New Developments with Thrombosis and Hemostasis: ASH 2022

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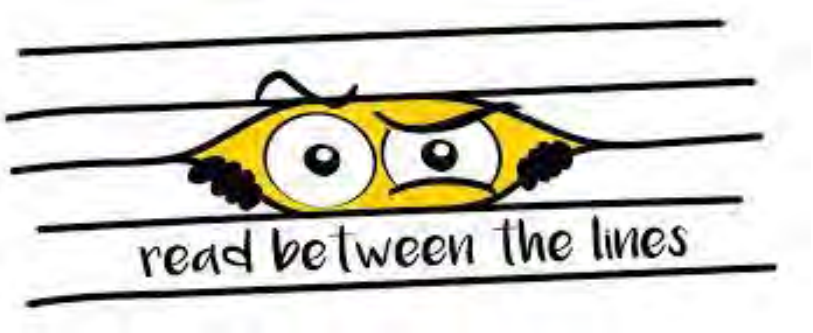
Disclosures

- Financial conflicts of interest (not relevant to today's presentation)
  - Pfizer – consultant, research funding multicenter SCD trial
  - Takeda – research funding multicenter SCD trial
  - Bausch/Salix – research funding multicenter SCD trial

- Off label discussion: None

New Developments with Thrombosis and Hemostasis at ASH 2022

- New <<< Developments: no big “reveals”
- Data which may impact/reinforce current practices and line of research
- A few interesting notes “reading between the lines”



Objectives

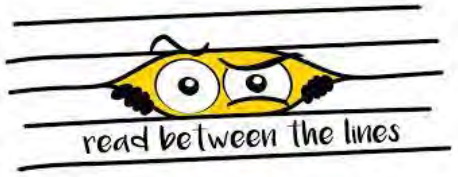
- Adapt anticoagulation use based on evolving data
  - LWMH in pregnancy
  - Patients with thrombocytopenia
  - COVID-19
  - Cancer thrombosis
- Describe the progress on next generation of novel anticoagulants which may come to clinical care
- Refine approach to von Willebrand disease
- Explain the contemporary data regarding gene therapy for hemophilia

LMWH vs. SOC for Recurrent Miscarriage

- Open-label randomized trial in women with 2 or more miscarriages and FVL, PGM, Prot C/S/AT (not APS)
  - 320 women enrolled, preconception up to 7 weeks
  - Standard of care vs. prophylactic doses of LMWH (e.g. enox 40 mg/dy, dalteparin 5000 U/day)
- No difference in subsequent live birth (71.6% vs. 70.9%)
  - No difference in birth weight
  - No difference in PIH, other pregnancy complications
- Significant increase in bleeding with LMWH (46% vs 23%)

Middeldorp, Low Molecular Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarrage and Inherited Thrombophilia (ALIFE2): An Open-Pable Phase III Randomized Controlled Trial, **LBA-5**

Reading Between the Lines…



- Study applies to women with positive thrombophilia testing but without a history of VTE
- No indication to test for thrombophilia in women with recurrent miscarriage: intervention with LMWH in these women did not change outcomes
- No reports of thrombosis during pregnancy, even in women not on LWMH

Middeldorp, Low Molecular Weight Heparin Versus Standard Pregnancy Care for Women with Recurrent Miscarrage and Inherited Thrombophilia (ALIFE2): An Open-Pable Phase III Randomized Controlled Trial, **LBA-5**

Anticoagulation and Thrombocytopenia

- 1075 a fib pts started on AC, 274 with plts <100K
  - 50% had plts < 75K
  - 46% on warfarin, 40% on apixaban; 75% on antiplt agents

	All patients (n=1075)	Thrombocytopenia (n=274)	Control (n=801)
Female	409 (38.0)	104 (38.0)	305 (38.1)
Age at diagnosis (median, range)	72 (26 - 95)	71 (36 - 95)	72 (26 - 95)
Concurent antiplatelet treatment	785 (73.0)	208 (75.9)	577 (72.0)
Comorbidities			
Cancer	157 (14.6)	63 (23.0)	94 (11.7)
Liver Disease	30 (2.8)	13 (4.7)	17 (2.1)
Kidney Disease	95 (8.8)	35 (12.8)	60 (7.5)
Anticoagulant agent			
Apixaban	425 (39.6)	108 (39.4)	317 (39.6)
Dabigatran	4 (0.4)	1 (0.4)	3 (0.4)
Rivaroxaban	127 (11.8)	34 (12.4)	93 (11.6)
Warfarin	519 (48.2)	131 (47.8)	388 (48.4)
CHA2DS2-VASc Score			
0-2	427 (39.7)	112 (40.9)	315 (39.3)
3-5	594 (55.3)	149 (54.4)	445 (55.6)
6-9	54 (5.0)	13 (4.7)	41 (5.1)

Iyengar, Bleeding Risk in Atrial Fibrillation and Thrombocytopenia: A Propensity Matched Cohort Study, **Abstract#141**

Anticoagulation and Thrombocytopenia

- Increased risk of bleeding in those with thrombocytopenia
  - Multivariate analysis: only risk factor - ↓plt count, RR 1.47
  - Antiplt therapy did not predict

	All patients (n=219)	Thrombocytopenia (n=74)	Control (n=145)
Bleeding Type			
Major	90 (41.1)	40 (54.1)	50 (34.5)
CRNMB	122 (55.7)	32 (43.2)	90 (62.1)
Minor	7 (3.2)	2 (2.7)	5 (3.4)
Location of Bleed			
Mucocutaneous	87 (39.7)	20 (27.0)	67 46.2)
Gastrointestinal	77 (35.2)	27 (36.5)	50 (34.5)
Intracranial	10 (4.6)	3 (4.1)	7 (4.8)
Pulmonary	10 (4.6)	3 (4.1)	7 (4.8)
Intramuscular	9 (4.1)	5 (6.8)	4 (2.8)
Retroperitoneal	4 (1.8)	2 (2.7)	2 (1.4)
Pericardial	3 (1.4)	2 (2.7)	1 (0.7)
Other	19 (8.7)	12 (16.2)	7 (4.8)

