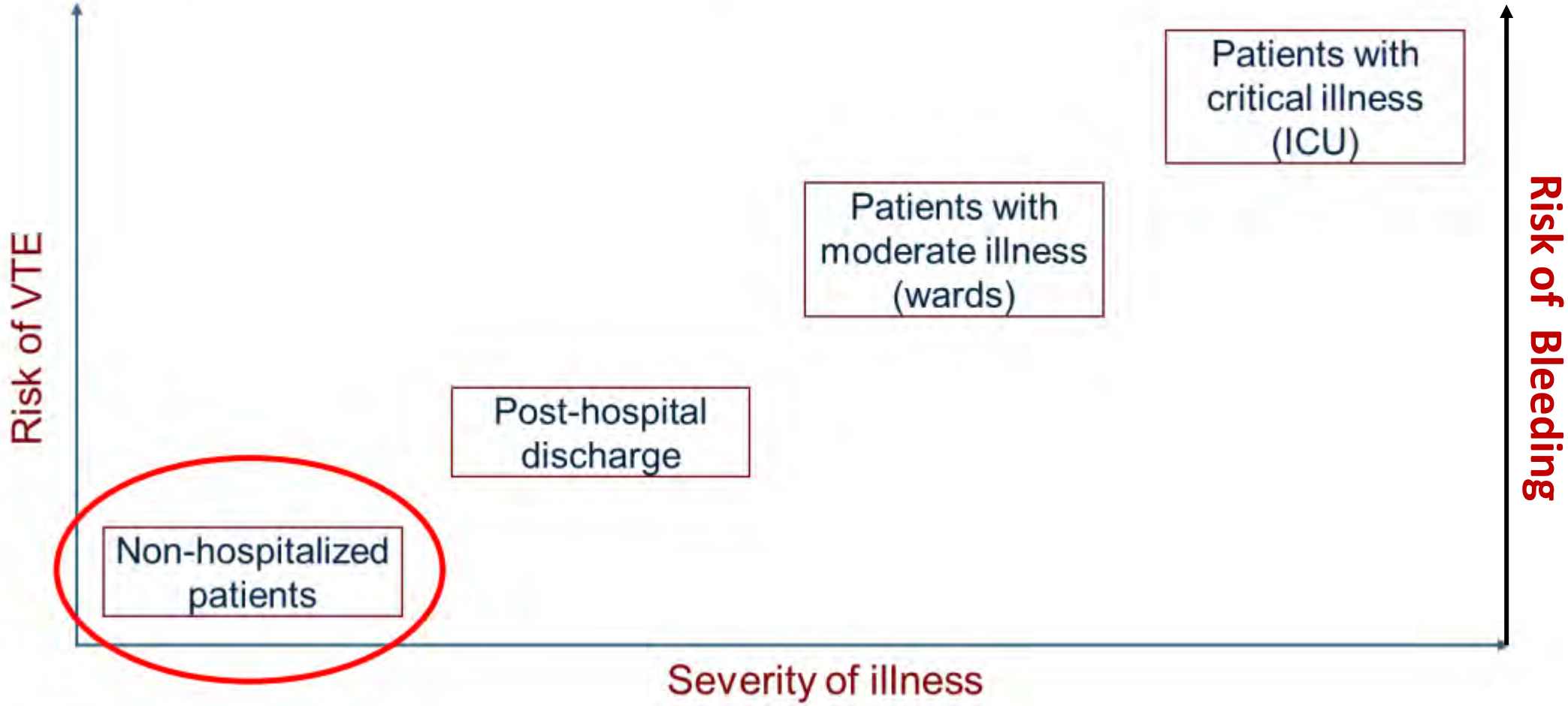
Dalteparin 200 IU/kg SQ daily X 30d and then 150 IU/Kg SQ daily





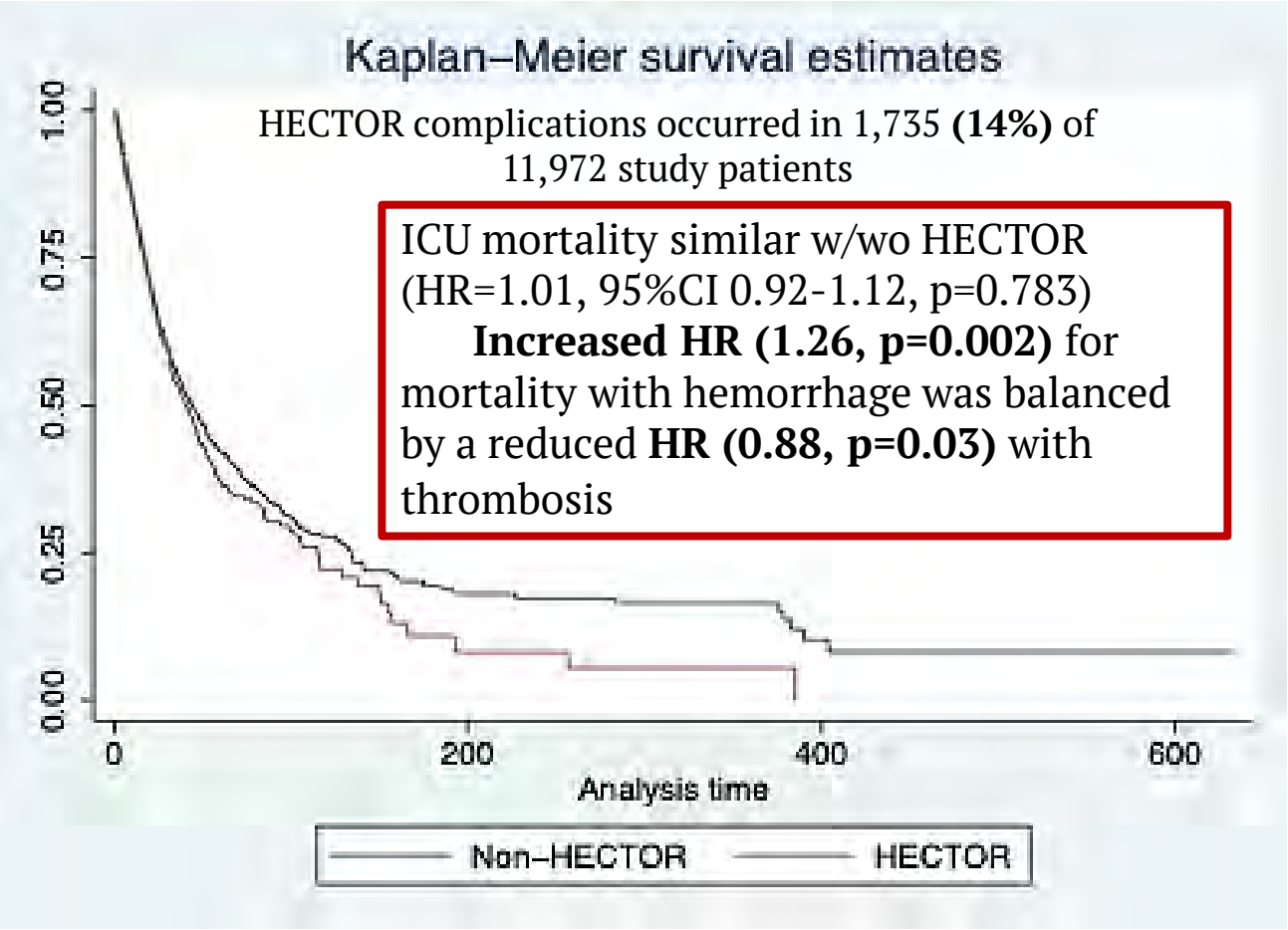
Agnelli C et al. Engl J Med 2020; 382:1599-1607 DOI: 10.1056/NEJMoa1915103

Risks of VTE and Bleeding are Proportional with COVID Severity



Hemorrhagic, Coagulopathic, and Thrombotic (HECTOR) Complications Among Critically-Ill Patients with COVID-19: An International COVID-19 Critical Care Consortium Study

Fanning J et al. https://abstracts.isth.org/abstract/hemorrhagic-coagulopathic-and-thrombotic-hector-complications-among-critically-ill-patients-with-covid-19-an-international-covid-19-critical-care-consortium-study/. Accessed August 7, 2022.



Acute thromboses in 10% of HECTOR pts, of whom:
57% with pulmonary embolism,
33% with myocardial infarction
7.4% with deep vein thrombosis
3.9% with ischemic stroke

Hemorrhagic complications in 4.9% pts of whom:
48% with gastrointestinal bleeds
14% with hemorrhagic stroke
13% with pulmonary hemorrhage

DIC in 11 0.09%

Univariate analysis risk factors: DM, HBP, ECMO, cardiac/renal disease

COVID-19 Treatment Guidelines: NIH Panel's Statement on Anticoagulation in Hospitalized Patients With COVID-19 For Prophylaxis of VTE or Arterial Thromboembolism

Last Updated: January 5, 2022

For Hospitalized Adults Requiring Low-Flow Oxygen and Are Not Receiving ICU Level of Care

With D-dimer above ULN: **Therapeutic-dose heparin (plts>50K, no need for anticoagulation)**

LMWH is preferred over unfractionated heparin

LMWH should continue for 14 d or until hospital discharge, whichever comes first

Recommend against therapeutic-dose oral AC for VTE prophylaxis or prevention of COVID progression

For Hospitalized Adults Receiving ICU Level of Care (Including High-Flow Oxygen)

