The Hemophilia Treatment Journey: To Factor and Beyond!

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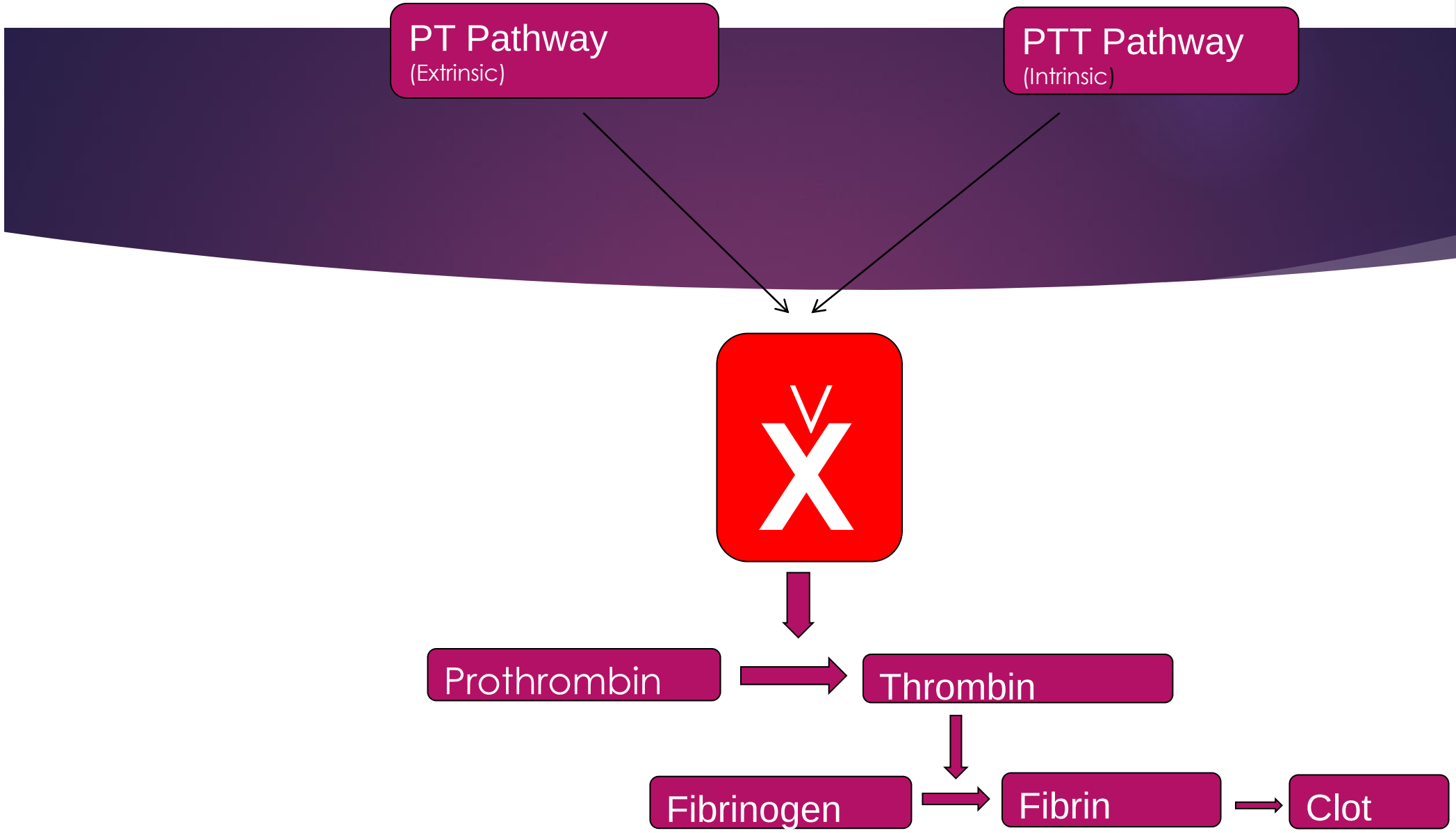
Disclosures

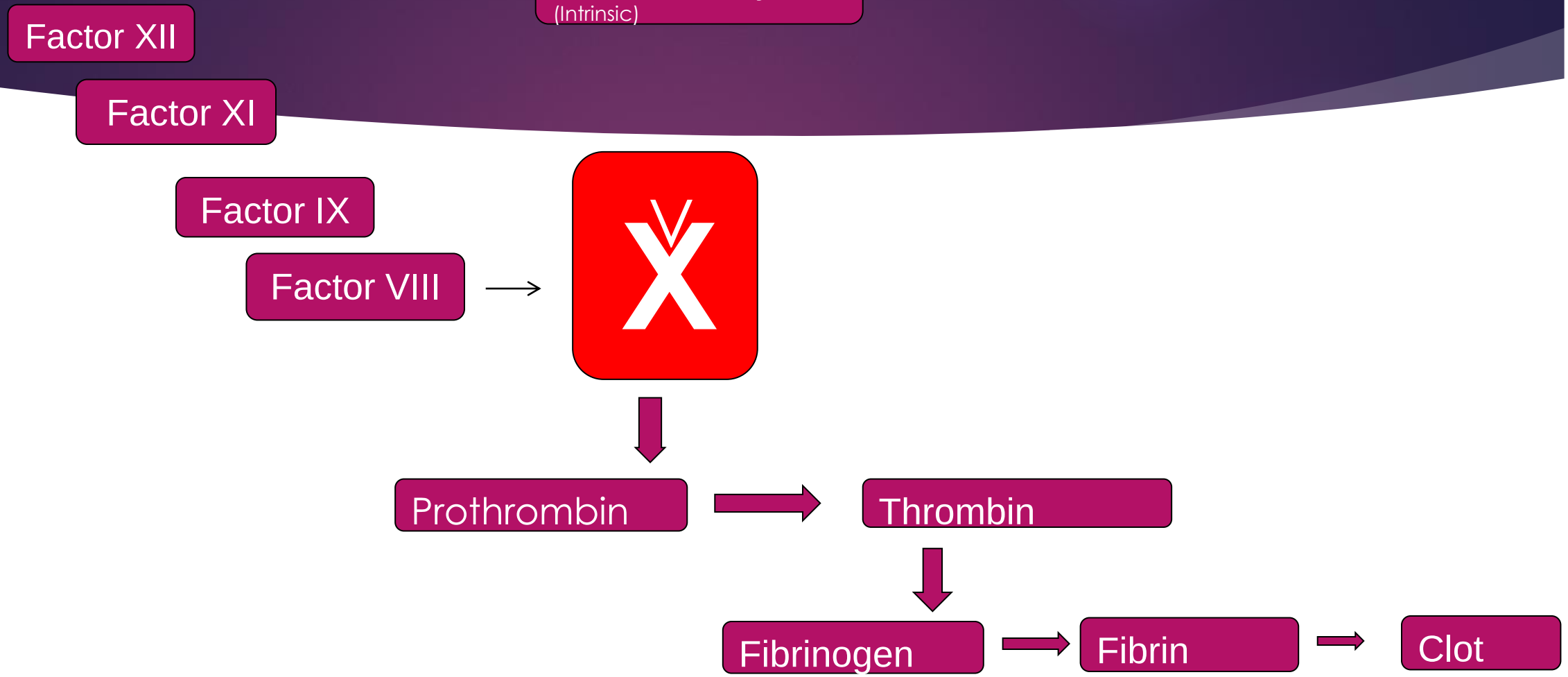
- Member of the Speaker Bureau for Genentech
- Advisory Board participant for Sanofi Genzyme

Outline/Objectives

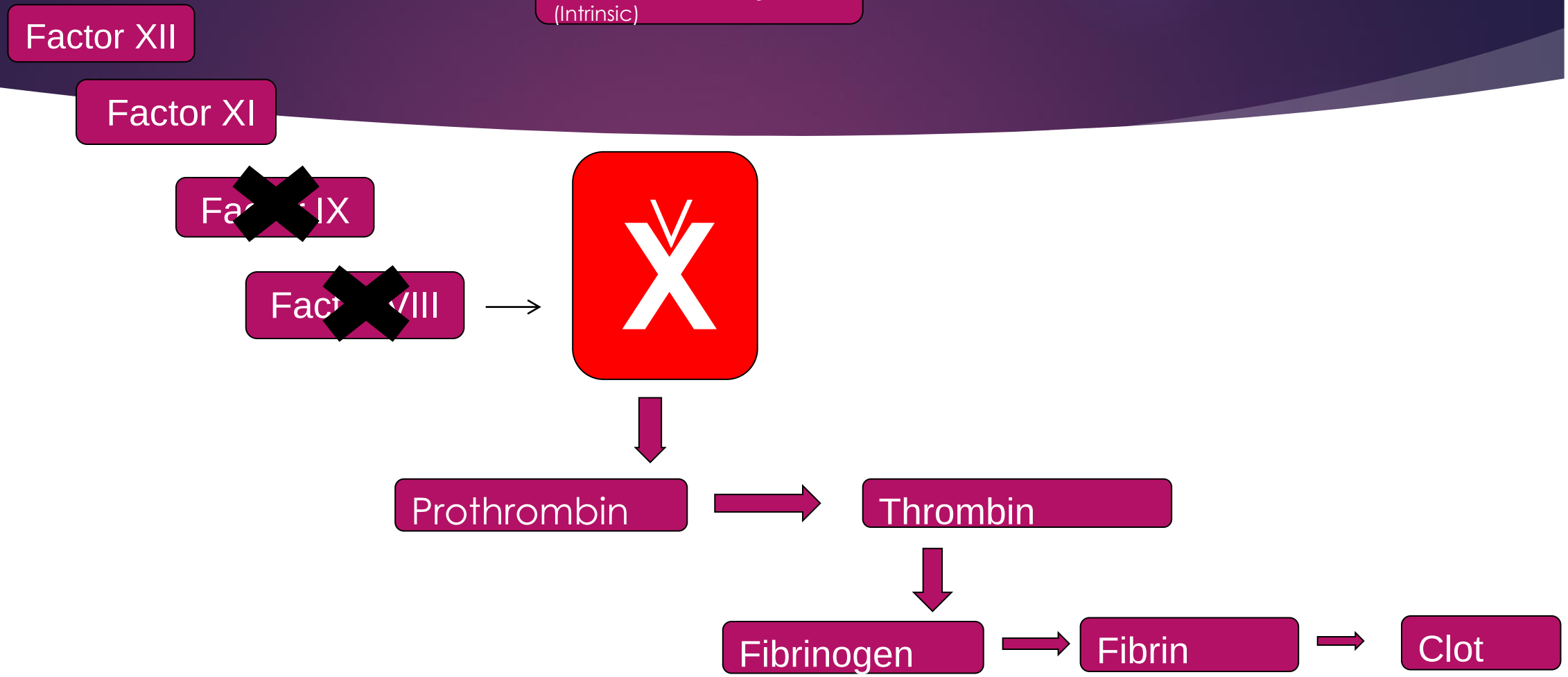
- Review the role of factor VIII and factor IX in coagulation physiology
- Discuss Hemophilia basics
- Review factor replacement therapy for bleeding symptoms and bleeding prophylaxis
- Discuss non-factor replacement therapy options
- Discuss the role of gene therapy for hemophilia