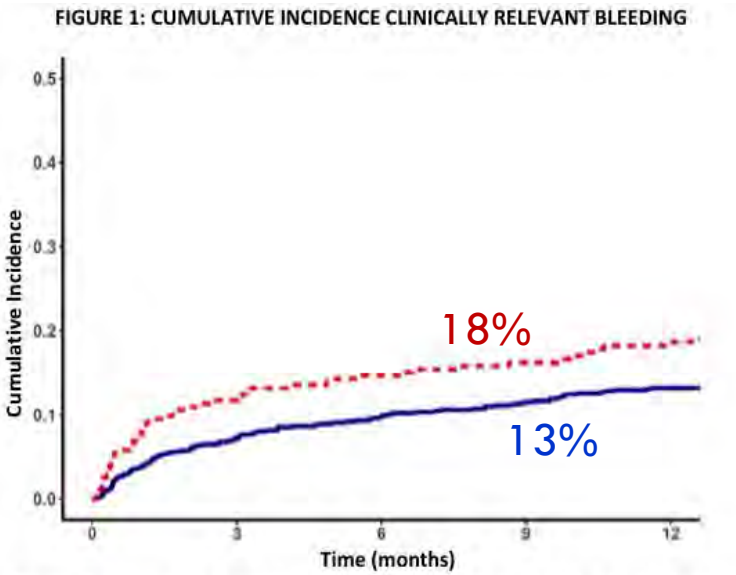
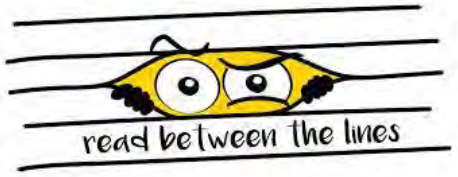


Figure 1: There was a significant difference in the cumulative incidence of clinically relevant bleeding between patients with thrombocytopenia (red line) and controls (blue line) (P < 0.001, Gray test)

- Add platelet count to risk scores?

Iyengar, Bleeding Risk in Atrial Fibrillation and Thrombocytopenia: A Propensity Matched Cohort Study, **Abstract#141**

Reading Between the Lines…



- 75% of people in this study were on antiplatelet agents in addition to their anticoagulation
- Higher bleeding was not associated with the use of these antiplatelet agents

- So why do we tell people who go on an anticoagulant that they can't take a dose of ibuprofen for a headache or intermittent NSAIDs for a bad knee?
  - The vast majority of people will do well
  - Effect of NSAIDs on platelets are short-acting and reverse once the drug is stopped (in contrast to ASA, clopidogrel, etc)

COVID-19 and Anticoagulation

- Guidelines/expert opinion for anticoagulation for COVID:
  - Hospitalized patients
    - Prophylactic anticoagulation in ICU
    - Therapeutic anticoagulation in non-ICU patients (even without thrombosis)
  - No prophylaxis recommended for outpatients
- Based on studies conducted in 2020/early-mid 2021:
  - "Wild type" and delta variant of SARS-CoV-2
  - Unvaccinated populations
- Scarce recent data regarding current situation
  - Omicron: Lower risk of severe illness, thrombosis, and death
  - Higher rates of vaccination, impact of specific therapies

Beverly Hunt, COVID-19 and Thrombosis, **Presidential Symposium**

COVID & Anticoagulation

- Australasian COVID-19 Trial (ASCOT): pragmatic randomized open-label trial, recruited February 2021 – April 2022
  - 1526 hospitalized non-ICU COVID-19 patients, 31% vaccinated
    - 619 to prophylactic (low-dose) LMWH
    - 620 to intermediate-dose LMWH
    - 285 to prophylactic dose LMWH + low-dose aspirin
    - 50 to therapeutic LMWH
  - No difference at D28 for death or need for organ support:

LD LMWH	ID LMWH	LD LWMH + ASA	Therapeutic AC
5.9%	4.2%	7.2%	14%

  - Thrombosis rate 0.8%, bleeding rate 0.4%

McQuilten, Anticoagulation and Antiplatelet Strategies in Non-Critically Ill Patients with COVID-19, **Abstract #133**

COVID-19 and Thrombosis

- Vaccine-Induced Thrombocytopenia and Thrombosis (VITT)
  - Very rare: 1 in 100,000 after adenoviral-based COVID vaccines
  - Even rarer cases possibly associated with mRNA vaccines
  - Atypical sites: 50% CVT, 30% splanchnic vein
  - Antibody to platelet-factor 4 (in absence of heparin)
  - No obvious predisposing factors
  - Single oral abstract notes evidence of endothelial cell activation
- Long-haul COVID and "micro-clots" – "amyloid fibrin"
  - Only described in a single lab – hasn't been reproduced

    Kell, *Biochem J,* 2022, 479:537
  - Found by this lab in other conditions (DM, rheumatoid arthritis) but not associated with symptoms similar to long-haul COVID

Cancer-Associated Thrombosis: ASH Guidelines 2021

CLINICAL GUIDELINES

blood advances

Check for updates

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

Gary H. Lyman,[1,2,*] Marc Carrier,[3,*] Cihan Ay,[4] Marcello Di Nisio,[5] Lisa K. Hicks,[6] Alok A. Khorana,[7] Andrew D. Leavitt,[8,9] Agnes Y. Y. Lee,[10,11] Fergus Macbeth,[12] Rebecca L. Morgan,[13] Simon Noble,[14] Elizabeth A. Sexton,[15] David Stenehjem,[16] Wojtek Wiercioch,[13] Lara A. Kahale,[17,†] and Pablo Alonso-Coello[18,†]

https://ashpublications.org/bloodadvances/article/5/4/927/475194

ASH Guidelines on VTE: Prevention and Treatment in Patients with Cancer, **ASH Special Interest Session**

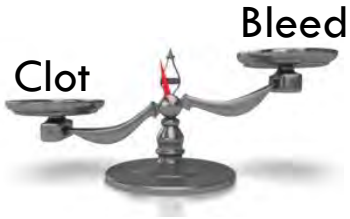
Assessing Risk of Venous Thrombosis in Ambulatory Cancer Patients

Khorana Score

Patient Characteristic	Risk Score
Site of Primary Cancer	
➢ Very High Risk (stomach, pancreas)+brain, per ASCO	2
➢ High Risk (lung, lymphoma, gynecologic, bladder, testicular)	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

Risk category	Score	Risk of symptomatic VTE
High risk	≥3	7.1–17.7%
Intermediate risk	=1–2	1.8–4.8%
Low risk	=0	0.8–1.5%

NNT = 25



NNH = 1000

ASH Guidelines on VTE: Prevention and Treatment in Patients with Cancer, **ASH Special Interest Session**

Recommendations for Prophylaxis Ambulatory Cancer Patients

- In **ambulatory patients with cancer at high risk of thrombosis** receiving systemic therapy, the ASH guideline panel suggests thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis *(conditional recommendation based on moderate certainty in the evidence about effects)*.