Prophylactic-dose heparin as VTE prophylaxis unless a contraindication exists

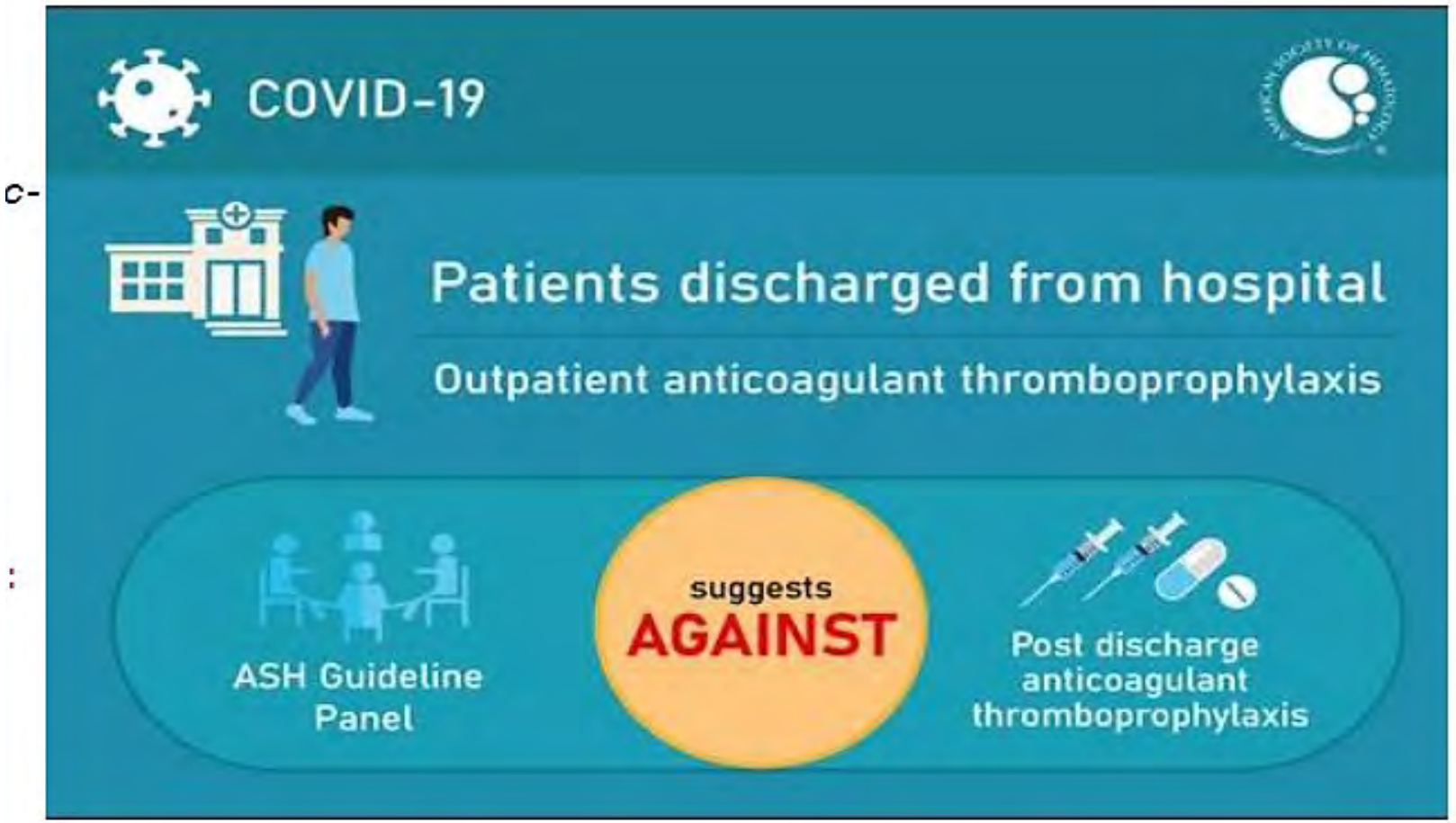
Recommend against intermediate-dose (e.g., enoxaparin 1 mg/kg daily)

If started on therapeutic-dose heparin while on low-flow oxygen and then transferred to ICU, switch from therapeutic to **prophylactic-dose heparin** unless a VTE is confirmed

For Hospitalized Pregnant Adults

Recommend using **prophylactic-dose anticoagulation**

Anticoagulation for Patients with COVID-19 Being Discharged From Hospital: ASH Guideline Panel

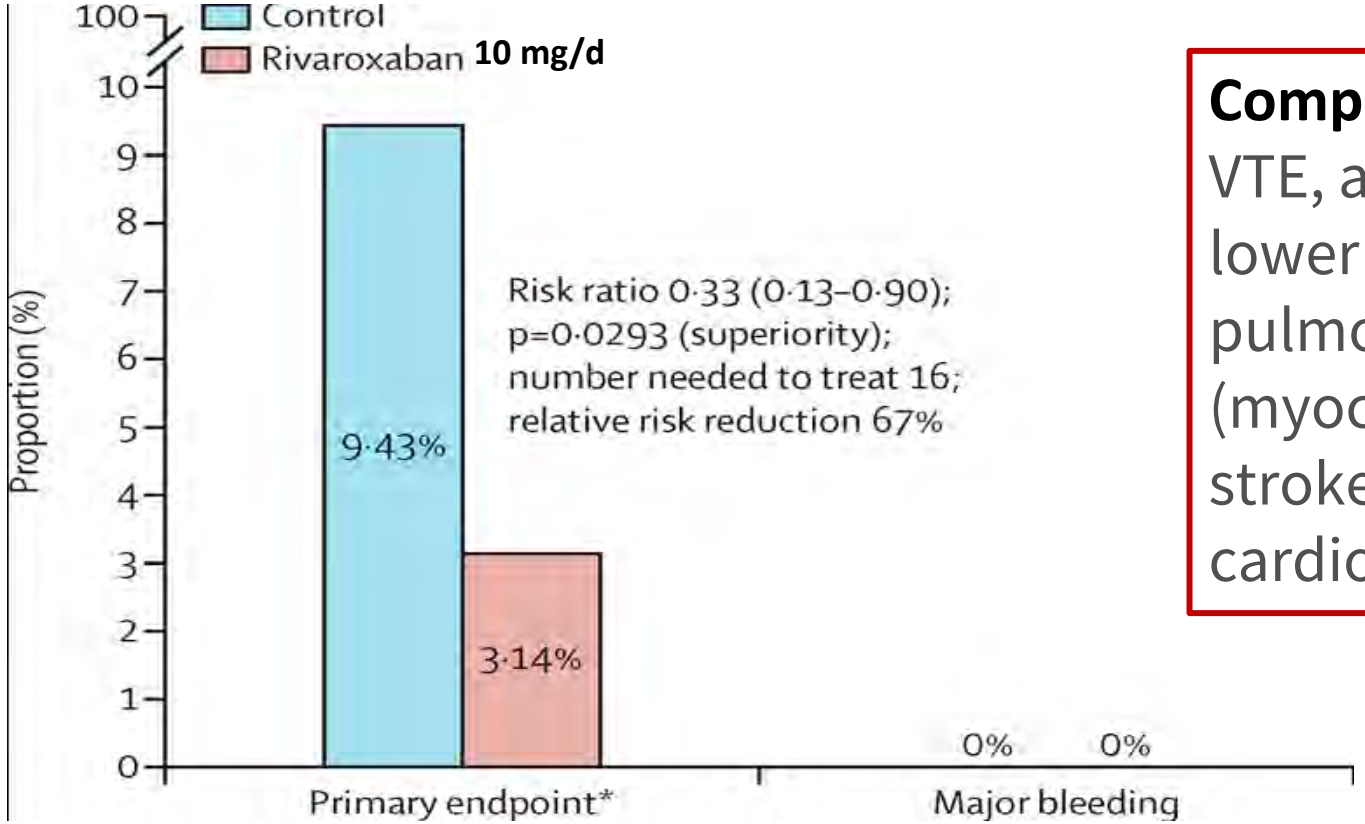


(conditional recommendation based on very low certainty in the evidence)

https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19

Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial

Ramacciotti E et al. *Lancet 399; p50-59*
DOI: 10.1016/S0140-6736(21)02392-8

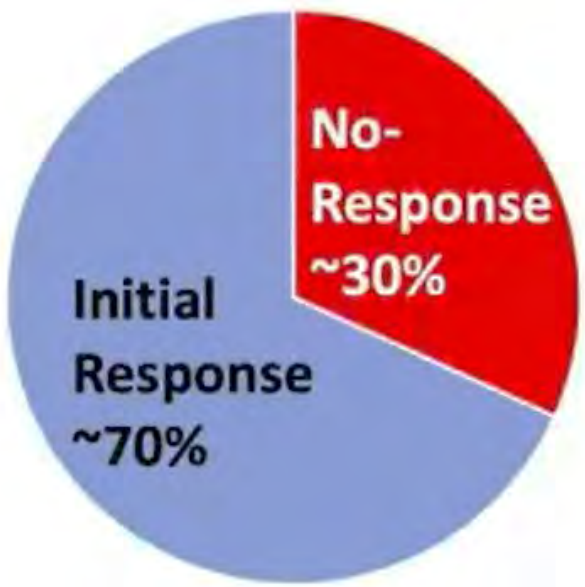


Composite endpoint: Symptomatic or fatal VTE, asymptomatic VTE detected by bilateral lower limb venous Doppler ultrasound and CT pulmonary angiogram, symptomatic ATE (myocardial infarction, non-hemorrhagic stroke, and major adverse limb event), and cardiovascular death at day 35

Background

First-line therapies

- Corticosteroids
- IVIG
- anti-D



6 Months

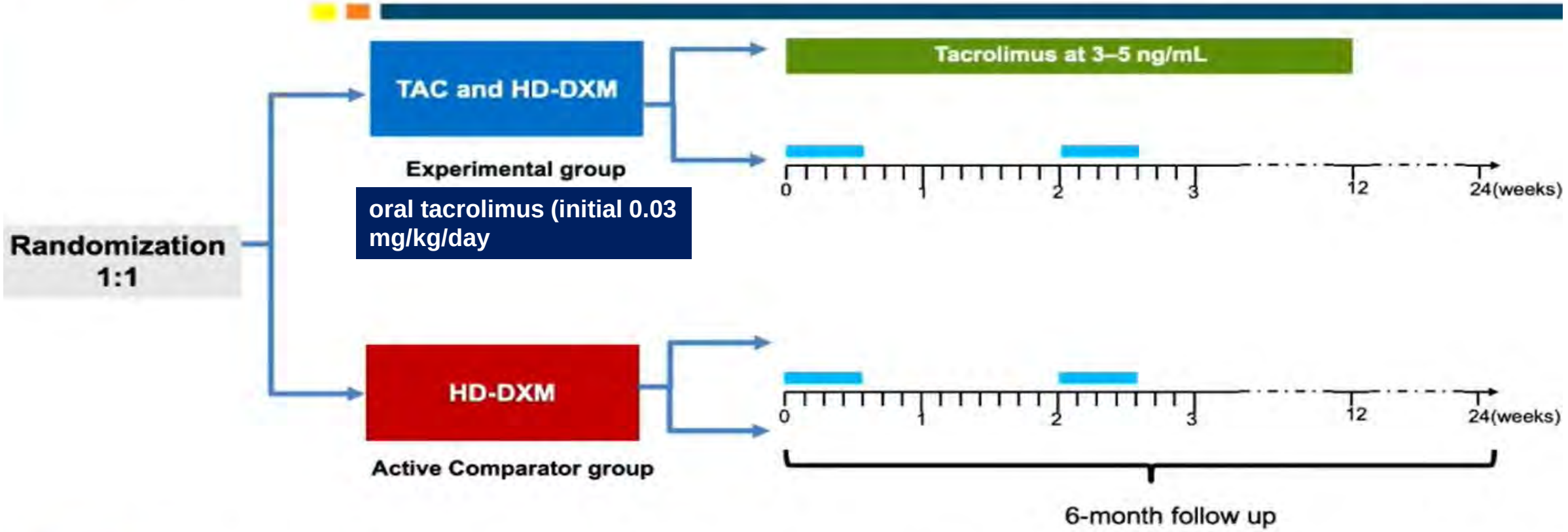
- A high proportion of ITP patients develop drug resistance or relapse after current first-line therapy, and rarely achieve sustained remission
- Long-term effective first-line treatment options need to be addressed

Blood. 2016;127(3):296-302
Blood 2009 113:2386-2393
Clin Med Insights Blood Disord. 2016; 9: 15–22.