PT Pathway
(Extrinsic)
PTT Pathway
(Intrinsic)
X
Prothrombin
Thrombin
Fibrinogen
Fibrin
Clot

PTT Pathway
(Intrinsic)



PTT Pathway
(Intrinsic)



PTT Pathway
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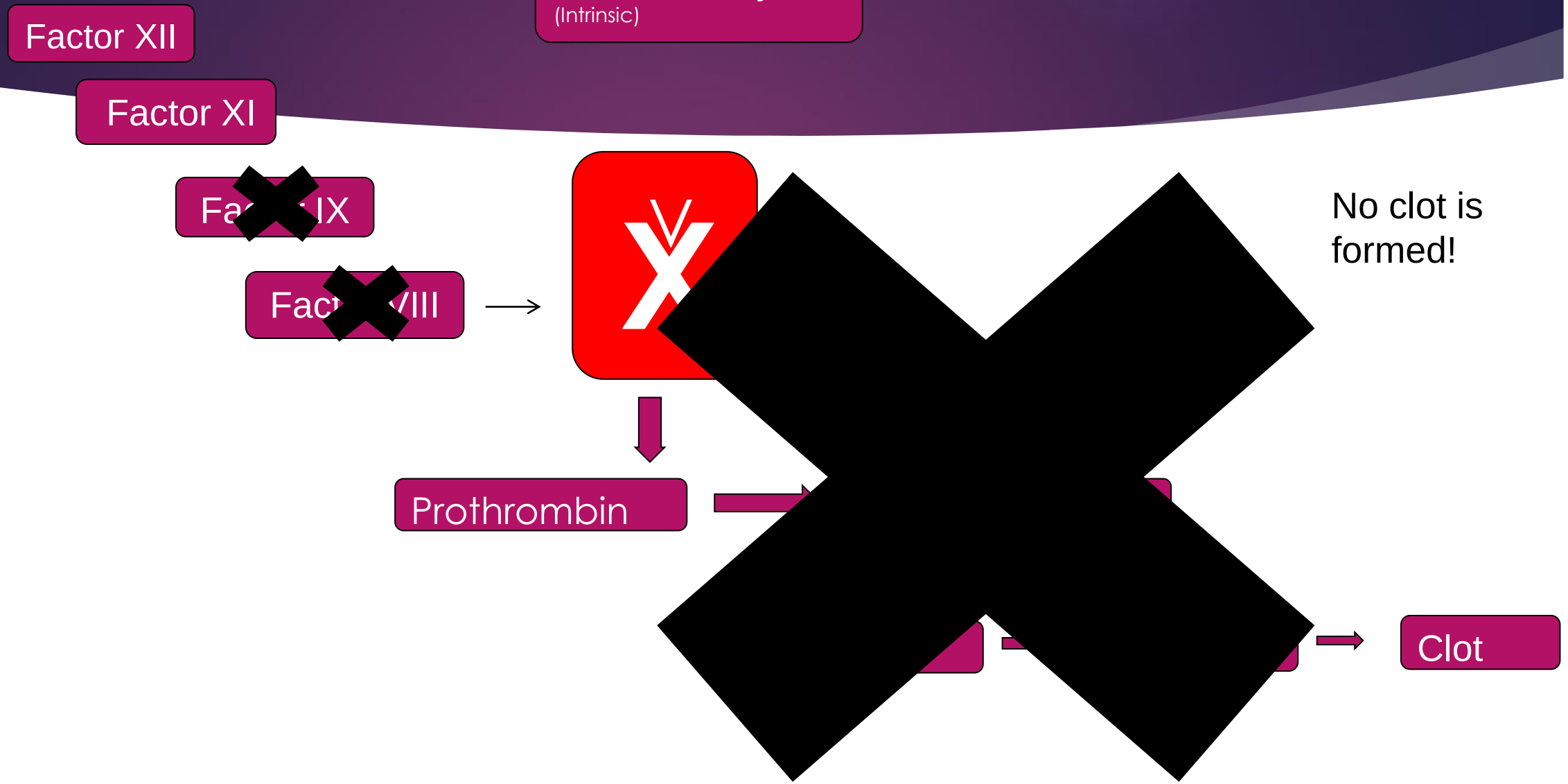
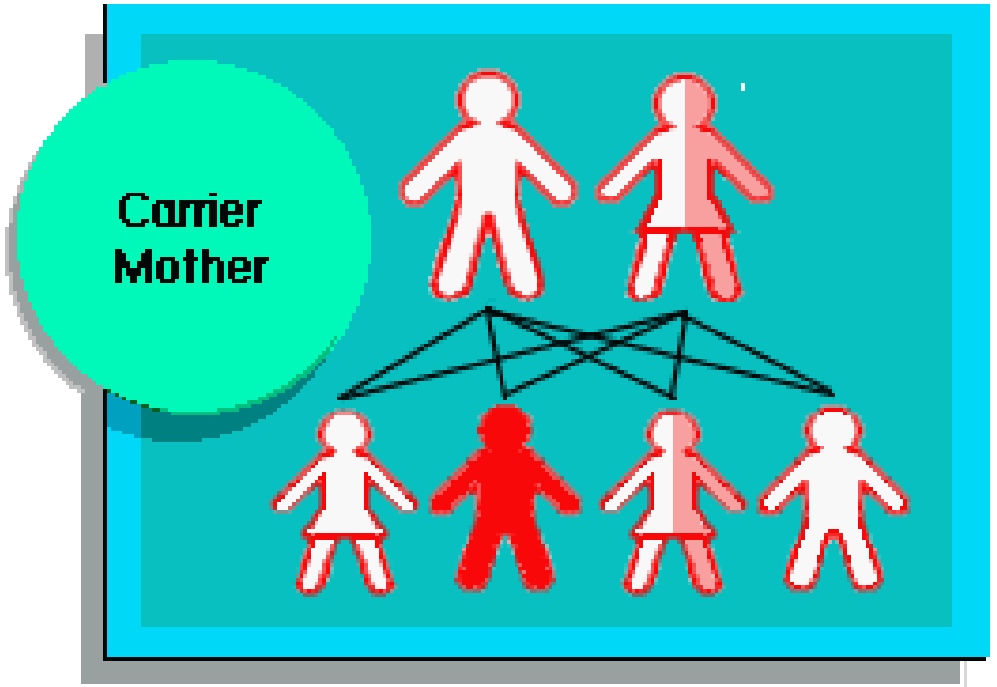


Hemophilia Review

- Deficiency of factor VIII or factor IX
  - Factor VIII deficiency is approx. 1/5000 males
  - Factor IX deficiency is approx. 1/20-30,000 males
- X-linked recessive
  - Mostly affects males, but can have female hemophilia patients
- Mothers are the carriers

Carrier Mother

- One normal gene and one affected gene
- Daughter has 50:50 chance of being a carrier
- Son has 50:50 chance of having hemophilia