Outcomes (Quality of Evidence)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no thromboprophylaxis	Risk difference with DOAC thromboprophylaxis
● Mortality	**RR 0.94** (0.64 to 1.38)	185 per 1,000	**11 fewer deaths per 1,000** (67 fewer to 70 more)
● PE	**RR 0.24** (0.12 to 0.47)	60 per 1,000	**46 fewer PEs per 1,000** (53 fewer to 32 fewer)
● Symptomatic DVT	**RR 0.61** (0.31 to 1.21)	95 per 1,000	**37 fewer DVTs per 1,000** (66 fewer to 20 more)
● Major bleeding	**RR 1.65** (0.72 to 3.80)	14 per 1,000	**9 more bleeds per 1,000** (4 fewer to 40 more)

Quality of Evidence (GRADE): Low ● Moderate ● High ●

Implementation of Recommendations

- Prophylaxis reduces VTE without significantly increasing bleeds
  - VTE rates increasing: 1%/yr in 1997 to 3.4%/yr in 2017
  - Increased mortality in cancer patients with VTE
  - Increased bleeding risk with therapeutic anticoagulation in cancer pts compared to non-cancer patients
- Implementation efforts in Baylor system (safety net hospital) and MD Anderson in Houston, TX
  - Incorporating risk score into EMR, harder to include bleeding risk
  - Commentary of speakers and audience
    - Challenging to integrate into work flow
    - "Patients already overwhelmed" with other concerns
    - Provider uncertainty about benefit, concern about bleeding

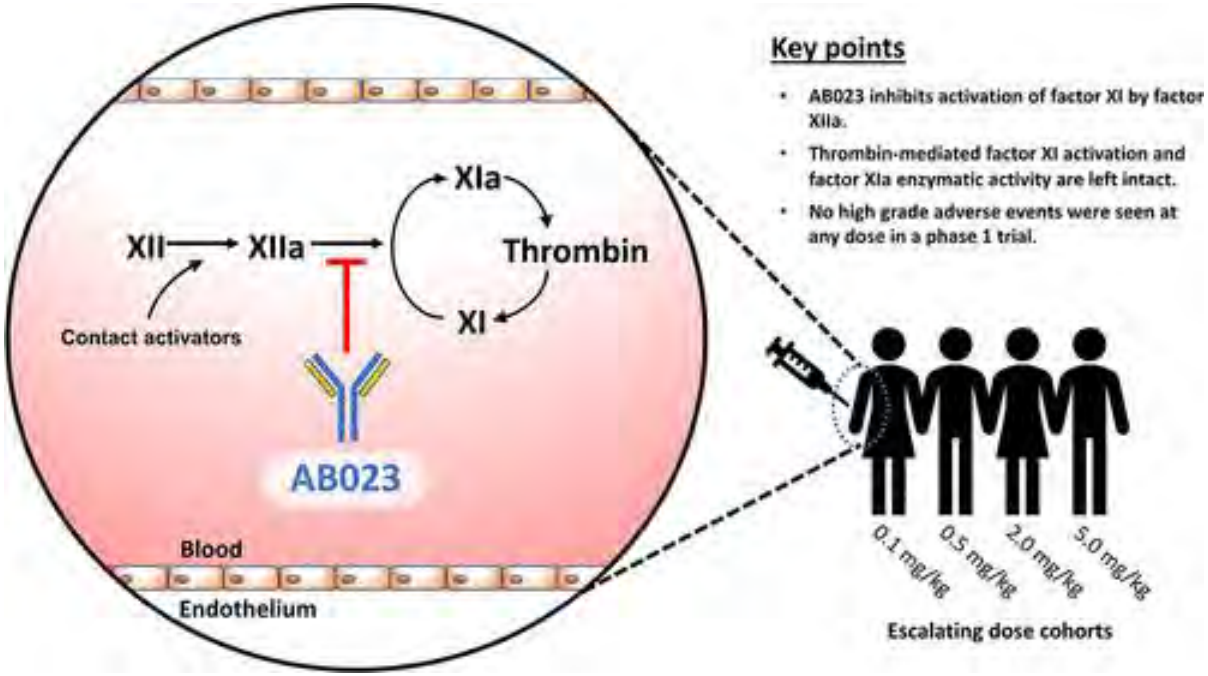
DOAC for Catheter Thrombosis in Cancer

- CATHETER 3 study of apixaban
  - 70 cancer pts with catheter-related UE DVT, CrCl >30 ml/min
    - Not AML or MM
    - Plts >75K, no dual antiplatelet therapy
    - Treated with 7 days of dalteparin, then apixaban 5 mg bid
  - No removal of catheter for thrombosis, all remained functional
  - 1 recurrent DVT at 10 days, switched to LMWH
  - 8.6% with bleeding (2 major, 4 clinically relevant) in first 2 mo
- Author stated he now defers the initial course of LMWH, uses only the DOAC (apixabn)

Kovacs, A Prospective Study of Apixaban for Central Venous Catheter Associated Upper Extremity Deep Vein Thrombosis in Cancer Patients: Catheter 3, **Abstract #517**

Prevention of Catheter Thrombosis

- AB023 – monoclonal antibody that inhibits activation of Factor XI and contact activation pathway



Pfeffer, Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Cancer Patients Undergoing Central Line Placement: A Phase 2 Clinical Trial, **Abstract #518**

Prevention of Catheter Thrombosis

- Phase 2 study of single iv dose of AB023 (Ab inhibition of activation of FXI) within 24 hr of catheter placement in 22 cancer patients
  - Khorana score ≤2
  - Port - 20, PICC – 1
  - Endpoint: US on D14
  - Placebo n=11

    AB023 n=11

Table 1. Demographic and clinical characteristics

	Total	Intervention Group	Control Group
Patients	22	11	11
Sex			
Male	14	6	8
Female	8	5	3
Age, median (IQR)	60.5 (51.25 - 68.25)	56 (50.5 - 67.5)	64 (53 - 67.5)
Weight (kg), mean (SD)	92.25 (23.5)	98.03 (19.45)	86.48 (26.65)
Cancer-directed therapy in the 30 days preceding enrollment (n)	3	1	2
Tumor type			
Lung	2	1	1
Pancreatic	5	4	1
Colorectal	5	3	2
Lymphoma	6	2	4
Sarcoma	2	1	1
Head and Neck	2	0	2
Cancer stage			
I	2	2	0
II	2	1	1
III	9	5	4
IV	9	3	6