Abstract 13: Tacrolimus Plus High-Dose Dexamethasone Versus High-Dose Dexamethasone Alone As First-Line Treatment for Adult Immune Thrombocytopenia: The Phase 2, Open Label, Randomized Trial (TARGET 020)

Zhuo-Yu An et al

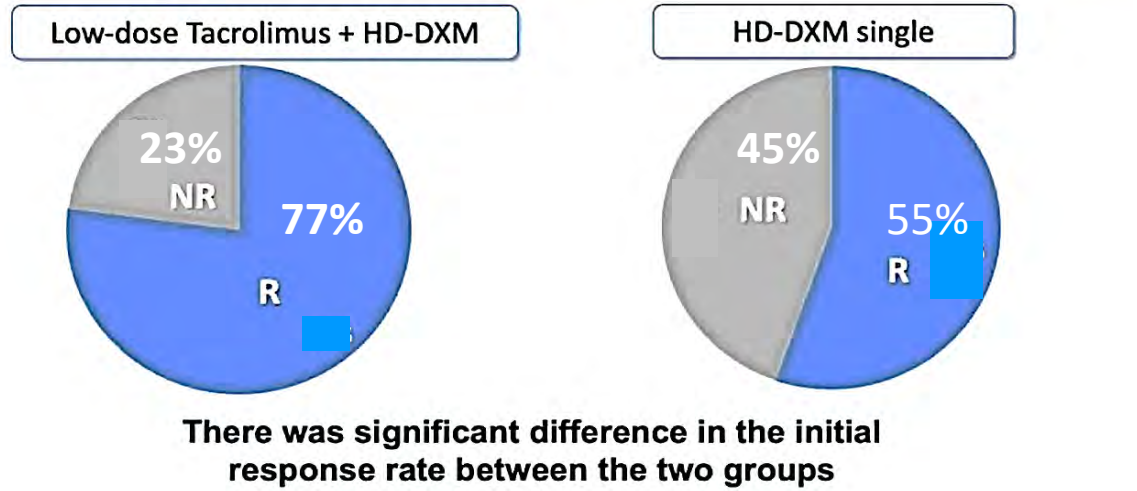
Multicenter Study Design-Intervention



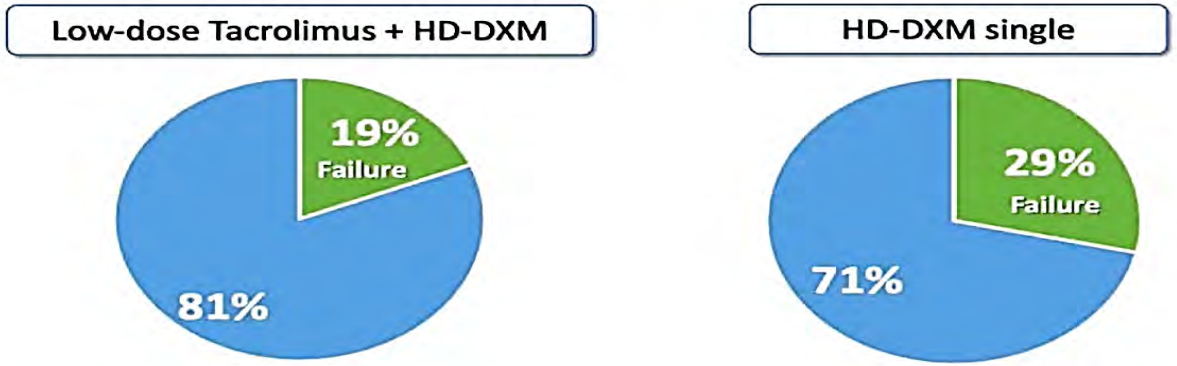
The 4-day course of dexamethasone (40mg qd * 4d) was repeated in the case of lack of response by day14
This trial was registered with *ClinicalTrials.gov* (NCT04747080).

Abstract 13: Tacrolimus Plus High-Dose Dexamethasone Versus High-Dose Dexamethasone Alone As First-Line Treatment for Adult Immune Thrombocytopenia: The Phase 2, Open Label, Randomized Trial (TARGET 020) *Zhuo-Yu An et al* *ASH 2021*

Results II day-14 response

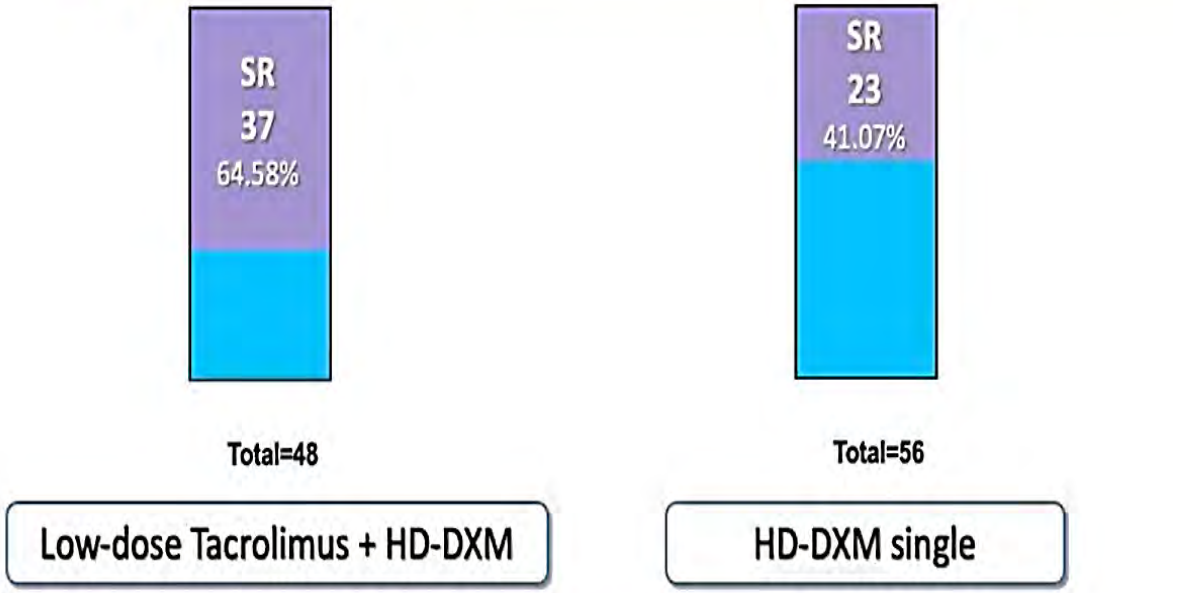


There was significant difference in the initial response rate between the two groups



Fewer patients in the combination group experienced relapse than in the monotherapy group;

Results IV 6 months response rate

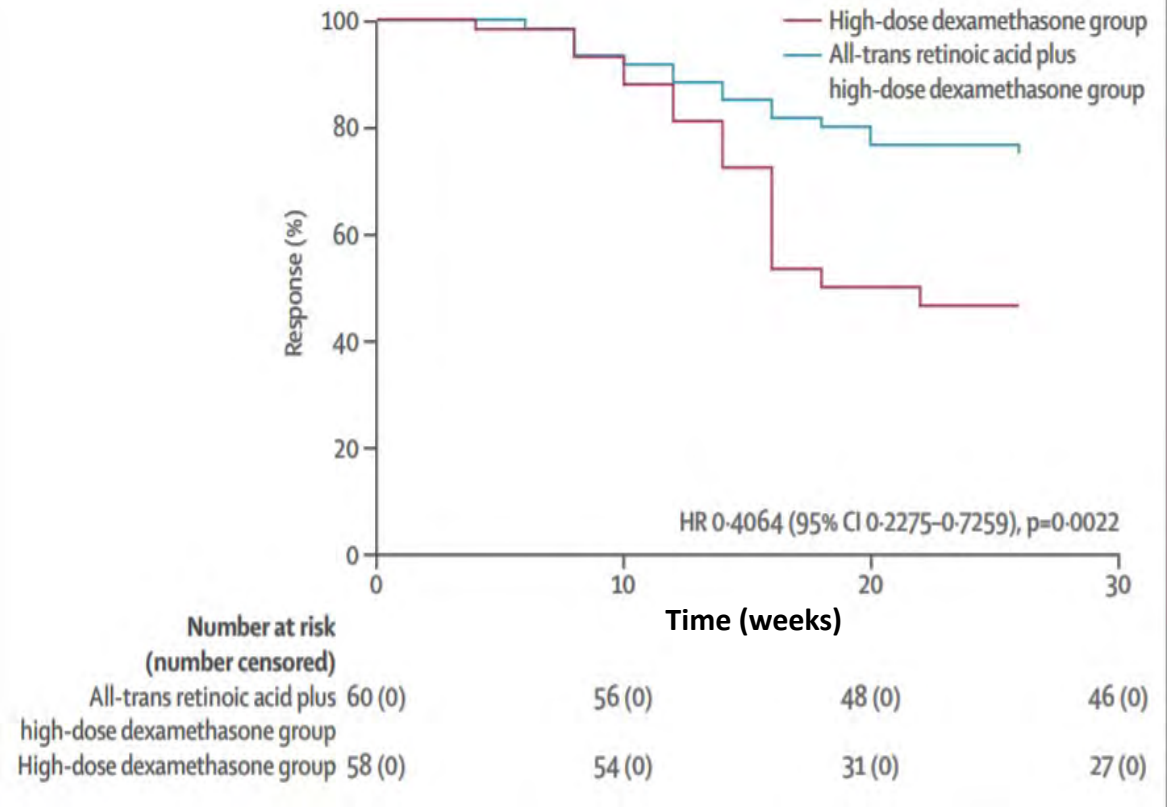


Low-dose Tacrolimus group had a significant higher sustained response rates after 6 months