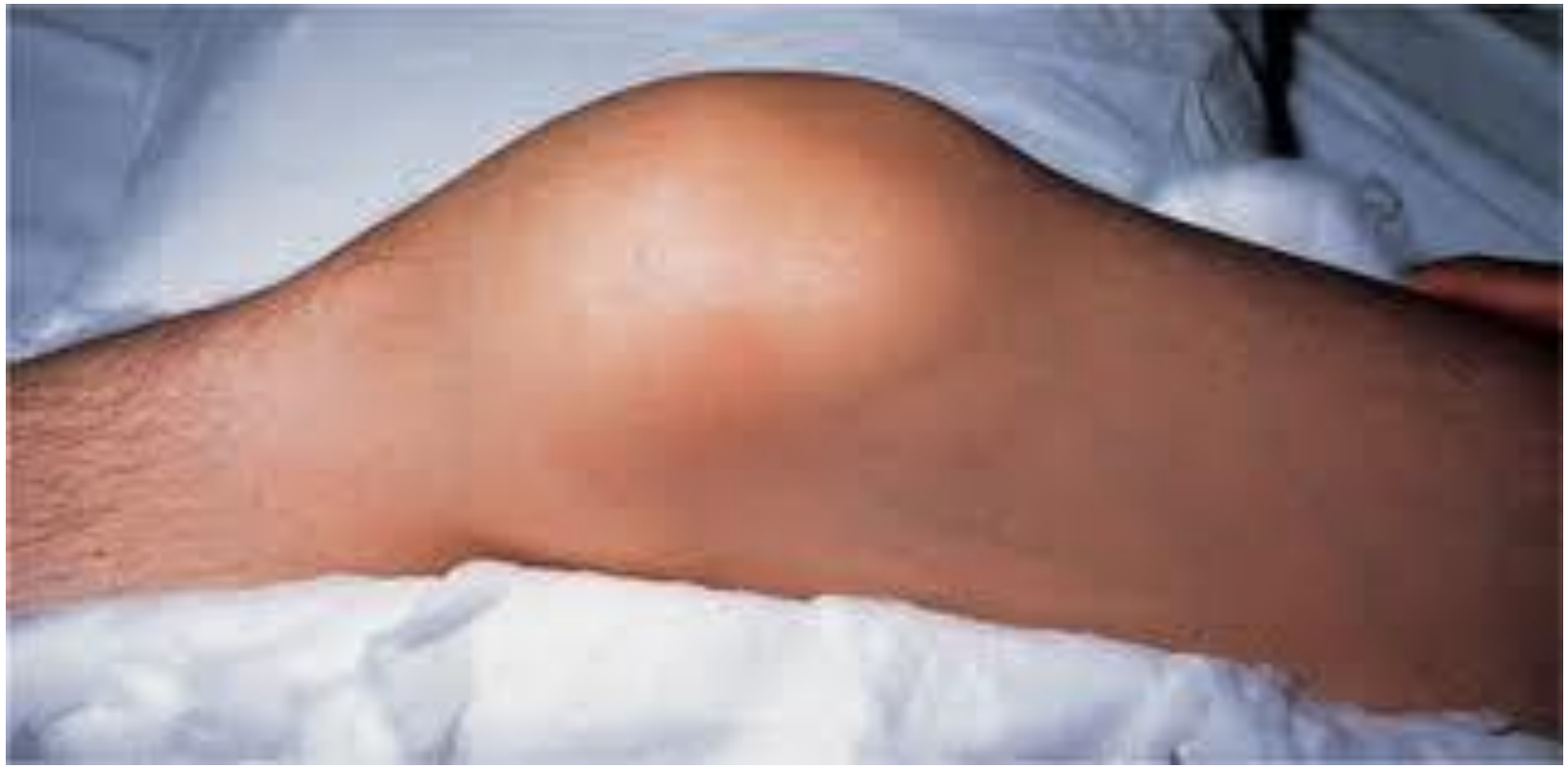


Degrees of Hemophilia

- Mild Hemophilia (5-50%)
  - Very minor bleeding with trauma and sometimes does not need to have factor replacement
- Moderate Hemophilia (1-5%)
  - Can have severe bleeding after minor trauma
- Severe Hemophilia (<1%)
  - Severe Spontaneous Bleeding anywhere

Hemophilia bleeding symptoms

- Hemarthrosis
  - Hallmark bleeding symptom
- Large muscle bleeds
- Bleeding after circumcision
- Significant bruising



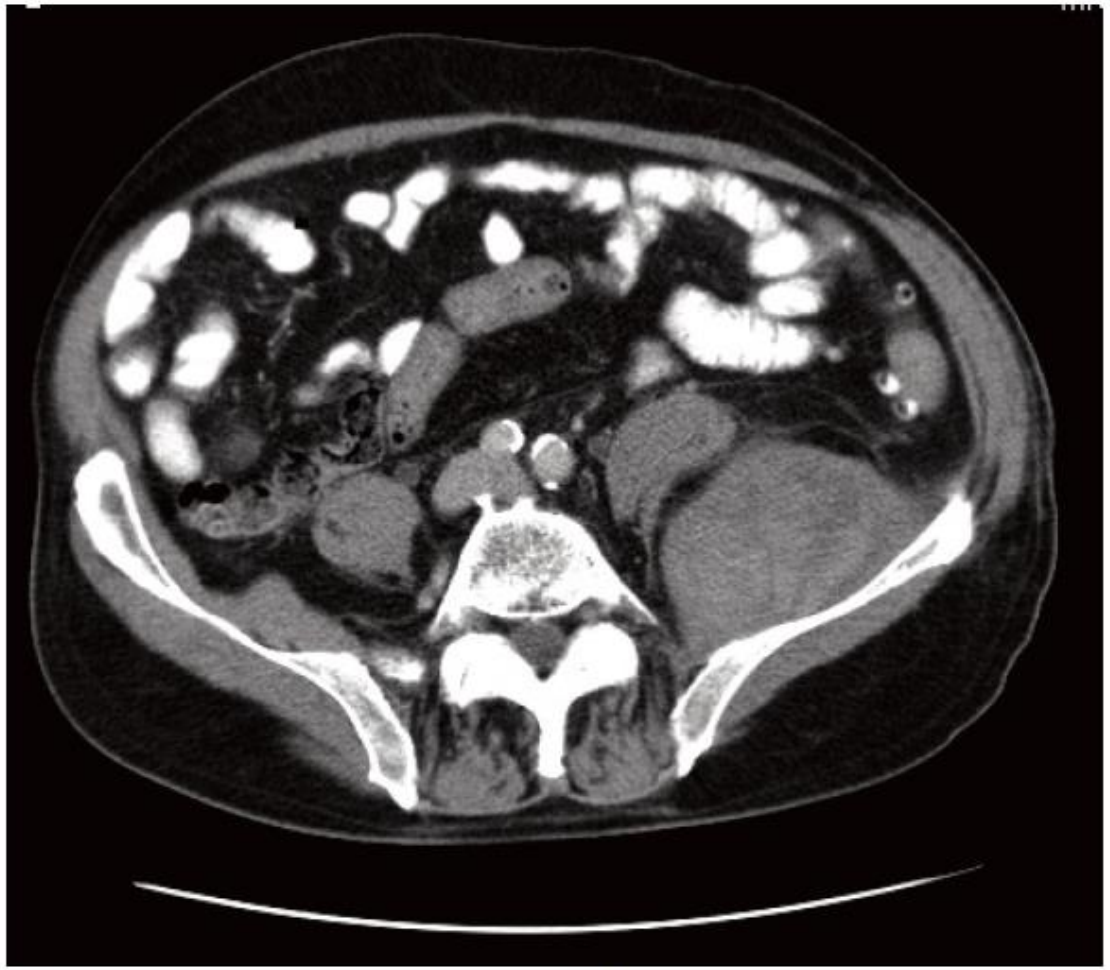
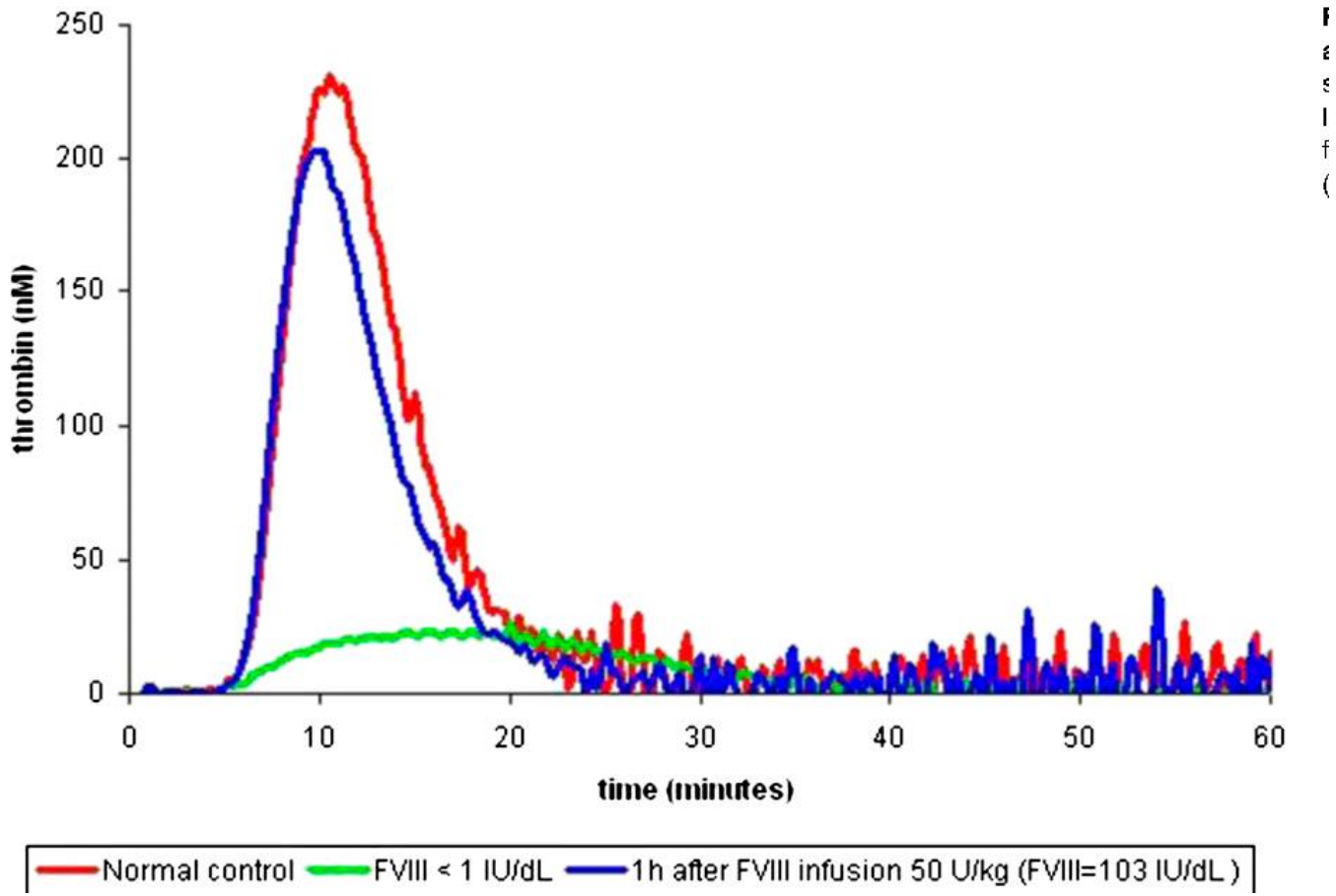


Figure 1. *Large retroperitoneal hemotoma seen on the left iliacus muscle.*

Bleeding Treatment

- Factor VIII Replacement
  - 1u/kg increases factor level by 2%
- Factor IX Replacement
  - ~1u/kg increases factor level by 1%



Young G, et al. Thrombin generation and whole blood viscoelastic assays in the management of hemophilia: current state of art and future perspectives. Blood 2013.