Pfeffer, Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Cancer Patients Undergoing Central Line Placement: A Phase 2 Clinical Trial, **Abstract #518**

Prevention of Catheter Thrombosis

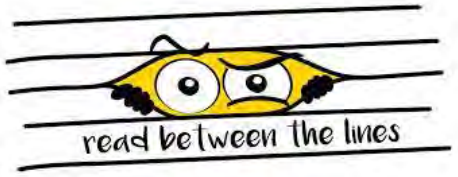
- F/U ultrasound D14: 13% with thrombus (vs. 40% in placebo)

	Total	Intervention Group	Control Group
Central Access Outcomes *			
Catheter thrombus at the time of ultrasound (%) ‡	5(27)	1(13)	4(40)
Mean aPTT at time of ultrasound (sec)		50.76	28.73
Catheter occlusion requiring TPA within study window (#)	0	0	0
Post-ultrasound events			
Catheter thrombus outside of observation period	1	1	0
Use of TPA outside study window	4	4	0
Systemic thrombus	2	1	1

At/after D70

Pfeffer, Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Cancer Patients Undergoing Central Line Placement: A Phase 2 Clinical Trial, **Abstract #518**

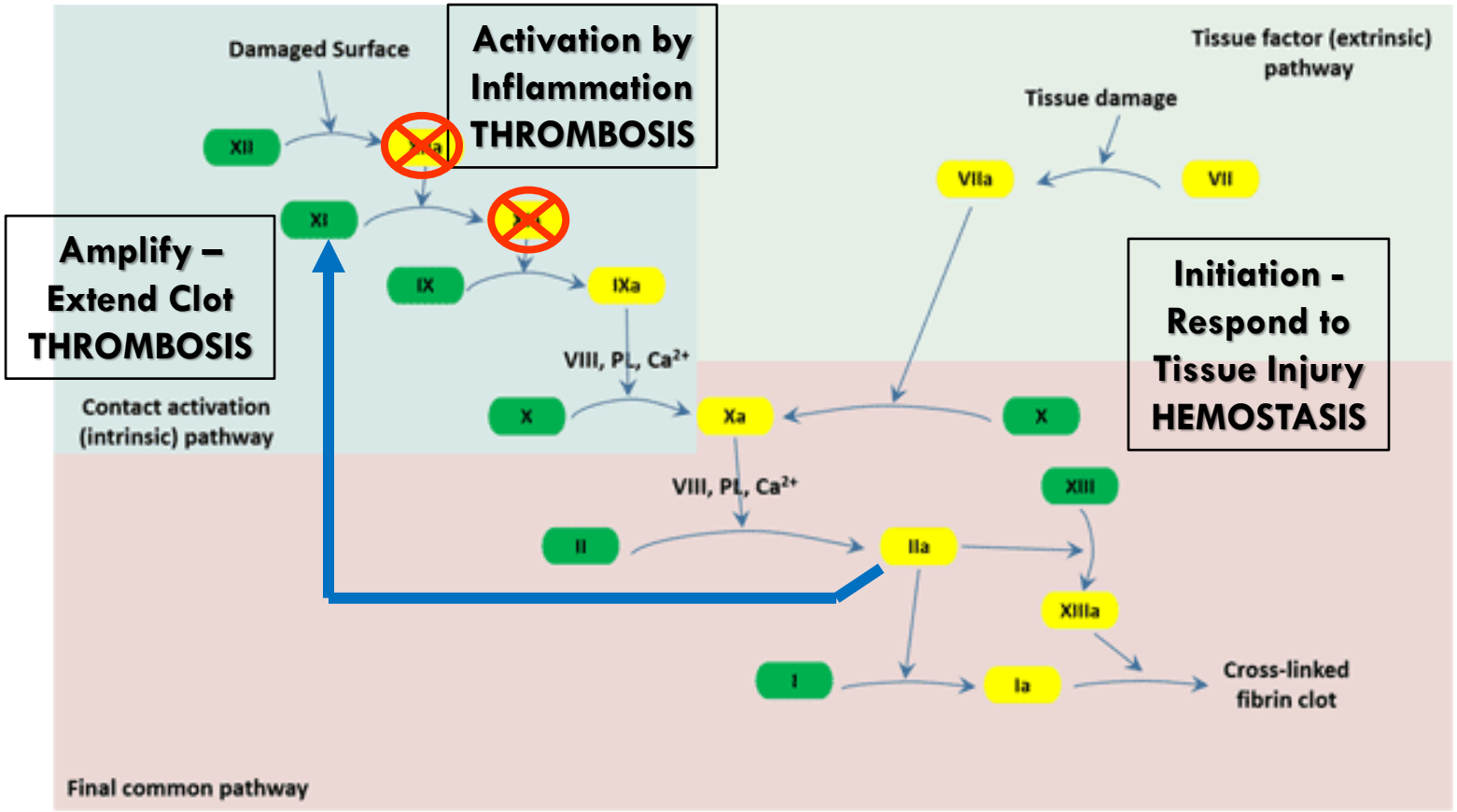
Reading Between the Lines…



- Rate of subclinical thrombus seen by ultrasound was 40% at two weeks without prophylaxis
- This novel agent will need to be redosed
- Average aPTT was still 50 seconds at two weeks
  - Bleeding wasn't worse
  - But what if you needed to interrupt this anticoagulation for a procedure or bleed?

Pfeffer, Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Cancer Patients Undergoing Central Line Placement: A Phase 2 Clinical Trial, **Abstract #518**

Update on Contact Activation Inhibitors



New Therapeutic Targets for Thrombosis That Do Not Cause Bleeding, **Scientific Session**
Ageno, "Coming Soon to a Pharmacy Near You? FXIa Inhibitors and Other Novel Strategies to Prevent or Treat Venous Thromboembolism", **Thrombosis Prevention and Treatment Educational Session**

Update on Factor XI Inhibitors

- Meta-analysis of FXI inhibitors in total knee arthroplasty

Clinical VTE

Study	Drug	FXI-Inhibitor Events	FXI-Inhibitor Total	LMWH Events	LMWH Total	Risk Ratio random (95% CI)	Weight	Risk Ratio random (95% CI)
FXI-ASO TKA	IONIS-FXI-Rx	39	205	21	69		22.0%	0.63 (0.40 to 0.99)
FOXTROT	Osocimab	85	441	20	76		24.4%	0.73 (0.48 to 1.12)
ANT-005 TKA	Abelacimab	22	299	22	101		16.9%	0.34 (0.20 to 0.58)
AXIOMATIC-TKR	Milvexian	108	796	54	252		36.8%	0.63 (0.47 to 0.85)
TOTAL (95% CI)		**254**	**1741**	**117**	**498**		**100.0%**	**0.59 (0.37 to 0.94)**