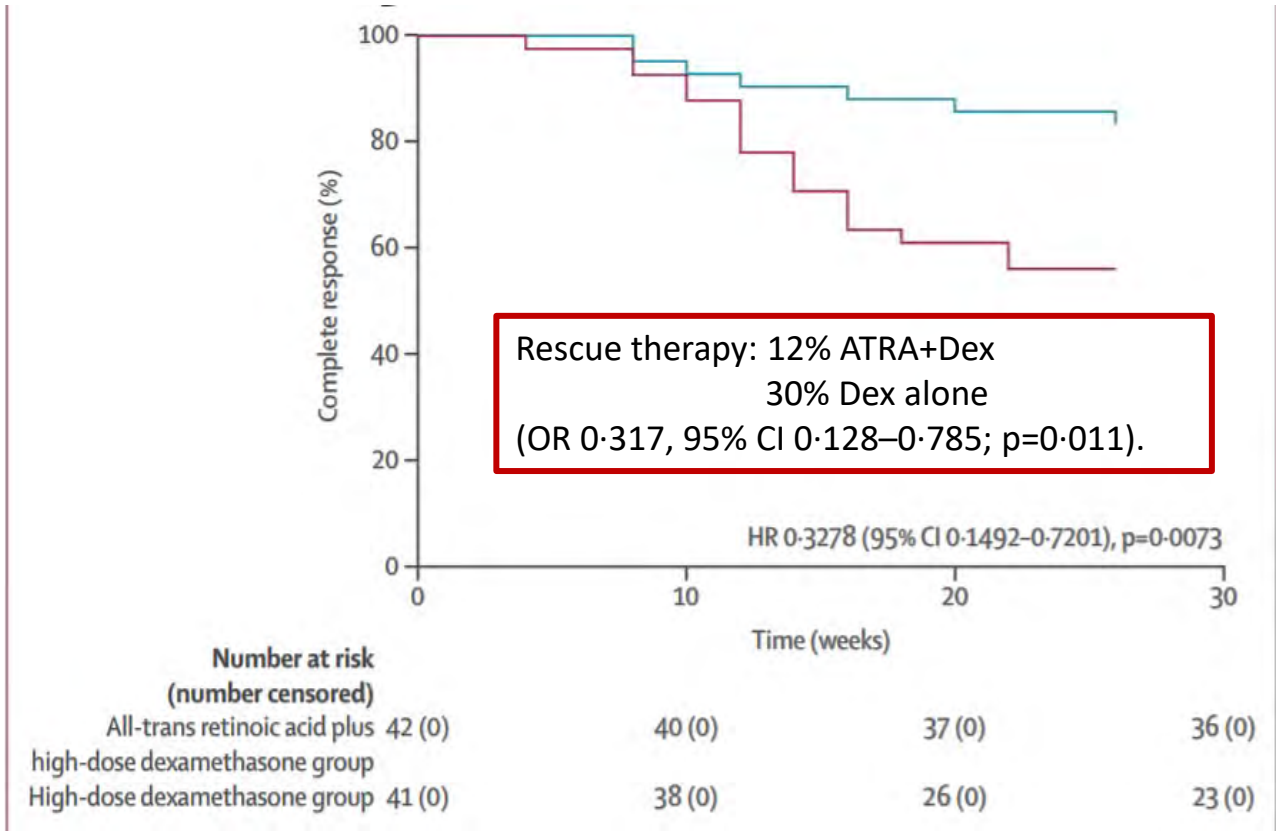
All-trans retinoic acid plus high-dose dexamethasone as first-line treatment for patients with newly diagnosed immune thrombocytopenia: a multicentre, open-label, randomized, controlled, phase 2 trial

Huang Q-S et al. Lancet Haematol 2021; 8: e688–99

Durable response in Partial Responders (≤50k platelets)



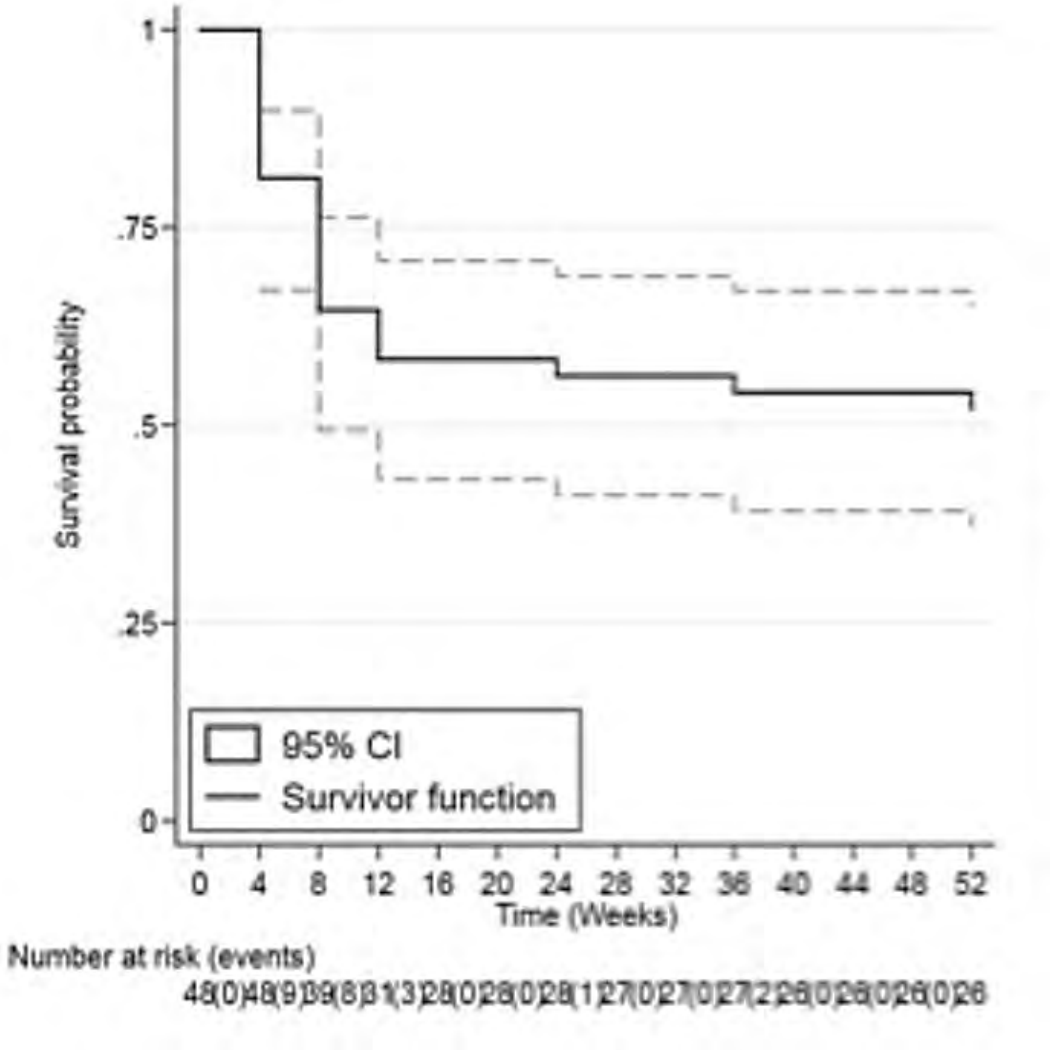
Durable response in Complete Responders (>50k platelets)



Rescue therapy: 12% ATRA+Dex
30% Dex alone
(OR 0·317, 95% CI 0·128–0·785; p=0·011).

40 mg/d IV dexamethasone X 4 d [repeat on d14 if no response] + 10 mg po all-trans retinoic acid bid X 12 wks

ASH 2021 Abstract 583: Rate of Prolonged Response after Stopping Thrombopoietin-Receptor Agonists Treatment in Primary Immune Thrombocytopenia (ITP): Results from a Nationwide Prospective Multicenter Interventional Study (STOPAGO) Mahevas M et al



- Persistent or chronic primary ITP with stable platelet count > 100k for more than 2 months on TPO-RAs
- Treatment with TPO-RA for at least 3 months

- Taper eltrombopag 25 mg q2 wks; 1 ug/kg romiplostim q1 wk; all TPO-RAs stopped at 10 wks

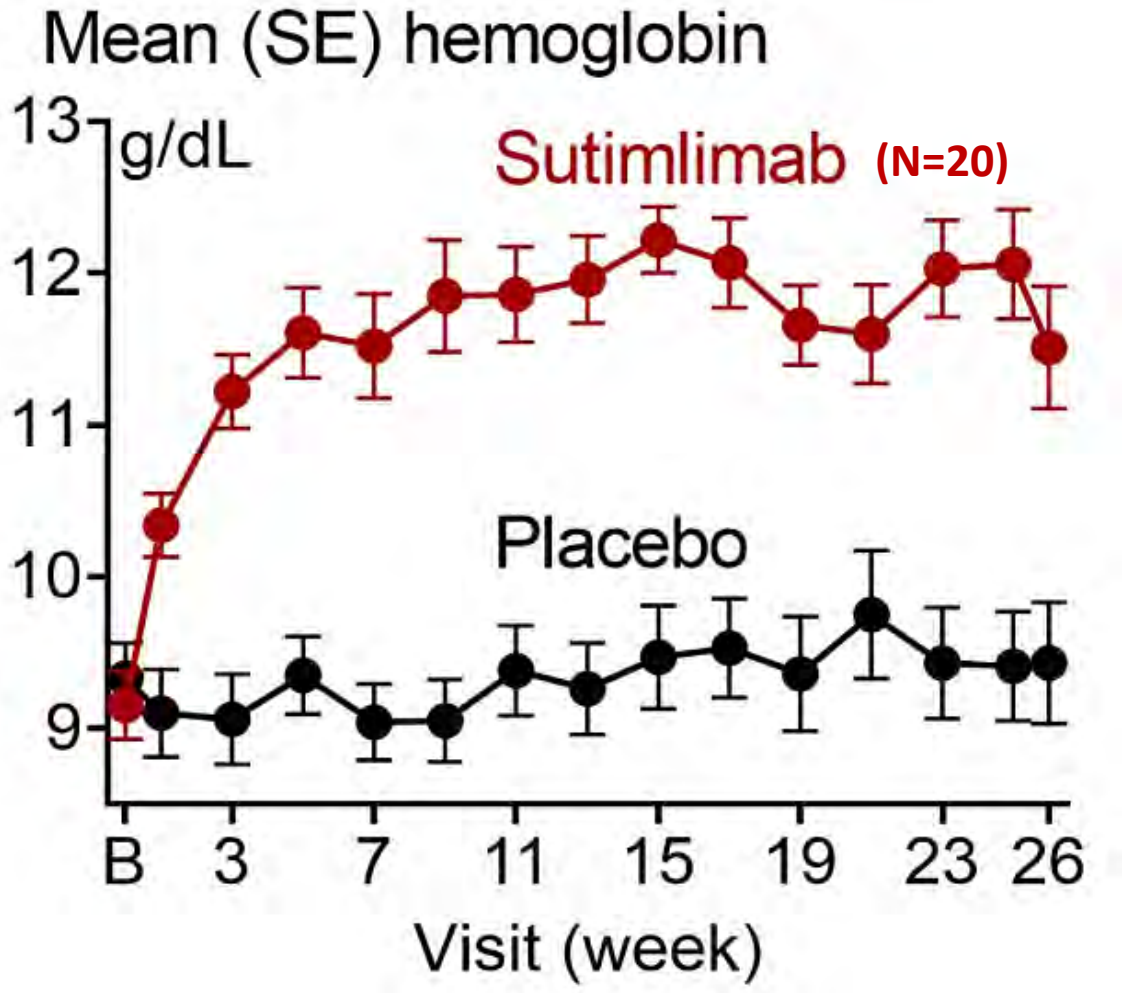
- **At week 24 post D/C TPO-RAs: CR = 55%**
- **At week 52 post D/C TPO-RAs: CR = 52.1%**