Starting our Hemophilia Treatment Journey!

LET ME INTRODUCE……

Chuckles the Coag Chimp

- HTC Team Member/Mascot
- World Traveler
- Twitter handle: @coagchimp

Chuckles Story

- Term male born via SVD
- Had excessive bleeding after circumcision
- Laboratory studies showed normal PT and prolonged PTT of 85 seconds
- Factor VIII level <1% and factor IX level 24%
  - Factor VIII usually elevated at birth and factor IX lower than older children

Infancy

- Relatively uneventful
- Developing normally
- Slight bruising with immunizations
- Now starting to become more mobile

Treatment options

- Now with Chuckles moving much more how should we treat his severe hemophilia?
  - On Demand factor therapy?
  - Prophylaxis therapy?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 9, 2007 VOL. 357 NO. 6

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Marilyn J. Manco-Johnson, M.D., Thomas C. Abshire, M.D., Amy D. Shapiro, M.D., Brenda Riske, M.S., M.B.A., M.P.A., Michele R. Hacker, Sc.D., Ray Kilcoyne, M.D., J. David Ingram, M.D., Michael L. Manco-Johnson, M.D., Sharon Funk, B.Sc., P.T., Linda Jacobson, B.S., Leonard A. Valentino, M.D., W. Keith Hoots, M.D., George R. Buchanan, M.D., Donna DiMichele, M.D., Michael Recht, M.D., Ph.D., Deborah Brown, M.D., Cindy Leissinger, M.D., Shirley Bleak, M.S.N., Alan Cohen, M.D., Prasad Mathew, M.D., Alison Matsunaga, M.D., Desiree Medeiros, M.D., Diane Nugent, M.D., Gregory A. Thomas, M.D., Alexis A. Thompson, M.D., Kevin McRedmond, M.D., J. Michael Soucie, Ph.D., Harlan Austin, Ph.D., and Bruce L. Evatt, M.D.

Prophylaxis Treatment--Why?

Joint Outcome Study

- Examined giving boys regularly scheduled factor replacement vs. symptomatic care

- Primary outcome was the amount of joint cartilage damage in target joints as detected by radiology

Table 2. Outcome Data.*

Variable	Prophylaxis (N=32)	Enhanced Episodic Therapy (N=33)	P Value
MRI findings			
No. of participants with primary outcome data	27	29	0.73
Joint damage — no. (%)	2 (7)	13 (45)	0.002
No joint damage — no. (%)	25 (93)	16 (55)	
Radiographic findings			
No. of participants with primary outcome data	28	27	0.73
Joint damage — no. (%)	1 (4)	5 (19)	0.10
No joint damage — no. (%)	27 (96)	22 (81)	
No. of days in study			
Mean	1,497	1,490	0.95
Total	47,895	49,179	
Reported no. of factor VIII infusions			
Mean	653±246	187±100	<0.001
Total	20,896	6,176	
Reported no. of factor VIII units infused			
Mean	352,793±150,454	113,237±65,494	<0.001
[illegible]	[illegible]	[illegible]	
Joint hemorrhages (no./participant/yr)			
Mean	0.63±1.35	4.89±3.57	<0.001
Median	0.20	4.35	
[illegible]			
Mean	3.27±6.24	17.69±9.25	<0.001
Median	1.15	17.13	

* Plus–minus values are means ±SD. The data on MRI and radiographic findings include interim-analysis data for children who were removed from the study because of early joint failure.

Factor Prophylaxis Treatment

- 2-3x a week
- Usually done at 50% correction
- All done at home

A few years later…..

- Chuckles has been doing well with his 3x a week prophylaxis
- Started having more bruising and has had 3 knee bleeds over the past 2 months
- Has not missed any doses of his factor prophylaxis

Lab results

- Labs drawn approx. 12hrs after getting factor dose
  - PTT: 80 seconds
  - Factor VIII activity: <1%
  - Factor VIII inhibitor titer: 10.8

Factor Inhibitors

- Immune system develops neutralizing antibodies against factor protein
  - ~30% of factor VIII deficiency and 2-3% of factor IX deficiency

- Very difficult to treat bleeding

Bleeding Treatment for patients with inhibitors

- Use bypassing agents
- Activated prothrombin complex concentrate
  - Activated vitamin K dependent factors
- Recombinant factor VIIa

Table 2. Rates of efficacy by treatment and time point

Hours after infusion (N)	FEIBA, %	NovoSeven, %	90% confidence interval, %*	*P*
2† (48)	75.0	60.4	−0.73-29.90	.482
6 (47)	80.9	78.7	−11.42-15.67	.059
12 (45)	80.0	84.4	−18.08-9.19	.101
24 (42)	95.2	85.7	−1.29-20.33	.202
36 (41)	100.0	90.2	2.13-17.38	.129
48 (41)	97.6	85.4	2.05-22.34	.325

Efficacy is defined as effective or partially effective by patient rating. The 6-hour time point is the primary outcome.

*The 90% confidence interval for the difference in the proportions of patients' rating of efficacy for each of the treatments (columns 2 and 3). Rejecting the null hypothesis at the .05 level is equivalent, in this setting, to showing that the upper and lower limits of the confidence interval for the difference in efficacy fall within plus or minus 15%.

†Prior to the second dose of NovoSeven.

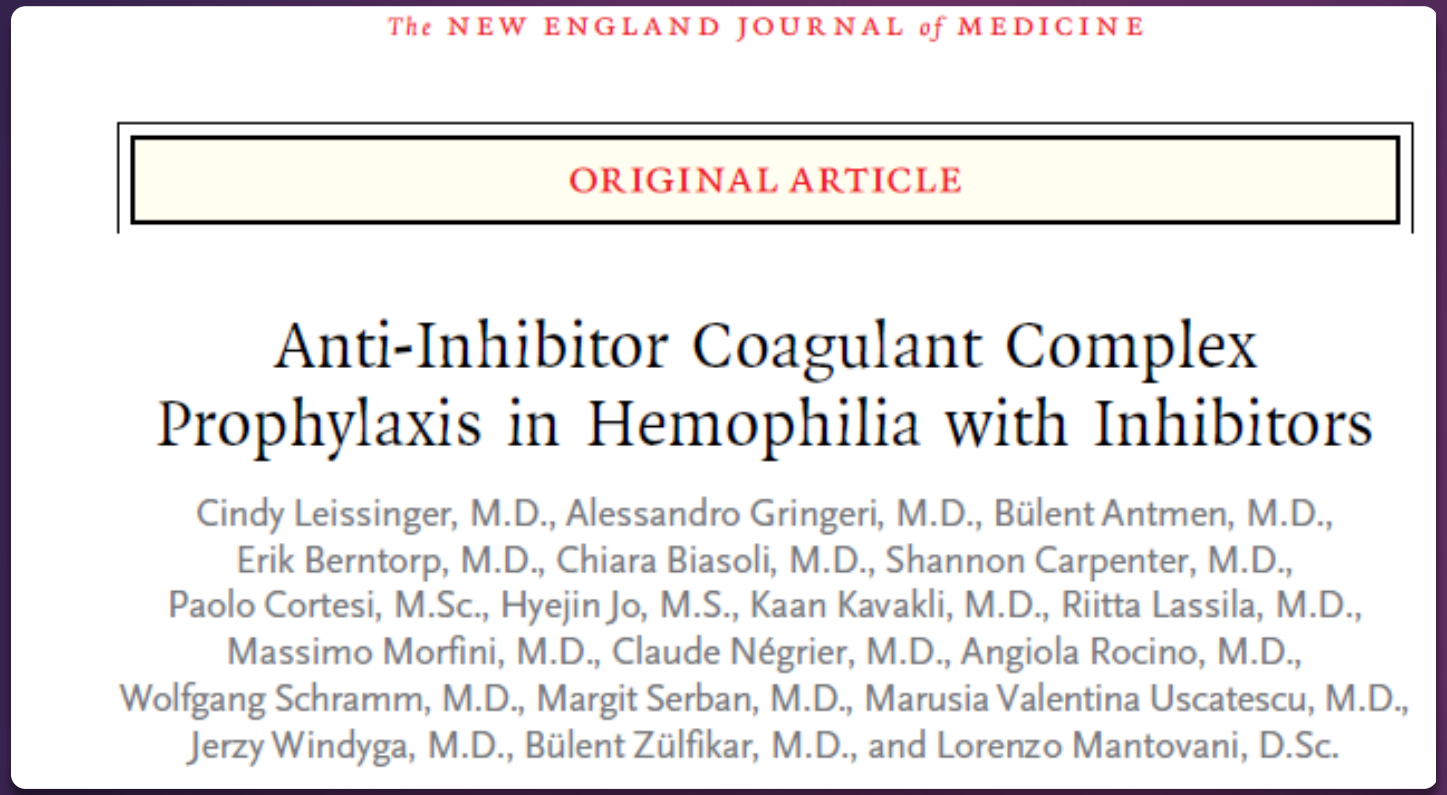
Table 5. Proportion reporting that bleeding had stopped by treatment and time point

Hours after infusion (N)	FEIBA, %	NovoSeven, %	90% confidence interval, %*	*P*
2† (47)	53.2	38.3	0.06-29.72	.495
6 (46)	76.1	65.2	−2.73-24.47	.309
12 (45)	77.8	75.6	−11.92-16.37	.069
24 (42)	90.5	85.7	−4.75-14.28	.038
36 (41)	95.1	87.8	−1.45-16.09	.075
48 (41)	95.1	92.7	−4.48-9.36	.001

*The 90% confidence interval for the difference in the proportions of patients' rating of whether the bleeding had stopped for each of the treatments (columns 2 and 3). Rejecting the null hypothesis at the .05 level is equivalent, in this setting, to showing that the upper and lower limits of the confidence interval fall within plus or minus 15%.

†Prior to the second dose of NovoSeven.