Test for heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 5.27$, df = 3, $p = 0.15$; $I^2 = 35\%$

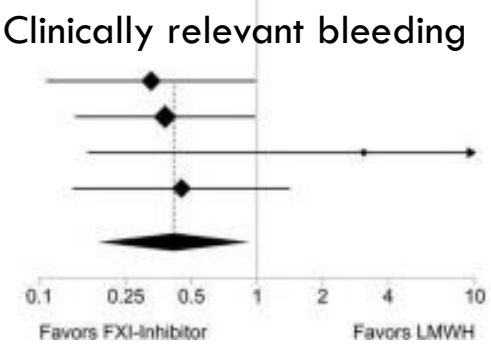
Test for overall effect: Z = -3.56, $p = 0.038$

Clinically relevant bleeding

FXI-ASO TKA	IONIS-FXI-Rx	6	221	6	72		29.2%	0.33 (0.11 to 0.98)
FOXTROT	Osocimab	13	585	6	102		39.6%	0.38 (0.15 to 0.97)
ANT-005 TKA	Abelacimab	4	305	0	104		4.2%	3.09 (0.17 to 56.88)
AXIOMATIC-TKR	Milvexian	7	923	5	296		27.1%	0.45 (0.14 to 1.40)
TOTAL (95% CI)		**30**	**2034**	**17**	**574**		**100.0%**	**0.41 (0.19 to 0.92)**

Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.07$, df = 3, $p = 0.56$; $I^2 = 0\%$

Test for overall effect: Z = -3.51, $p = 0.039$



- Decreased risk of VTE and bleeding, even in studies where treatment is given preoperatively

Nopp, *Front Cardiovasc Med* 2022;9:903029

Update on Factor XI/XII Inhibitors

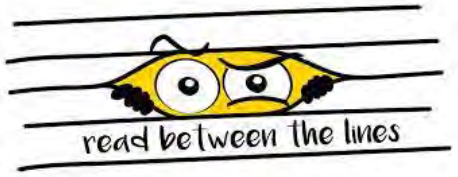
TABLE 1 | Overview of factor XI inhibitors in clinical trials.

Drug	Type	Mechanism	Administration route	Studies (NCT)	Population (N)	Comparator	Status
IONIS-FXI$_{Rx}$	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT01713361 NCT02553889 NCT03358030	TKA (300) ESKD (49) ESKD (200)	Enoxaparin Placebo Placebo	Published Published Completed
Osocimab	Monoclonal antibody to FXIa	Binds and inhibits FXIa	Intravenous, subcutaneous (monthly)	NCT03276143 NCT04523220	TKA (813) ESKD (686)	Enoxaparin/Apixaban Placebo	Published Ongoing
Abelacimab	Monoclonal antibody to FXI/FXIa	Binds and inhibits FXI and FXIa	Subcutaneous (monthly)	EudraCT 2019-003756-37 NCT04755283 NCT05171049 NCT05171075	TKA (412) AF (1,200) CAT (1,655) CAT (1,020)	Enoxaparin Rivaroxaban Apixaban Dalteparin	Published Ongoing Ongoing Ongoing
Milvexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT03891524 NCT03766581	TKA (1,242) Stroke (2,366)	Enoxaparin Placebo	Published Ongoing
Xisomab 3G3	Monoclonal antibody to FXI	Binds FXI and blocks activation by FXIIa	Intravenous (single dose)	NCT03612856 NCT04465760	ESKD (24) CRT (50)	Placebo None	Published Ongoing
Fesomersen	Antisense oligonucleotide of FXI	Inhibits FXI messenger RNA	Subcutaneous (weekly)	NCT04534114	ESKD (305)	Placebo	Ongoing
Asundexian	Small molecule inhibitor of FXIa	Binds and inhibits FXIa	Oral (daily)	NCT04218266 NCT04304534 NCT04304508	AF (753) AMI (1,592) Stroke (1,790)	Apixaban Placebo Placebo	Published Completed Ongoing

AF, atrial fibrillation; CAT, cancer-associated thrombosis; CRT, catheter-related thrombosis in cancer patients; ESKD, end-stage kidney disease; TKA, total knee arthroplasty.

Nopp, *Front Cardiovasc Med* 2022;9:903029

Reading Between the Lines…



- Long half-life and ability to dose weekly or monthly is very convenient
- However, much of the data to date is in prophylaxis (ortho surgery, ESRD/dialysis access) with relatively low doses
- More bleeding with higher doses in Phase I/II studies
- Little or no discussion about how to reverse this form of anticoagulation

Diagnosis of type 1 von Willebrand Disease

- Focus on phenotype, not testing
- Emphasis on the ISTH BAT
  - Each item has scale of 0-4 based on severity
  - Total of 56 possible points but
    - ≥6 abnormal for adult female
    - ≥4 abnormal for adult male
    - ≥3 abnormal for children
  - Abnormal result prompts
    - Testing
    - Lends credence to interpretation of results…

Item number	ISTH-BAT
1	Epistaxis
2	Cutaneous bleeding
3	Bleeding from minor wounds
4	Oral cavity bleeding
5	Bleeding after tooth/teeth extraction
6	Gastrointestinal bleeding
7	Bleeding after surgery or major trauma
8	Menorrhagia
9	Postpartum haemorrhage
10	Muscle haematomas (spontaneous)
11	Haemarthrosis
12	CNS bleeding (spontaneous)
13	Haematuria
14	Other bleeding ► Excessive umbilical stump bleeding. ► Cephalohaematoma. ► Bleeding at circumcision. ► Venipuncture bleeding. ► Suction bleeding. ► Ovulation bleeding (woman).