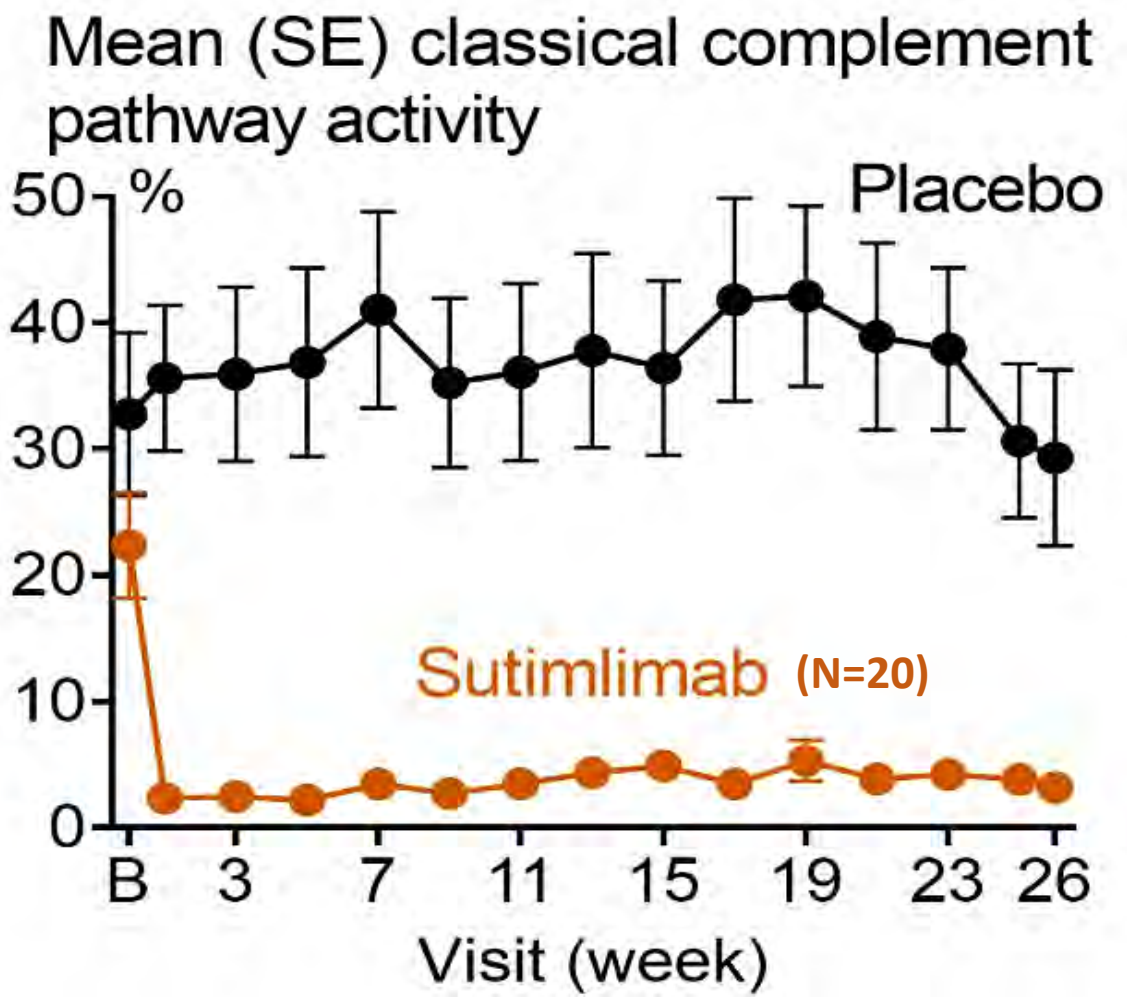
- **If relapse, median time post D/C TPO-RA = 8 wks**
- **Restart TPO-RA, CR reestablished = 2 wks**

- ITP duration, TPO-RA duration before D/C, platelet count at inclusion, TPO-RAs drug class were not predictive of sustained response

ASH 2021 Abs 349: Inhibition of Complement C1s By Sutimlimab in Patients with Cold Agglutinin Disease (CAD): Efficacy and Safety Results from the Randomized, Placebo-Controlled Phase 3 CADENZA Study

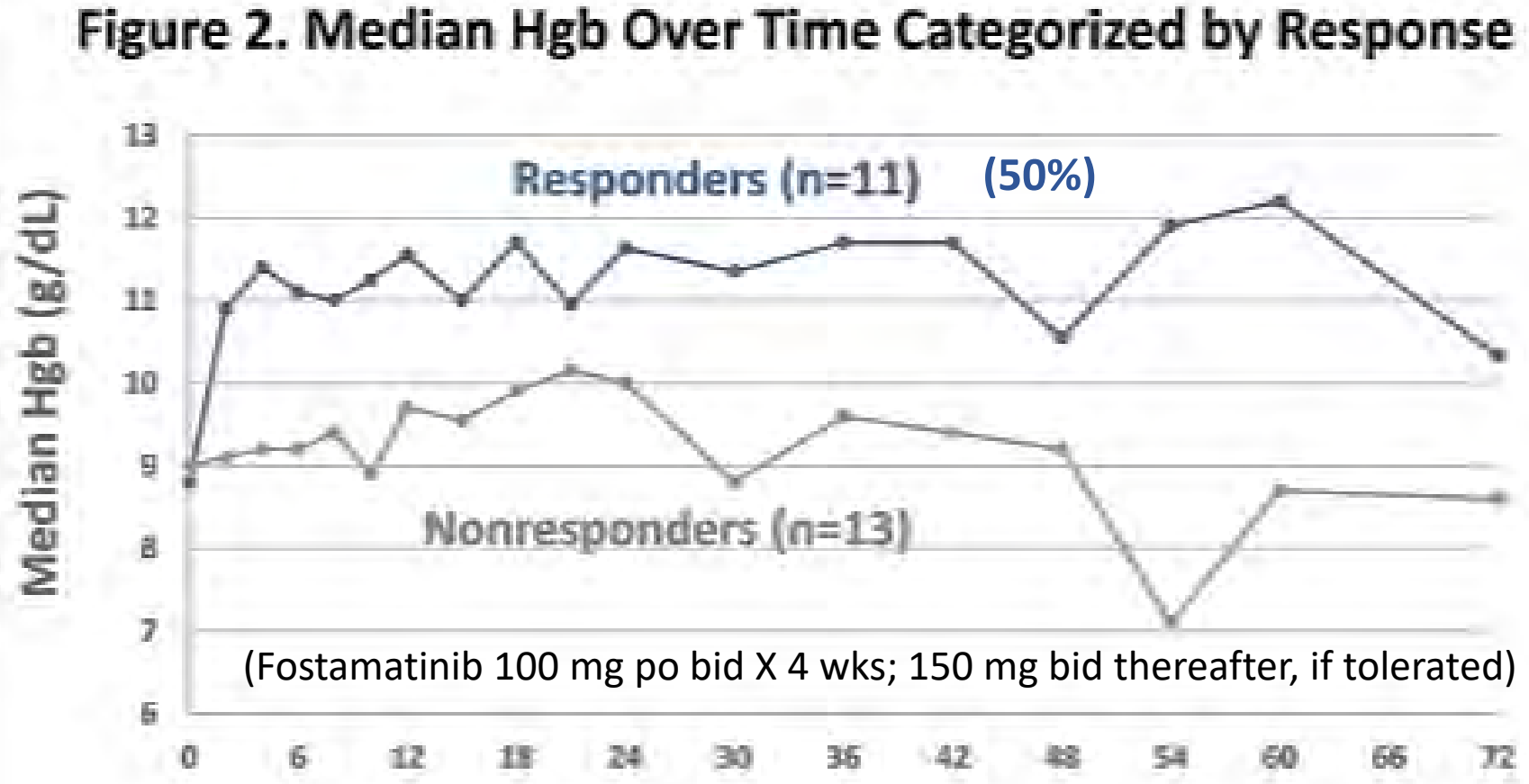
Roeth A et al.





ASH 2021 Abs 932: Update on the Phase 3 Clinical Trial of Fostamatinib for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Pietek C et al



2022 SSC 18.09 Thrombopoietin (TPO)-Mimetics and Thrombocytopenia in Cancer Soff G

(off label use)

TPO-RA in Solid Tumors: Current Status

- **Romiplostim. Shown to be effective in CIT, based on two phase 2 studies, one large romiplostim treatment pathway analysis and one extension study.**
  - **Romiplostim is effective to reverse persistent CIT, and maintenance is also effective to allow for long-term chemotherapy, with no adverse safety signal.**
  - **Can be given same day as chemotherapy.**
- Selection includes underlying thrombocytopenia, not chemotherapy naïve.
- Predictors of poor response: pelvic XRT, extensive bone metastasis, (+/- temozolomide)
- Underlying thrombocytopenia, relative preservation of ANC and Hgb.
- No signal of increased thrombosis, or other adverse safety issues.
- Soff et al, 2019, Le Rhun et al 2019, Al-Samkari et al 2021, Wilkins et al 2022.