Astermark, et al. Blood. 2007; 109:546-551



Bypassing agent prophylaxis

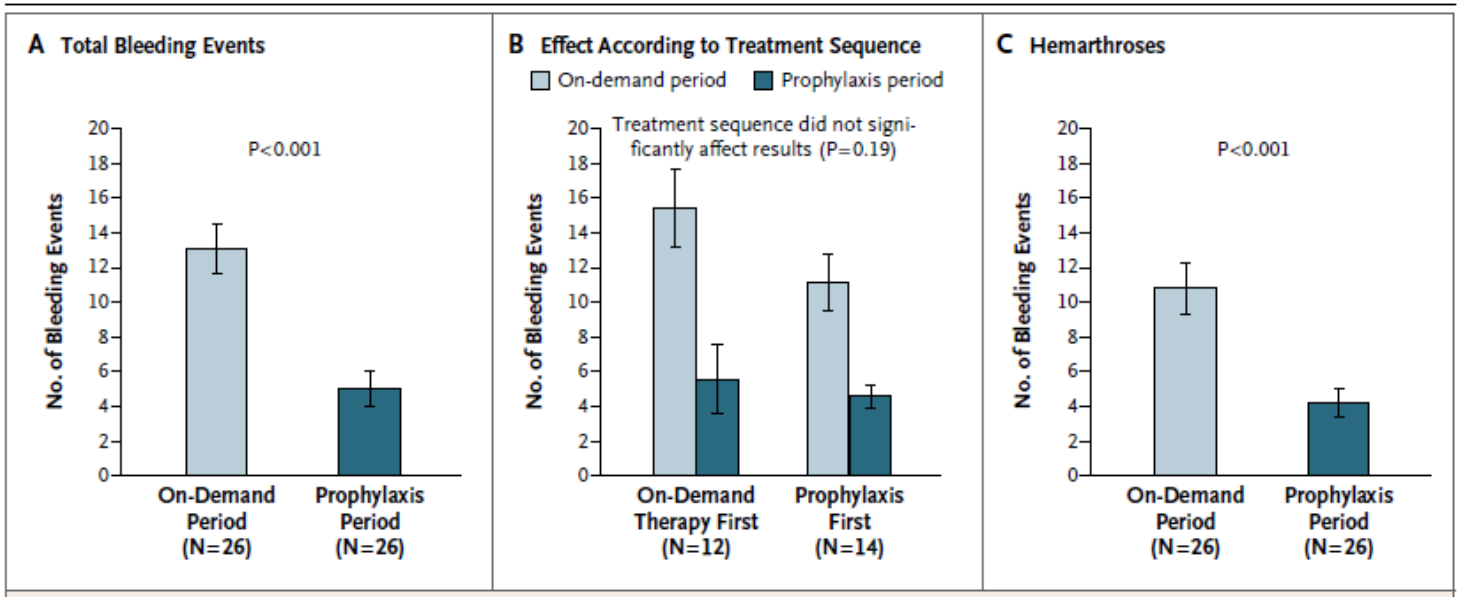


Figure 2. Bleeding Episodes during the Two Treatment Periods.

Panel A shows the mean number of total patient-reported bleeding events, according to the treatment period. A mean of 13.1 bleeding events were reported during the 6-month on-demand period, and 5.0 bleeding events were reported during the 6-month prophylaxis period. Episodes of joint bleeding accounted for approximately 80% of total bleeding episodes. Bleeding was also noted at other sites, including the muscles, other soft tissues, and body cavity. Intracranial and surgical bleeding also occurred. As shown in Panel B, no difference was noted in the treatment (prophylactic) effect on the basis of the order in which patients were randomly assigned to treatment. Panel C shows the mean number of hemarthroses according to the treatment period. A mean of 10.8 joint-bleeding episodes were reported during the on-demand period, and 4.2 joint-bleeding episodes were reported during the prophylaxis period. I bars indicate standard errors.

Do we treat the inhibitor?

- Yes we can!
- Immune tolerance therapy

Immune Tolerance Therapy

- Give high doses of factor daily
- Conditions the immune system to not recognize the factor as foreign
- Hope to stop making the antibody
- Successful in 60-70% of hemophilia A patients

International Immune Tolerance Study

- Compared low dose factor infusion vs. high dose
  - 50u/kg/dose 3x a week vs. 200u/kg/dose daily
- Monitored patients for several factors
  - Inhibitor eradication
  - Bleeding episodes

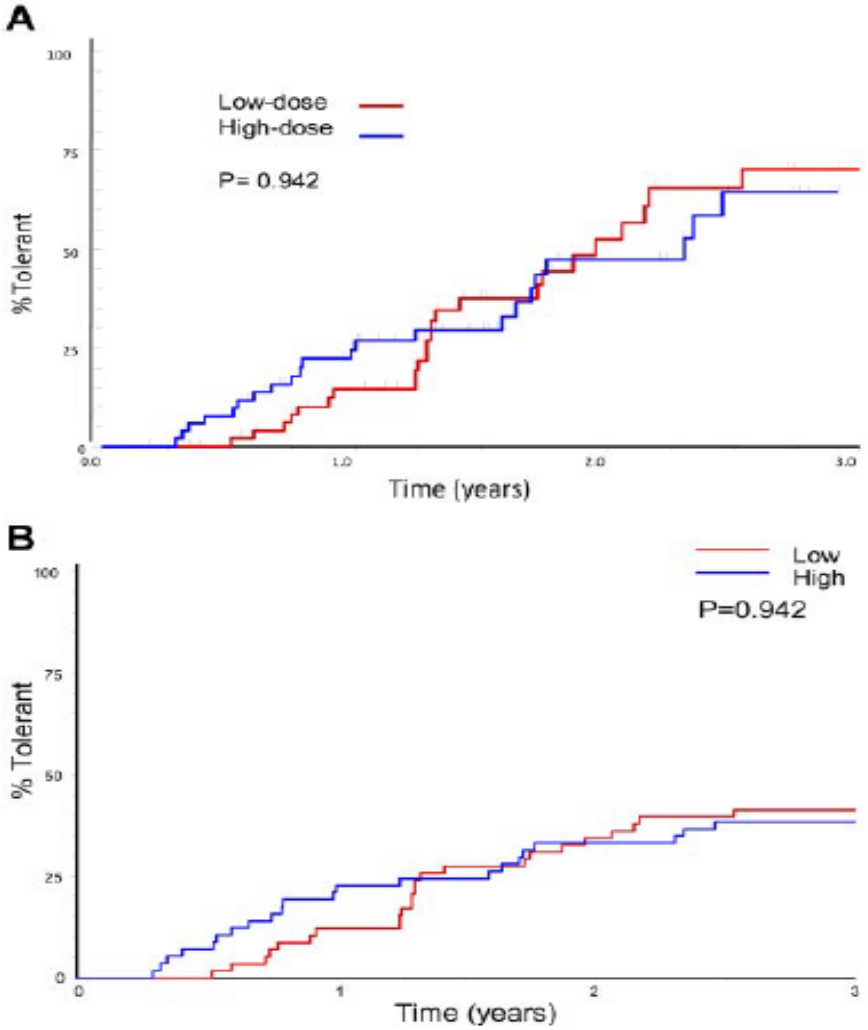


Figure 3. Time to success by treatment arm. (A) Kaplan-Meier plot showing the time to tolerance for the 66 patients who achieved a success, partial success, or failure end point, broken down by HD and LD treatment arm. (B) Intention-to treat Kaplan-Meier plot showing the time to tolerance for all 115 patients randomized and broken down by treatment arm. This plot shows no significant difference between treatment arms (P = .942), but a lower success rate because those not completing ITI or who were withdrawn for logistical reasons are also included.

May CM, et al. Blood 2012;119(6):1335-1344

Table 4. Time to achieve ITI milestones by treatment arm reported as median (IQR) mo

	n	LD	n	HD	*P*
Phase 1: start of ITI to negative titer	29	9.2 (4.9-17.0)	31	4.6 (2.8-13.8)	.017
Phase 2: negative titer to first normal recovery	27	13.6 (8.7-19.0)	23	6.9 (3.5-12.0)	.001
Phase 3: normal recovery to tolerance	24	15.5 (10.8-22.0)	22	10.6 (6.3-20.5)	.096

Table 7. All intercurrent bleeding by treatment arm and phase of ITI

	Regimen	Bleeds, n	HR	95% CI	*P*
All ITI (n = 58 vs 57)	LD	684	2.2	1.34-3.62	.0019
	HD	282			
Phase 1 (n = 58 vs 57)	LD	573	2.27	1.29-4.01	.0046
	HD	241			
Phase 2 (n = 27 vs 23)	LD	47	3.4	0.84-13.8	.088
	HD	4			
Phase 3 (n = 24 vs 22)	LD	9	5.18	0.71-38.0	.110
	HD	3			
Phase 4 (n = 24 vs 22)	LD	54	1.70	0.80-3.63	.170
	HD	32			

Phase 1 indicates the time from the start of ITI until the Bethesda titer is negative; phase 2, from phase 1 until the FVIII recovery is normal; phase 3, from phase 2 to normal half-life; and phase 4, 12-month prophylactic phase after the half-life has normalized.

May CM, et al. Blood 2012;119(6):1335-1344

Chuckles Treatment

- Started on high dose ITI
- Placed on recombinant factor VIIa for bleeding prophylaxis
- Minimal bleeding symptoms
- Successfully tolerized in 1.5 years
- Restarted back on his factor VIII product 3x a week

Fast forward a few years……

- Chuckles is now a teenager
- Still doing prophylaxis 3x a week, but is really tired of having to do so many infusions
- Misses infusions here and there because he forgets to do them
- Wondering if there are any other options out there b/c he has heard about some newer factor products

Extended Half Life Factor Products

- Recombinant factor VIII and factor IX product modified to extend the half life of each factor
  - Fc Fusion protein
  - Albumin
  - PEG

- Normal half lives
  - Factor VIII: 10-12hrs when coupled with von Willebrand factor
  - Factor IX: 18-24hrs

Generic name	Name	Technology	Cell line	Molecule length	Mean half-life, h
Eftrenanocog alfa	Alprolix®	Fc-fusion	HEK	full-length	82
Albutrepenonacog alfa	Idelvion®	albumin-fusion	CHO	full-length	102
Nonacog beta pegol	Refixia®	site-specific PEGylation to activation peptide	CHO	full-length	93

HEK = Human embryonic kidney; CHO = Chinese hamster ovary.
[a]Note that methods to evaluate half-lives differed among studies.