Sidonio, Diagnostic pitfalls and conundrums in type 1 von Willebrand disease, **Educational Session**

Diagnosis of Type 1 von Willebrand Disease

- Emphasized 2021 ASH/ISTH/NHF/WFH guidelines: ISTH BAT
  - If you're a PCP, don't test if the BAT score in normal
  - If you're a hematologist, it's assumed referral was for a bleeding hx or abnormal coag labs, so test but use BAT to judge severity
  - If first degree relative has vWD, test but use BAT to judge severity
- Challenges with borderline values (e.g. vWF Act 30-50%)
  - May be of uncertain clinical significance with normal ISTH BAT
  - Levels may be misleading (masking deficiency) with:
    - Estrogen exposure
    - Iron deficiency (up to 27% of women have low levels once iron-replete)
    - Levels increase toward normal with aging, even in vWD disease patients (30-60% of pts) – but does not reduce bleeding

Sidonio, Diagnostic pitfalls and conundrums in type 1 von Willebrand disease, **Educational Session**

von Willebrand Disease & Heavy Menstrual Bleeding

- Guidelines recommend treatment but don't specify what
- Cross-over study of 36 women with vWD, HMB
  - 2 cycles with each treatment:
    - Tranexamic acid 1300 mg po tid x first 5 days
    - rVWF 40 IU/kg on first day
  - Outcome: pictoral blood loss assessment

    (score >100 = > 80 ml blood loss)
  - Results
    - Significant reduction in PBAC
    - Less frequent "flooding" (44.4% vs. 59.7%)
- Tranexamic acid better, easier, cheaper

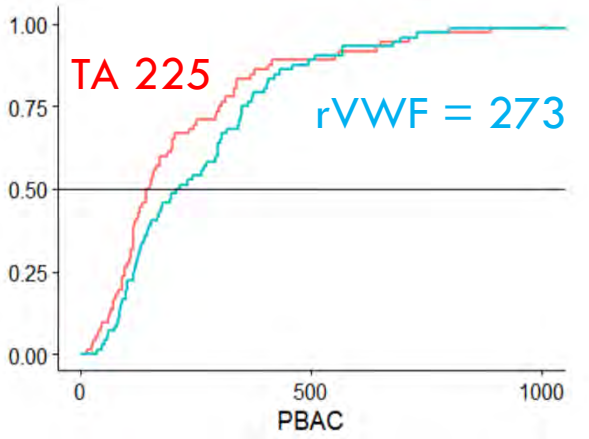
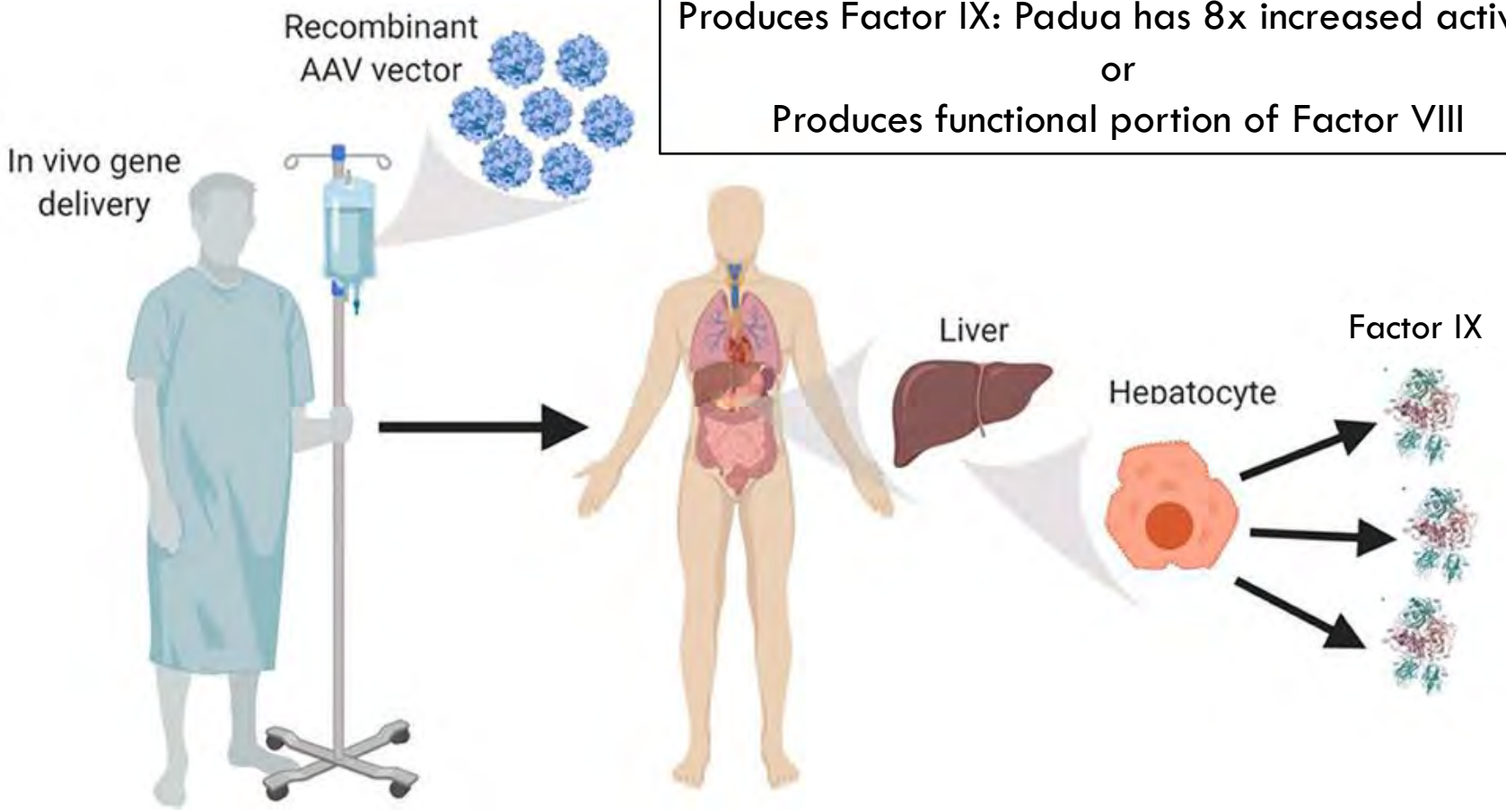


Fig 1. PBAC Blood Loss by Treatment. Cumulative distribution function comparing PBAC score after tranexamic acid, TA——, vs. recombinant VWF, rVWF——, p=0.038.