NO INCREASED THROMBOTIC EVENTS OBSERVED IN CIT PATIENTS

TPO-RA in Solid Tumors: Current Status

- **Eltrombopag:**
  - Two phase 2 studies Eltrombopag were negative.
  - **Placebo patients did well without need for intervention.**
    - Kellum et al. Current Medical Research and Opinion, 26:2010
    - Winer et al, Int J Hematol (2017) 106:765–776
- **Avatrombopag**
  - Phase 3 trial. Placebo controlled.
  - **Key exclusion criteria included previous history of CIT.**
  - **Placebo patients did well without need for intervention.**
    - Al-Samkari et al Lancet Haematol 2022; 9: e179–89

Is the question of the efficacy of oral TPO-RA(s) in CA CIT resolved with 3 negative trials”

Placebo groups did better than expected

Multiple solid tumors/chemo regimens in relatively chemo naïve populations

Given 5 d pre and post chemo regimen

2022 SSC 18.09 Thrombopoietin (TPO)-Mimetics and Thrombocytopenia in Cancer Soff G

(off label use)

Hematologic Malignancies

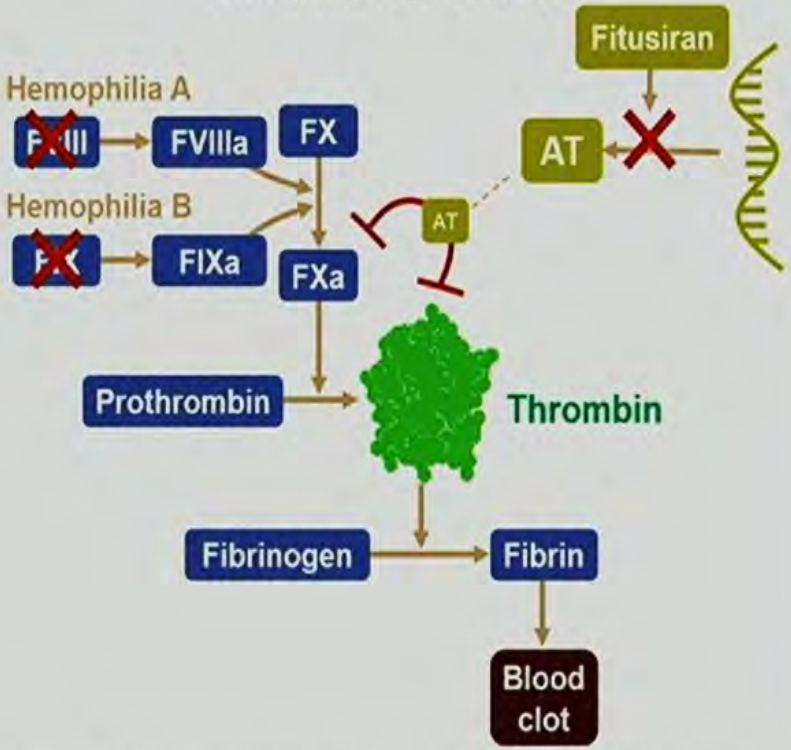
- **Acute Myeloid Leukemia:**
  - Eltrombopag failed to show improvement in platelet counts, and trend towards higher death on study.
    - Frey et al. Lancet Haematol 2018.
  - Separate study of mixed AML and high-risk MDS, treated with eltrombopag, also showed safety signal of death and arterial thrombosis, without providing significant platelet benefit.
    - Mittelman et al. Lancet Haematol 2018; 5: e34–43

- **Lymphoma/Stem Cell Transplant:**
  - Currently no controlled studies support efficacy. (a number of case series only).

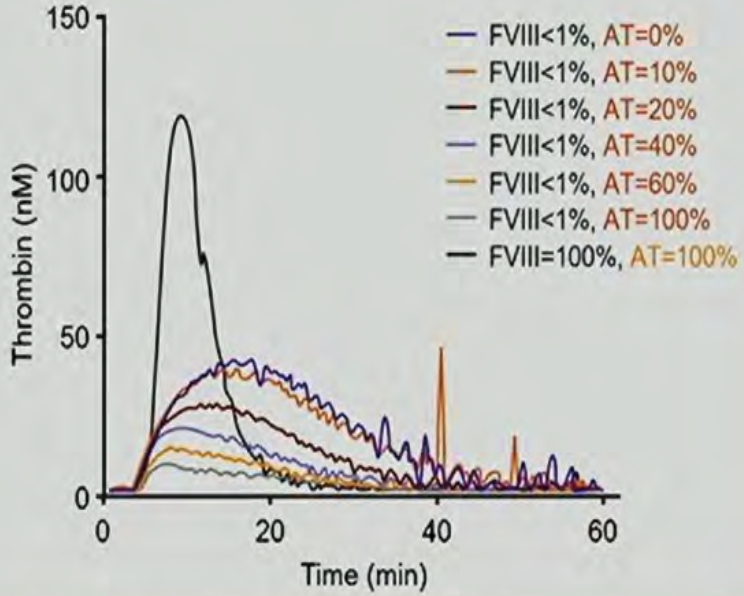
ASH 2021: Fitusiran, an Investigational siRNA Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: First Results from a Phase 3 Study to Evaluate Efficacy and Safety in People with Hemophilia a or B without Inhibitors (ATLAS-A/B) Paper Number: LBA-3; Alok Srivastava et al.

Thrombin Generation Matters

Site of action of fitusiran[1–3]

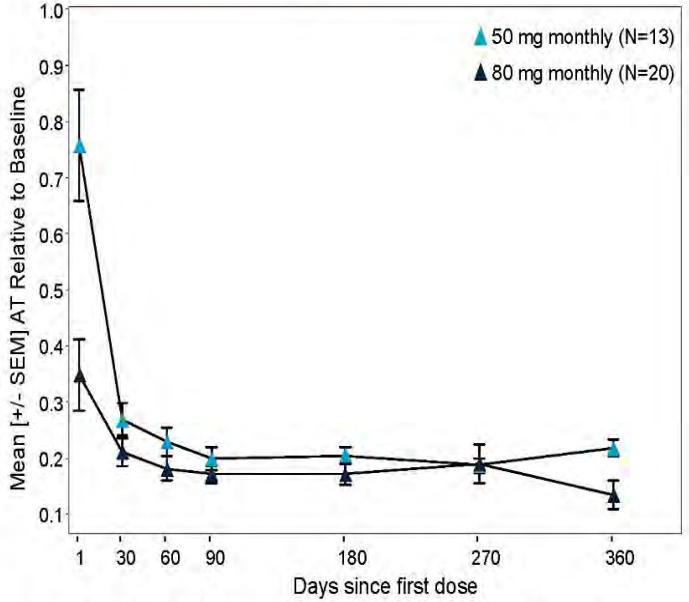


Ex vivo thrombin generation in human hemophilia A plasma depleted of AT[4]



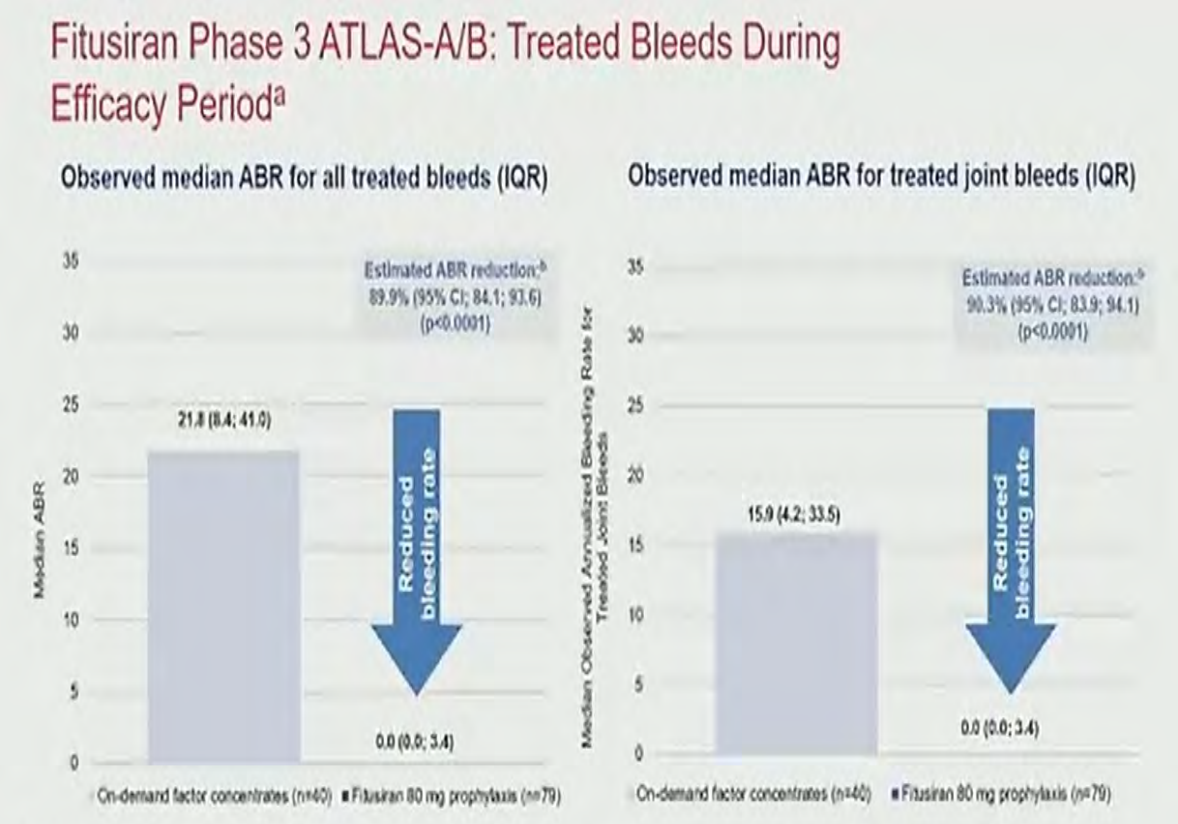
1. Pasi KJ, *et al. N Engl J Med.* 2017;377:819–828. 2. Machin N and Ragni M. *J Blood Med.* 2018;9:135–40. 3. Pasi KJ, *et al. J Thromb Haemost.* 2021;19(6):1436–46. 4. Sehgal A, et al. Nat Med 2015;21(5):492–7.
AT, antithrombin.