Factor IX products

Graf L. Transf Med Hemother 2018;45:86-91

Generic name	Name	Technology	Cell line	Molecule length	Mean half-life, h
Efmoroctocog alfa	Elocta®	Fc-fusion	HEK	BDD	19
Rurioctacog alfa pegol	Adynovi®	PEGylation to surface exposed lysine	CHO	full-length	14–16
Turoctocog alfa pegol	–	single site-specific PEGylation to O-linked glycan in B-domain	CHO	BD truncated	19
Damoctocog alfa pegol	–	site-specific PEGylation to cysteine1805	BHK	full-length	19
Lonoctocog alfa	Afstyla®	covalently linked heavy and light chain with increased affinity for vWF	CHO	BDD	14.5

HEK = Human embryonic kidney; CHO = Chinese hamster ovary; BHK = baby hamster kidney; vWF = von Willebrand Faktor; BDD = B-domain deleted; BD = B-domain.

[a]Note that methods to evaluate half-lives differed among studies.

Factor VIII products

Graf L. Transf Med Hemother 2018;45:86-91

Factor VIII EHL

- Issues with extending factor VIII half life
- Due to von Willebrand factor

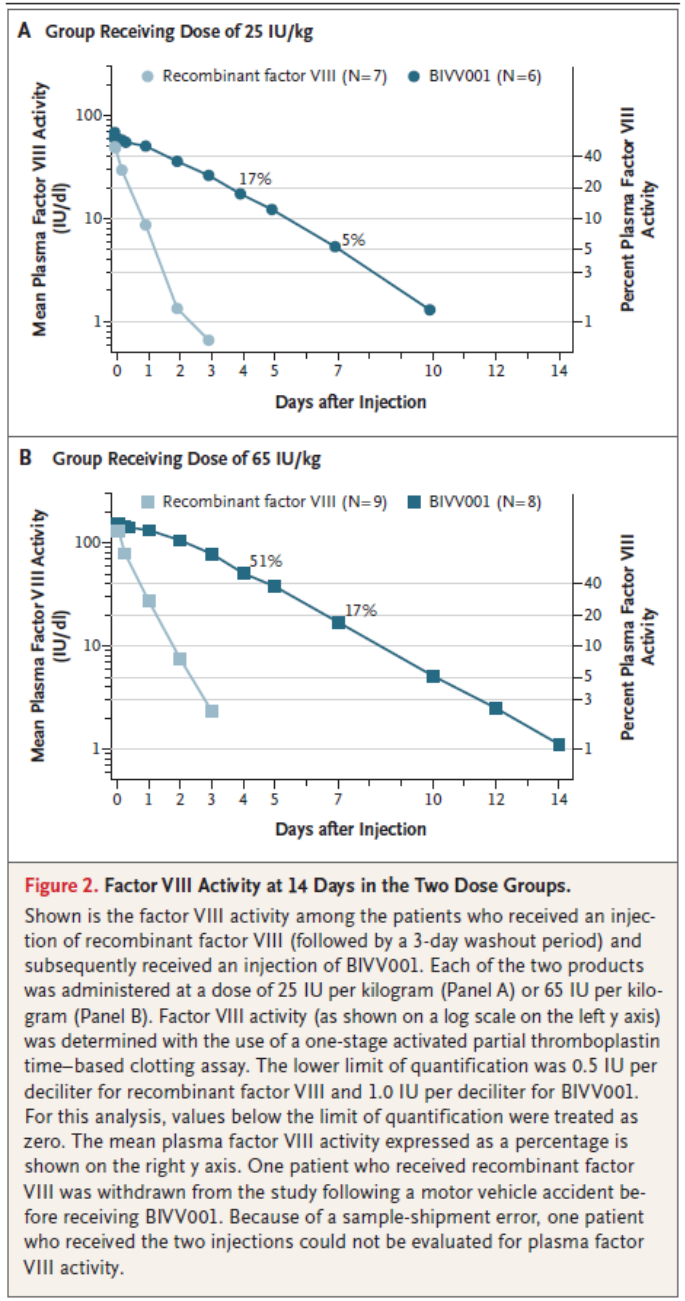


Figure 2. Factor VIII Activity at 14 Days in the Two Dose Groups.

Shown is the factor VIII activity among the patients who received an injection of recombinant factor VIII (followed by a 3-day washout period) and subsequently received an injection of BIVV001. Each of the two products was administered at a dose of 25 IU per kilogram (Panel A) or 65 IU per kilogram (Panel B). Factor VIII activity (as shown on a log scale on the left y axis) was determined with the use of a one-stage activated partial thromboplastin time–based clotting assay. The lower limit of quantification was 0.5 IU per deciliter for recombinant factor VIII and 1.0 IU per deciliter for BIVV001. For this analysis, values below the limit of quantification were treated as zero. The mean plasma factor VIII activity expressed as a percentage is shown on the right y axis. One patient who received recombinant factor VIII was withdrawn from the study following a motor vehicle accident before receiving BIVV001. Because of a sample-shipment error, one patient who received the two injections could not be evaluated for plasma factor VIII activity.

BIVV001

Konkle B, et al. N Eng J Med 2020;383:1018-27

Extended Half life product treatment

- May do PK testing to ensure right dose for patient
  - Due to varying metabolism
  - Personalized bleeding prophylaxis
  - Take factor levels a different time points

Back to Chuckles……

- Chuckles has now been switched to an extended half life factor VIII product
- After PK testing, able to change his infusion scheduled to 2x a week
- Getting really tired of having to infuse twice a week
  - Starting to miss doses and has been having more bleeds due to this
- Wondering if any new options are available
  - Non IV therapy possible?

Non-factor products

- Molecules to treat bleeding disorders which are not part of the coagulation system
- Either work like a factor protein or inhibit coagulation system protein(s)

Non-factor products

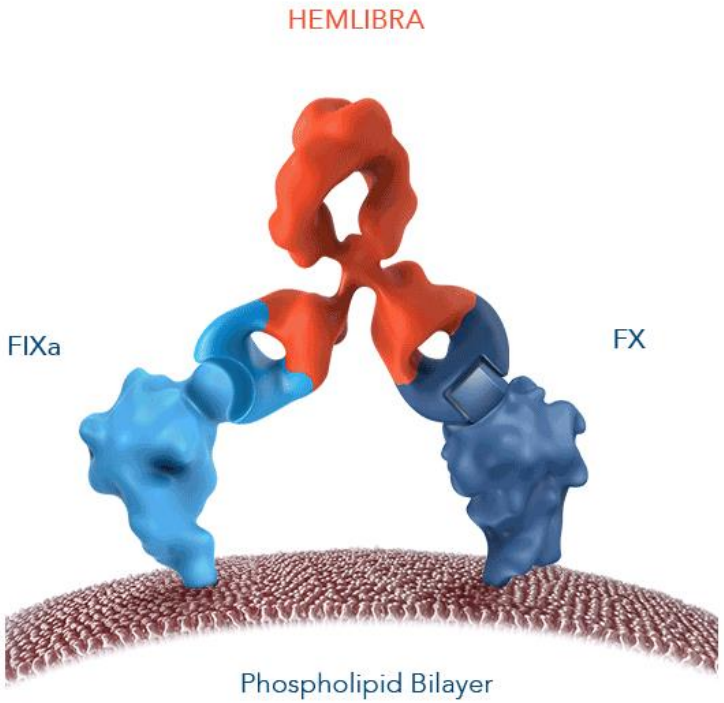
- Emicizumab
- Fitusiran

Non-factor products

- Emicizumab
- Fitusiran

Emicizumab

- Bispecific monoclonal antibody
- Binds to activated factor IX and factor X to push the coagulation system forward
  - Acts like factor VIII
- Does not look like factor VIII protein
  - Immune system/inhibitors do not recognize it as foreign



From hemlibra.com

Emicizumab

- Originally designed to treat patients with factor VIII inhibitors
  - Now is FDA approved for both patients with AND without inhibitors
- Only used for prophylaxis….NOT for bleeding episodes
- Administered subcutaneously
  - Weekly, every 2 weeks, every 4 weeks