Ragni, Multicenter, Randomized Crossover Trial Comparing Recombinant Von Willebrand Factor and Tranexamic Acid for Heavy Menstrual Bleeding in Von Willebrand Disease, **Abstract #590**

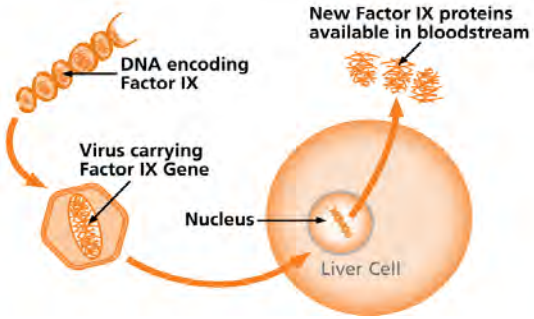
Gene Therapy for Hemophilia

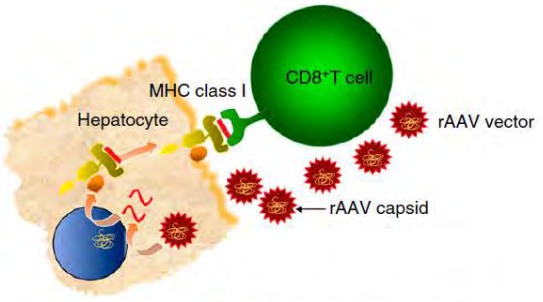
rAAV targets the liver: can simply inject iv
Produces Factor IX: Padua has 8x increased activity
or
Produces functional portion of Factor VIII



Gene Therapy for Hemophilia

- Sounds simple enough, but:
  - Pre-existing antibodies
  - One-time dosing
    - Antibodies form to viral vector
  - "Infecting the liver"
    - DNA integration OK, no mutagenesis noted (yet)
    - Capsid degraded and presented on the surface of the liver, prompting cellular immune response
    - Steroids needed in some cases
    - May limit protein production





George, ASH Education Book, *Hematology 2017*

Gene Therapy for Hemophilia B: AAV5-Factor IX or -Factor IX Padua

- Follow-up of Phase I-III studies
  - AMT-060: wild-type FXI, n=10, 3-5 yrs of follow-up
  - AMT-061/HOPE-B: Padua FXI variant, n=54, 2 yrs follow-up
- AMT-061 allowed people with neutralizing antibodies to AAV5; only 2 non-responders out of 54 treated
- Better FXI levels, lower annualized bleeding rate with Padua FXI variant (AMT-061)

Meisbach, Durability of Factor IX Activity and Bleeding Rate in People with Severe or Moderately Severe Hemophilia B after 5 Years of Follow-up in the Phase 1/2 Study of AMT-060, and after 3 Years of Follow-up in the Phase 2b and 2 Years of Follow-up in the Phase 3 Studies of Etranacogene Dezaparvovec (AMT-061), **Abstract #2142**

Gene Therapy for Hemophilia B: AMT-061: AAV5-Padua hFIX variant

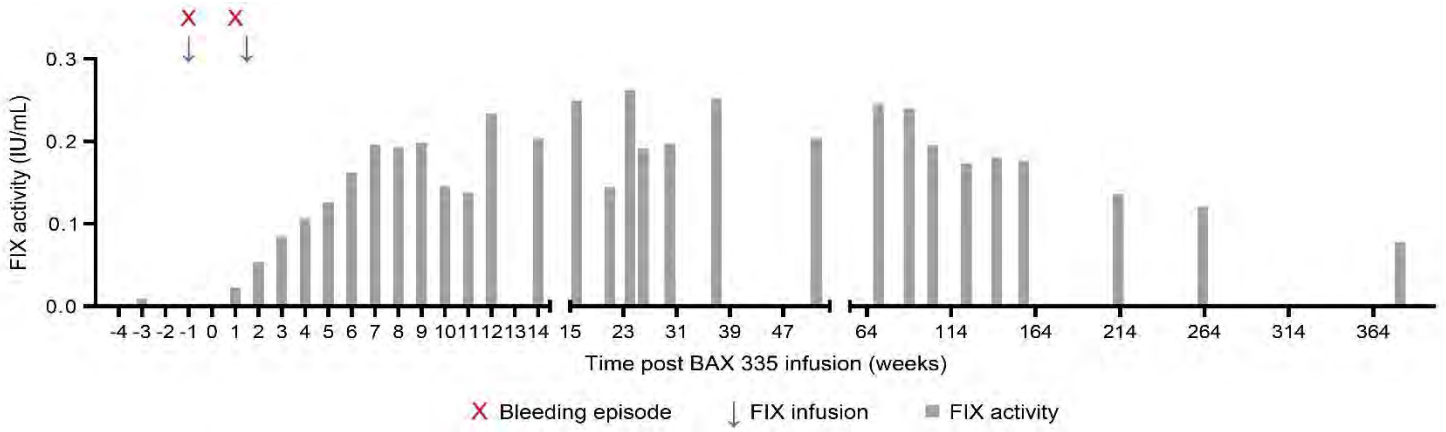
Table. Mean uncontaminated FIX activity levels and ABR after etranacogene dezaparvovec

		Week		Month					
	Baseline[a]	3	6	6	12	18	24	30	36
Phase 2b									
Mean FIX activity level (%)	n=1 5.10	n=3 23.40	n=3 30.57	-	n=3 40.77	n=2 46.95	n=3 44.20	n=3 50.03	n=2 36.90
Phase 3, full analysis set									
Mean FIX activity level (%)	n=54 1.19	-	-	n=51 38.95	n=50 41.48	n=50 36.90	n=50 36.66	-	-
Mean ABR (all bleeds)	n=54 4.18	-	-	-	0–12 months n=54 1.33	7–18 months n=54 1.51	7–24 months n=54 1.51	-	-
Phase 3, modified intent-to-treat population[b]									
Mean FIX activity level (%)	n=52 1.19	-	-	n=51 38.95	n=50 41.48	n=50 36.90	n=50 36.66	-	-
Mean ABR (all bleeds)	n=52 4.00	-	-	-	-	-	7–24 months n=52 0.95	-	-

Meisbach, Abstract #2142

Gene Therapy for Hemophilia B: BAX 335 Longer-Term Follow-Up

- BAX 335 is adeno-associated virus serotype 8 (AAV8)-based clotting factor IX (FIX) Padua (R338L) gene
- 8 pts in initial cohort, 6 with >5 years of follow-up
  - 7 of 8 lost hemostatic protection from bleeds
  - 1 participant maintained adequate levels for 7 year, no bleeds



- All have high titers of anti-AAV8 antibodies, precluding retreatment

Escobar, BAX 335 Hemophilia B Gene Therapy Phase 1/2 Clinical Trial: Long-Term Safety and Efficacy Follow-up, **Abstract #4780**