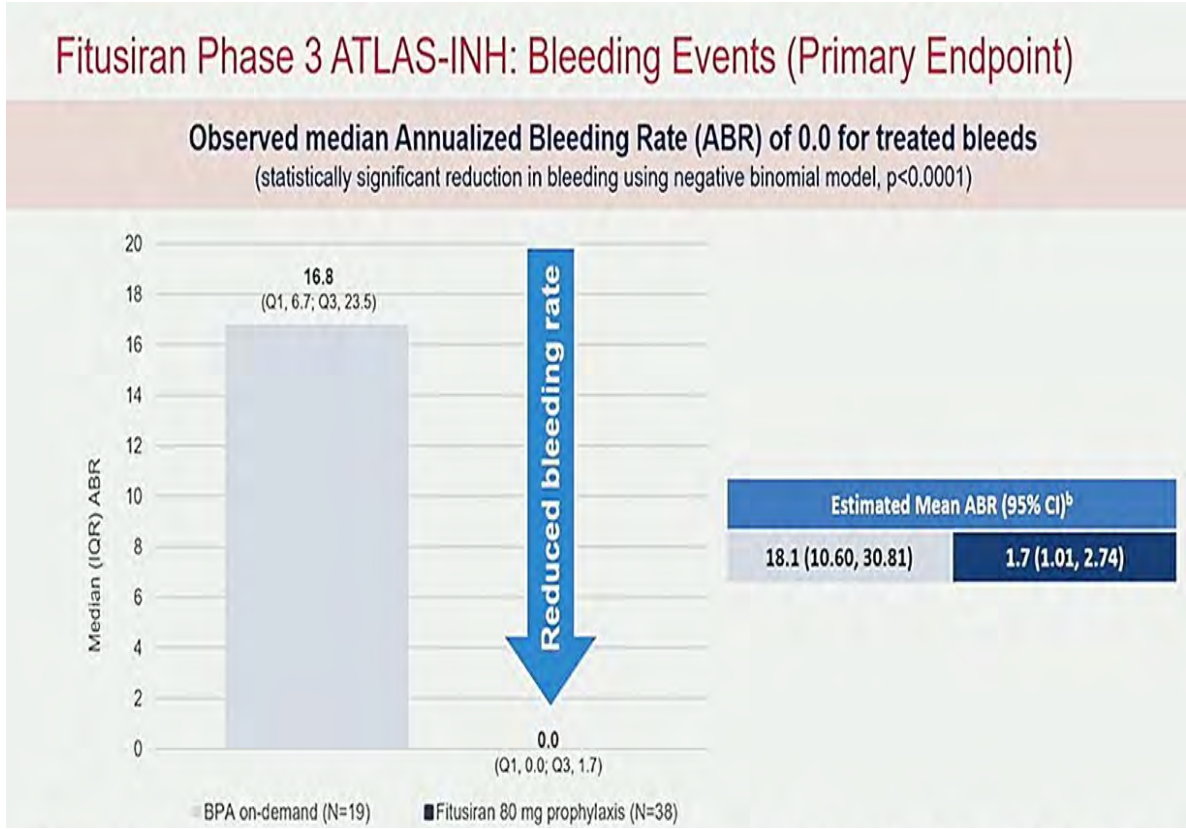
Antithrombin Levels



Days since first dose:	1	30	60	90	180	270	360
N†=13	13	13	13	13	10	10	6
N†=19	19	19	17	16	12	9	4

Small interfering mRNA (Fitusiran) rebalances hemostasis by ATIII inhibition

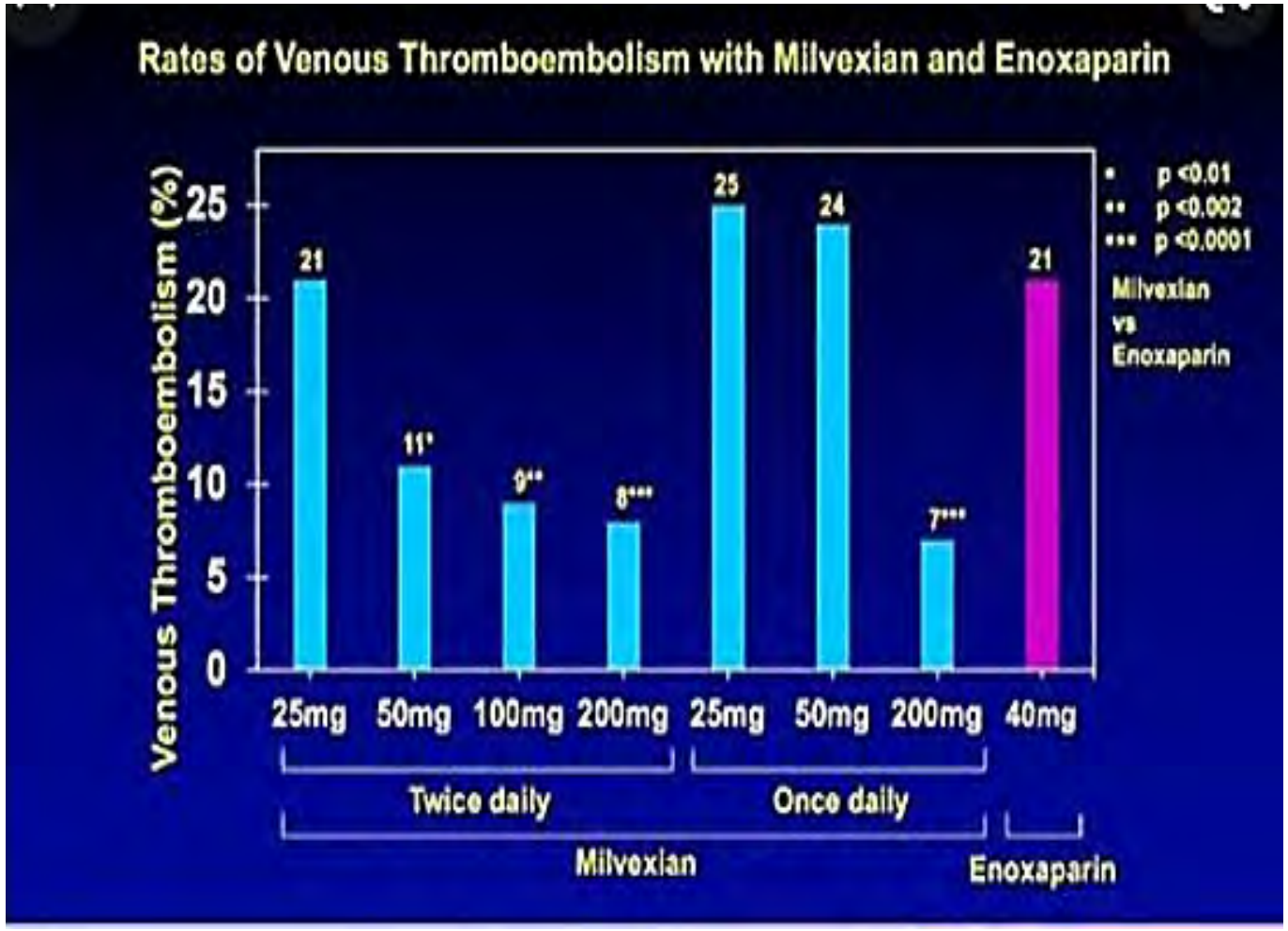




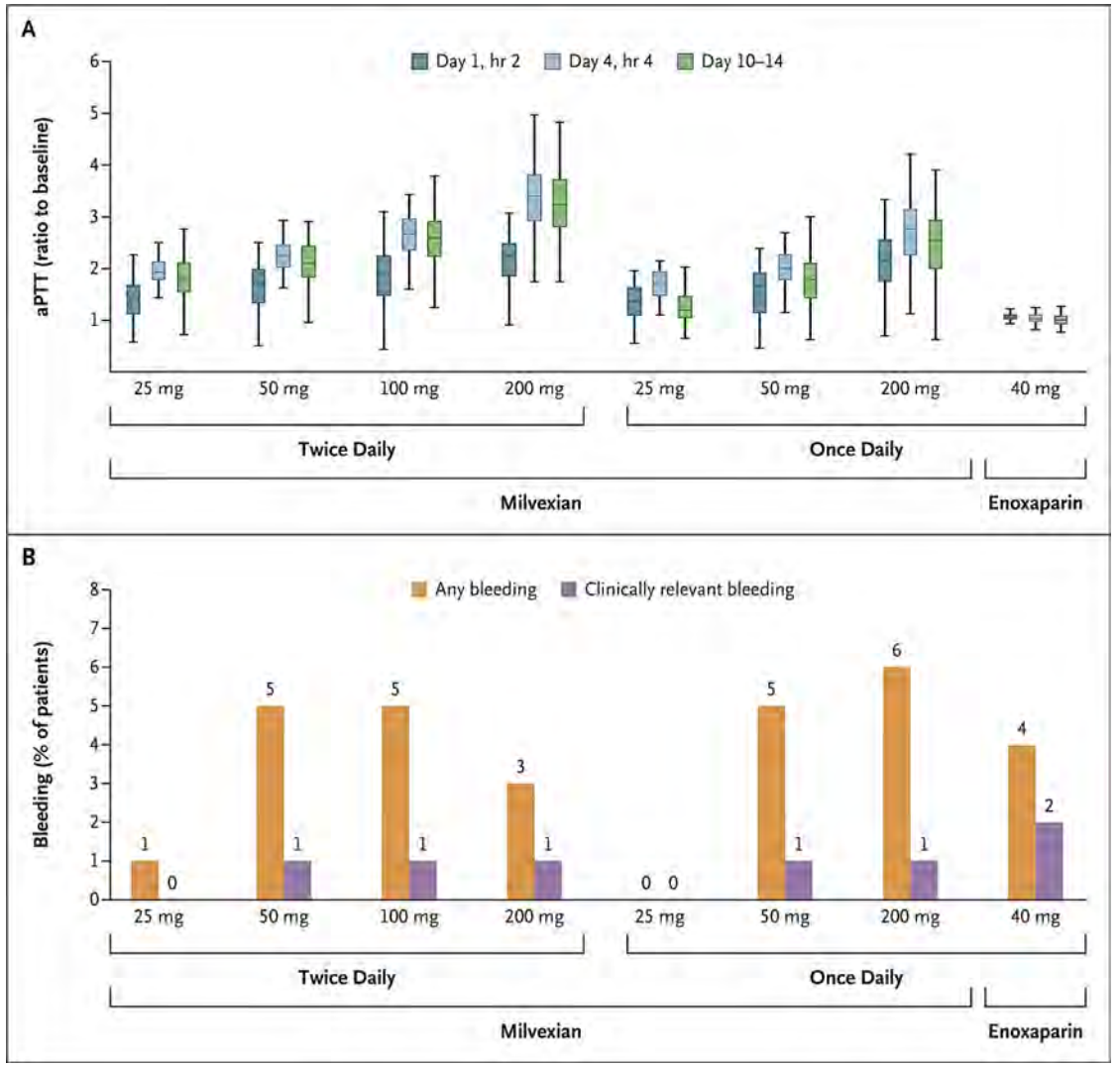
ASH 2021: LBA-3; Alok Srivastava et al.