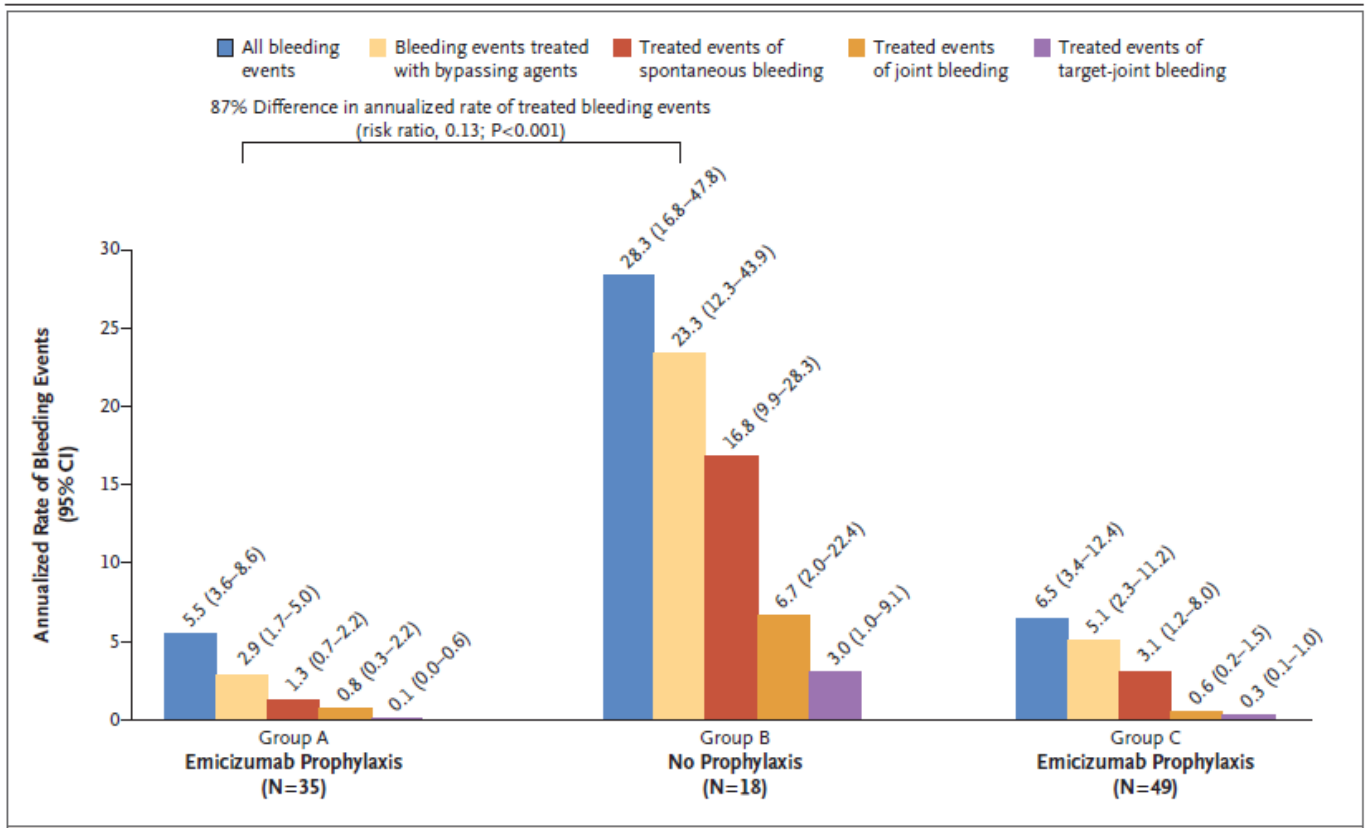


Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.

Oldenberg, et al. N Eng J Med 2017;377:809-18.

Table 1. Annualized Bleeding Rate among Participants Who Underwent Randomization and Had Received Episodic Factor VIII Treatment Previously.*

Variable	Group A: Emicizumab Once Weekly (N=36)	Group B: Emicizumab Every 2 Wk (N=35)	Group C: No Prophylaxis (N=18)
Median duration of efficacy period (range) — wk†	20.6 (17.3–40.6)	31.3 (7.3–50.6)	24.0 (14.4–25.0)
Bleeding events treated with factor VIII‡			
Annualized rate of bleeding events, model-based (95% CI)§	1.5 (0.9–2.5)	1.3 (0.8–2.3)	38.2 (22.9–63.8)
Rate ratio vs. control (95% CI)	0.04 (0.02–0.08)	0.03 (0.02–0.07)	—
Percent difference vs. control	–96‖	–97‖	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–2.5)	0.0 (0.0–1.9)	40.4 (25.3–56.7)
Percent of participants with 0 bleeding events (95% CI)	56 (38–72)	60 (42–76)	0 (0–18)
All bleeding events, regardless of treatment with factor VIII			
Annualized rate of bleeding events, model-based (95% CI)§	2.5 (1.6–3.9)	2.6 (1.6–4.3)	47.6 (28.5–79.6)
Rate ratio vs. control (95% CI)	0.05 (0.03–0.10)	0.05 (0.03–0.10)	—
Percent difference vs. control	–95‖	–94‖	—
Median annualized rate of bleeding events (IQR)	0.6 (0.0–3.9)	1.6 (0.0–4.0)	46.9 (26.1–73.9)
Percent of participants with 0 bleeding events (95% CI)	50 (33–67)	40 (24–58)	0 (0–18)
Percent of participants with 0–3 bleeding events (95% CI)	86 (70–95)	86 (70–95)	6 (<1–27)
Treated events of spontaneous bleeding			
Annualized rate of bleeding events, model-based (95% CI)§	1.0 (0.5–1.9)	0.3 (0.1–0.8)	15.6 (7.6–31.9)
Rate ratio vs. control (95% CI)	0.06 (0.02–0.15)	0.02 (0.01–0.06)	—
Percent difference vs. control	–94‖	–98‖	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.3)	0.0 (0.0–0.0)	10.8 (2.1–25.9)
Percent of participants with 0 bleeding events (95% CI)	67 (49–81)	89 (73–97)	22 (6–48)
Percent of participants with 0–3 bleeding events (95% CI)	94 (81–99)	100 (90–100)	39 (17–64)
Treated events of joint bleeding			
Annualized rate of bleeding events, model-based (95% CI)§	1.1 (0.6–1.9)	0.9 (0.4–1.7)	26.5 (14.7–47.8)
Rate ratio vs. control (95% CI)	0.04 (0.02–0.09)	0.03 (0.02–0.07)	—
Percent difference vs. control	–96‖	–97‖	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.9)	0.0 (0.0–1.3)	21.3 (14.5–41.3)
Percent of participants with 0 bleeding events (95% CI)	58 (41–74)	74 (57–88)	0 (0–18)
Percent of participants with 0–3 bleeding events (95% CI)	94 (81–99)	97 (85–100)	17 (4–41)
Treated events of target-joint bleeding¶			
Annualized rate of bleeding events, model-based (95% CI)§	0.6 (0.3–1.4)	0.7 (0.3–1.6)	13.0 (5.2–32.3)
Rate ratio vs. control (95% CI)	0.05 (0.02–0.14)	0.05 (0.02–0.15)	—
Percent difference vs. control	–95‖	–95‖	—
Median annualized rate of bleeding events (IQR)	0.0 (0.0–1.4)	0.0 (0.0–0.0)	12.8 (0.0–39.1)
Percent of participants with 0 bleeding events (95% CI)	69 (52–84)	77 (60–90)	28 (10–54)
Percent of participants with 0–3 bleeding events (95% CI)	97 (86–100)	97 (85–100)	39 (17–64)

Mahlangu, et al. N Eng J Med 2018;379:811-22.

Emicizumab Caveats

- Can treat bleeds with factor VIII (non inhibitor) and recombinant factor VIIa (inhibitor)
  - Would not use activated prothrombin complex concentrate due to risk of thrombotic microangiopathy and thrombosis
- Cannot draw standard coagulation labs (PTT, factor VIII activity, factor VIII inhibitor)
- Only for factor VIII deficiency. Cannot use for factor IX deficiency

Fitusiran

- Focuses more on thrombin generation
  - Does not focus on factor replacement therapy
- RNA interference molecule
  - Inhibits production of antithrombin
  - Makes patient antithrombin deficient

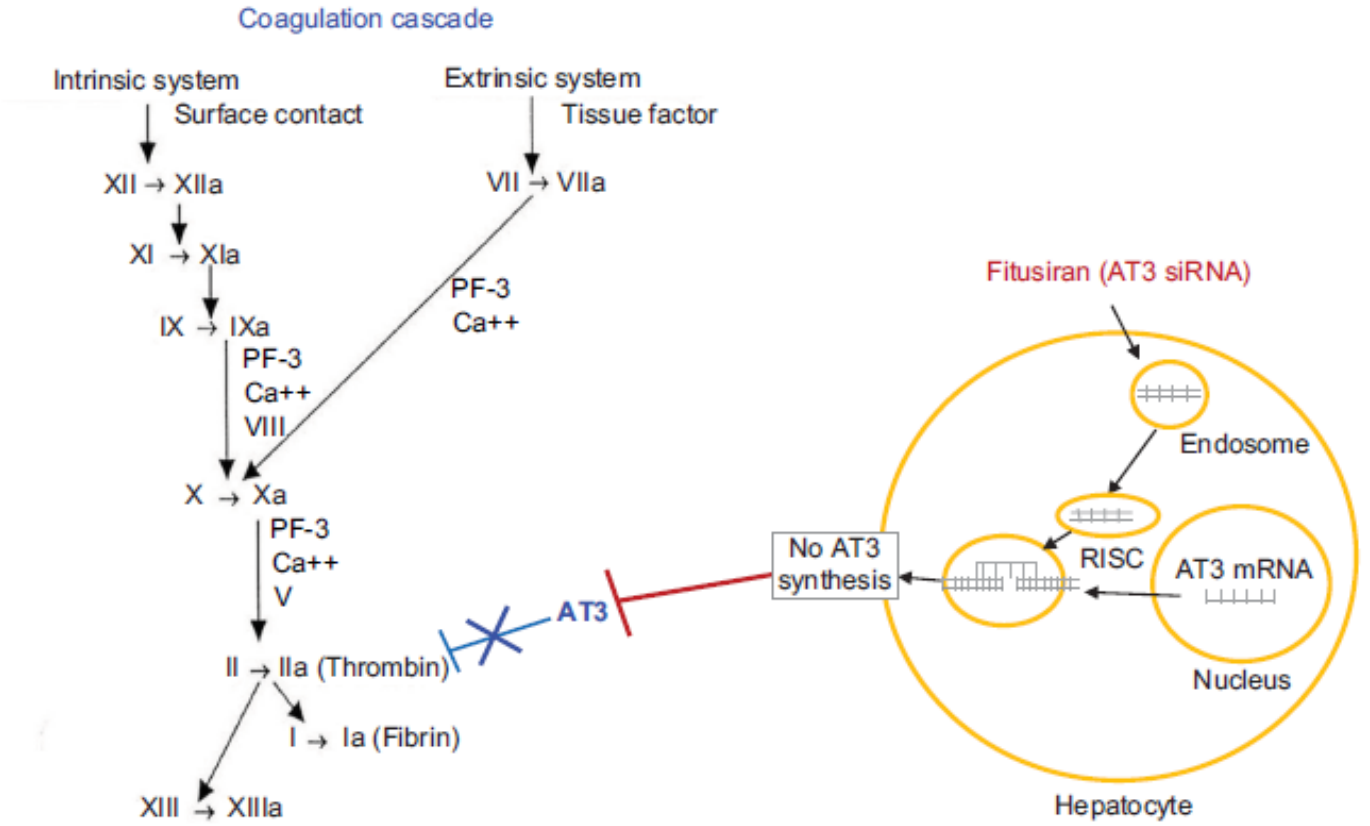
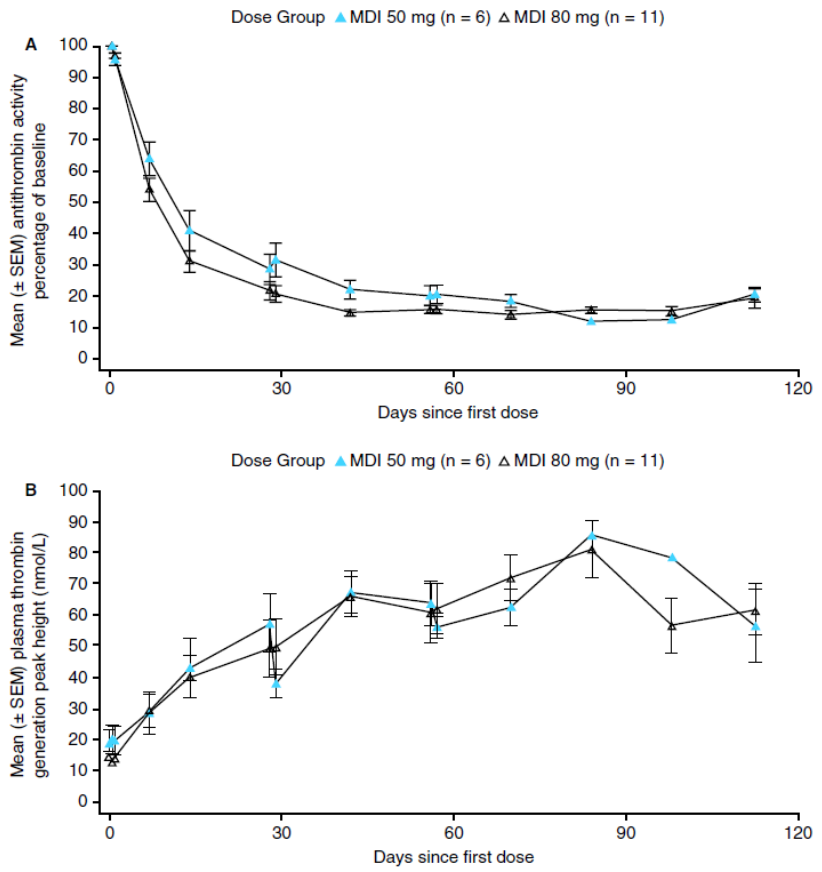