Gene Therapy for Hemophilia A: Giroctocogene Fitelparvovec (SB-525)

- Alta Study of rAAV6 vector: Phase I/II – data on 11 males
- 3-year follow-up: 2 pts with 12 bleeding events (levels ≤5%)

Table. Factor VIII Activity Levels by 1-Stage and Chromogenic Assay for the Giroctocogene Fitelparvovec 3e13-vg/kg Cohort

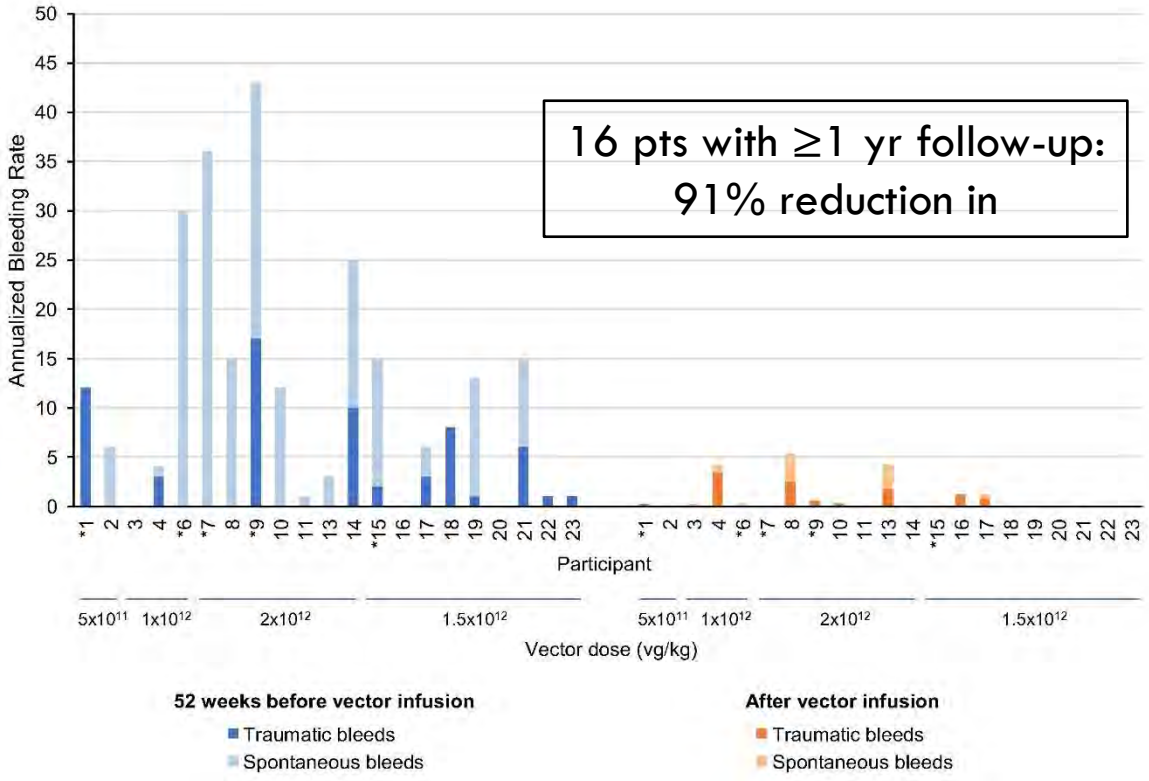
Factor VIII Activity, % Normal, Median (min, max)	Study Week						
Assay	**Week 12**	**Week 24**	**Week 52**	**Week 78**	**Week 104**	**Week 130**	**Week 156**
1-stage clotting	93.7	104.8	31.1	57.5	27.5	23.3	22.9
	(82.7, 167.7)	(30.5, 212.6)	(12.0, 191.3)	(3.8, 144.2)	(4.1, 99.1)	(5.4, 164.5)	(22.6, 129.0)
Chromogenic	62.1	70.1	20.1	40.1	16.3	12.3	12.5
	(51.8, 109.5)	(20.4, 123.8)	(7.8, 122.3)	(0.9, 114.7)	(0.9, 71.6)	(0.9, 113.2)	(11.8, 91.1)
Patients, n	5	5	4[a]	4[a]	5	4[a]	3[b]

[a] There was 1 patient each who was unable to attend visits at Weeks 52, 78, and 130.
[b] Two patients had not yet reached Week 156 at the time of the data cut.
min, max=minimum, maximum

Giersmaz, Updated Results of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults with Severe Hemophilia A, **Abstract #3461**

Gene Therapy for Hemophilia A: Phase I/II Study of SPK-8011

- Novel AAV capsid, liver specific promoter: FVIII levels 3-38%



Croteau, Long-Term Durable FVIII Expression with Improvements in Bleeding Rates Following AAV-Mediated FVIII Gene Transfer for Hemophilia A: Multiyear Follow-up on the Phase I/II Trial of SPK-8011, **Abstract #783**

New Developments at ASH 2022: Emphasis on "Development" Rather than "New"

- Anticoagulation
  - Reducing the indications for LWMH/anticoagulation during pregnancy
  - Potential for refining risk scoring for bleeding, considering plts
  - Likely reducing use in COVID (for those who had increased it)
  - Increasing the potential for new use of prophylaxis in cancer
- Reading between the lines
  - Rate of thrombosis associated with thrombophilia during pregnancy may be lower than most people think
  - Estimating risk of bleeding is complicated
  - COVID isn't COVID isn't COVID
  - Clotting on catheters is common, if subclinical

New Developments at ASH 2022: Emphasis on "Development" Rather than "New"

- Next class of anticoagulants may be those that inhibit contact activation, reducing thrombosis without affecting hemostasis – looking for the "sweet spot"
  - If long-acting, what about reversal? Do we have to?
  - May come to cancer-associated thrombosis sooner than later

- Still learning how to accurately diagnose the most common inherited bleeding disorder (vWD)
  - Emphasis on bleeding history over testing
  - "Non-specific" therapies like tranexamic acid provide options in the face of uncertainty

New Developments at ASH 2022:
Emphasis on "Development" Rather than "New"

- Gene therapy for hemophilia: closer on the horizon but still a work in progress
  - Over time (3-5 years) factor levels tend to drift downward and may disappear
  - Discrepancy between "numbers" (factor levels) and clinical outcomes (annualized bleeding rate) – important to assess both
  - Need to overcome antibody development to the viral vector
  - At $2-3 million per person, ideally only do it once


Thank you!