Young G et al. plenary number 4
https://ash.confex.com/ash/2021/webprogram

Specific factor XIa inhibition by a small oral molecule prevents VTE in TKR with low bleeding incidence

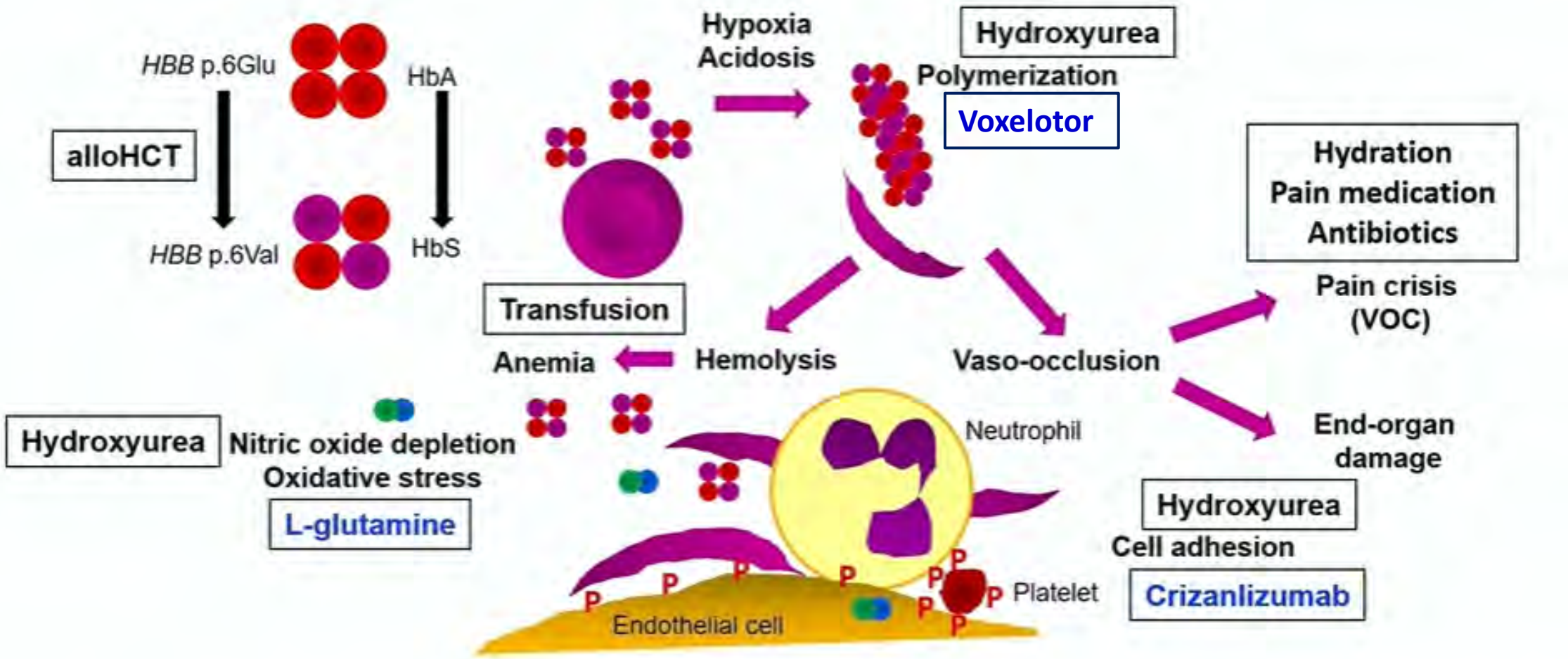


Weitz J. AHA 2021:Axiomatic-TKR



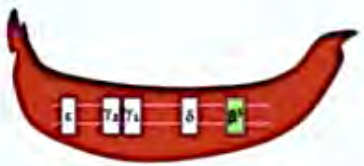
JI Weitz et al. N Engl J Med 2021;385:2161-2172

New Therapies for Sickle Cell Disease



Adapted from Costa FF & Fertrin KY in: "Sickle Cell Anemia: From Basic Science to Clinical Practice", Ch 12, Springer, 2016.

Gene therapy for SCD

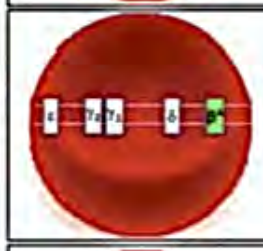


Gene Addition

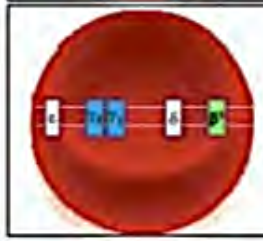
Gene Correction

HbF Induction

Addition of
- β-globin
- Anti-sickling β-globin (β^{T87Q}, $\beta^{A\Delta2}$, $\beta^{A\Delta3}$)
- γ-globin
- β/γ hybrids



Correction of A > T mutation by
- CRISPR-Cas9
- ZFNs
- TALENs



HbF induction through
- Using Chemical Inducers
- *BCL11A* Silencing
- *Erythroid-specific BCL11A* Enhancer Disruption
- *LRF/ZBTB7A* silencing
- *EHMT1/T2* inhibition
- Forced Chromatin Looping
- Generation of HPFH mutations

Limitations

- Low transduction efficiency
- Concern for insertional mutagenesis
- Question of immunogenocity
- Genotoxicity

- Low correction efficiency
- Off-target effects
- Low efficient delivery methods for nucleases
- Question of immunogenocity
- Genotoxicity
- Purity of edited cells

- Toxicity or variable outcomes for chemical inducers
- Robust HbF expression is needed
- Various phenotype in humans with heterozygous mutations for HbF regulator genes
- Knock-down/silencing of some regulator genes may lead to defective erythropoiesis
- Limited knowledge of physiological roles of regulator genes for immune cells

Demirci, Uchida & Tisdale. Cytotherapy. 2018 July ; 20(7): 899–910
Drysdale et al. Cell Stem Cell 2021; 28:191-208

Pros and cons of alloHCT vs. Gene therapy

- **AlloHCT – pros**
  - Data on longer follow up
  - Expanding donor pool: haplo
  - Can achieve 100% chimerism
- ***AlloHCT – cons***
  - GVHD
  - Immunosuppression
  - Long-term effects of radiation?

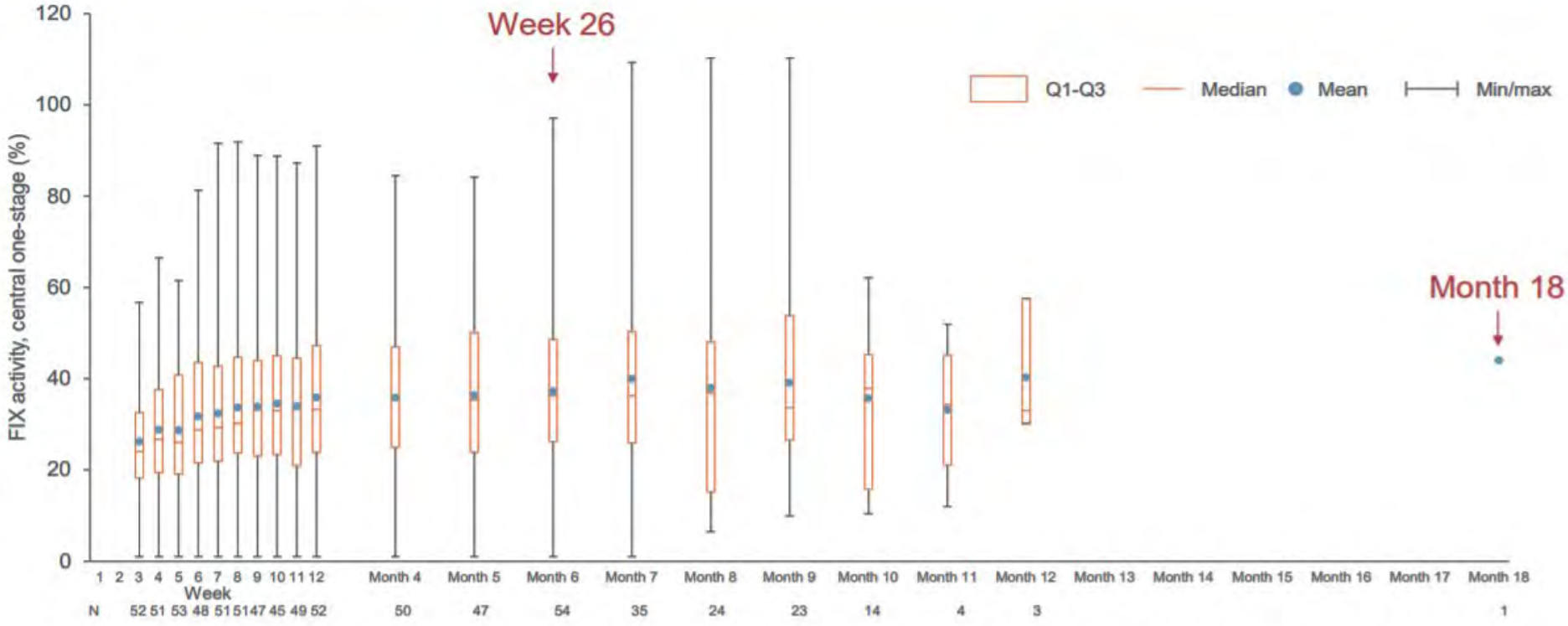
- **Gene therapy – pros**
  - No need for donor
  - Only needs 30% Hb replacement?
  - No GVHD
- ***Gene therapy – cons***
  - Cost
  - Off target effects, myeloid neoplasms?
  - Residual “mild” SCD?

Gene Therapies for the Hemophilias-AAV based Vectors- 2021

	Sponsor	Manufacturing Platform	Transgene	Capsid Serotype	Dose (vg/kg)	Phase
HB	UCL/St. Jude	Mammalian	scFIX	AAV8	$2x10^{11}$ to $2x10^{12}$	1/2
	Pfizer	Mammalian	ssFIX-R338L	SPK100	$5x10^{11}$	1/2, 3
	uniQure	Sl9 (insect)	ssFIX-R338L	AAV5	$2x10^{13}$	3
	Freeline	Mammalian	scFIX-R338L	AAVS3	$7.5x10^{11}$ $9.5x10^{11}$	1/2
HA	BioMarin	Sl9 (insect)	ssFVIII-SQ	AAV5	$6x10^{13}$	1/2, 3
	Sangamo/ Pfizer	Sl9 (insect)	ssFVIII-SQ	AAV6	$3x10^{13}$	1/2, 3 (on hold)
	Spark	Mammalian	ssFVIII-SQ	LK03	$5x10^{11}$ to $2x10^{12}$	1/2
	UCL/St. Jude	Mammalian	ssFVIII-V3	AAV8	$6x10^{11}$ to $6x10^{12}$	1/2
	Bayer/ Ultragenyx	Mammalian	ssFVIII-SQ	AAVhu37	$5x10^{12}$ to $2x10^{13}$	1/2

First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies

Overview of FIX activity[a]: Beyond 26 weeks



[a]Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject's historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%.
SD, standard deviation.

9

N=54 of whom 43 responded

Mean FIX at 26 wks near normal

No immuno-suppression needed

Neutralizing AAV5 Abs not excluded

Few bleeding events; no prophy FIX

Pipe SW, et al. ASH Annual Meeting 2020. Abstract LBA-6.

2022 OC 21.2 Hemostatic results for up to 6 years following treatment with valoctocogene roxaparvovec, an AAV5-hFVIII-SQ gene therapy for severe hemophilia A (ISTH 2022) Laffan M