Figure 1 Site of action of fitusiran on coagulation cascade.
Note: Fitusiran is an RNAi therapeutic that targets AT in the liver and interferes with AT translation by binding and degrading mRNA-AT, silencing AT gene expression, and preventing AT synthesis.
Abbreviations: AT, antithrombin; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, RNA interference.

Machin, et al. J Blood Med 2018:9 135-140.



) Effect of fitusiran on AT activity. Mean (± SEM) percentage of AT activity relative to baseline[a] in participants with
B with inhibitors receiving fitusiran once monthly. (B) Mean (± SEM) plasma thrombin generation peak height (nmol/L)
siran dose group. [a]As baseline AT levels may vary between individuals, percentage of AT activity for each participant was
/e to individual participant baseline measurements. Baseline measurements are the average of all predose measurements
f first dose excluding optional predose PK visits. The mean of these individual AT activity measurements is presented.
:T, antithrombin; MDI, multiple dose with inhibitors; PK, pharmacodynamics; SEM, standard error of the mean

Pasi, et al. J Thromb Haemost. 2021;19:1436-1446.

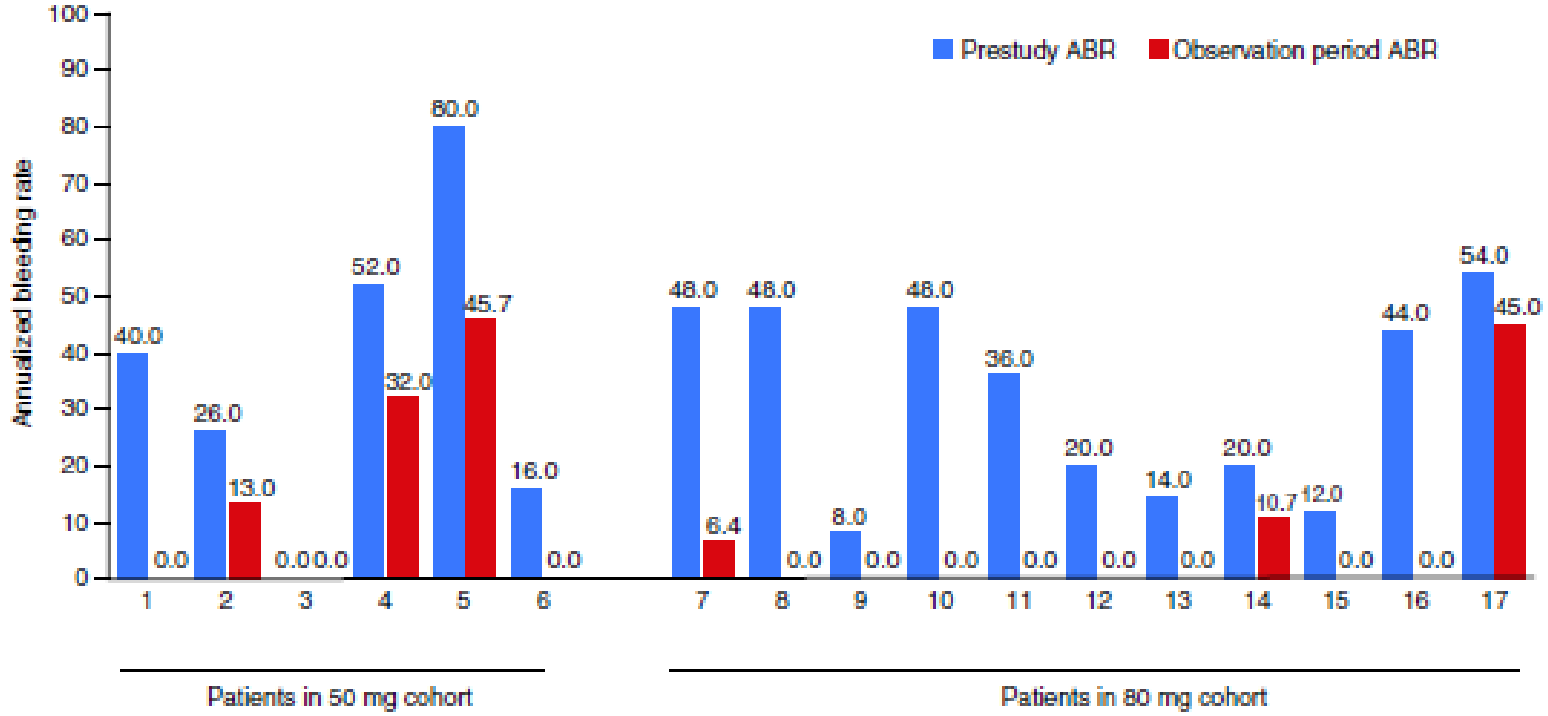


FIGURE 3 ABR during monthly fitusiran treatment in individual participants with hemophilia A or B with inhibitors. Prestudy ABR was calculated as the occurrence of clinically significant bleeds based on 6-month history multiplied by 2. Observation period ABR was estimated by the number of poststudy drug treatment bleeding episodes that occurred from day 29 until 8 weeks after the last dose of fitusiran. Abbreviation: ABR, annualized bleeding rate

Pasi, et al. J Thromb Haemost. 2021;19:1436-1446.

Fitusiran

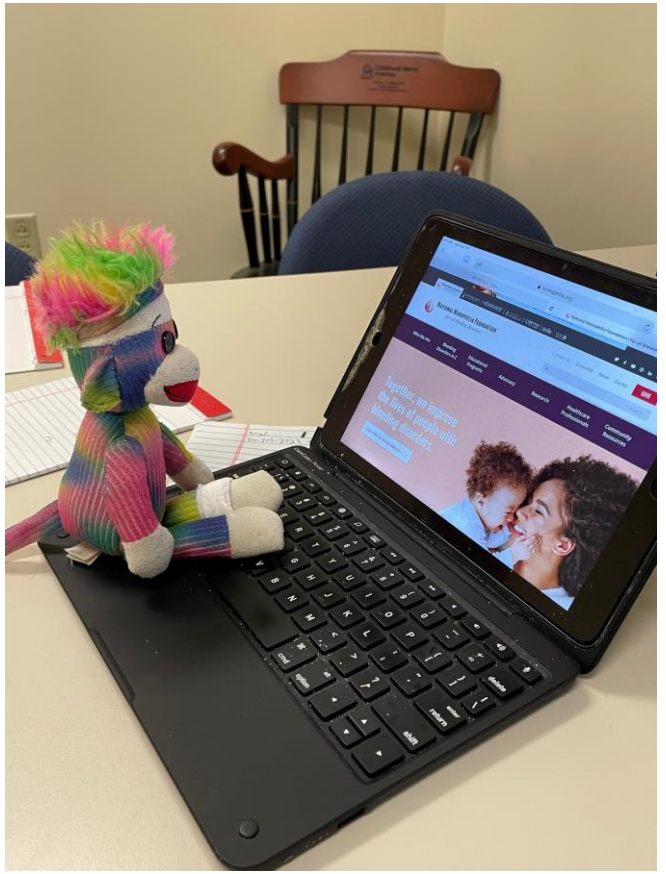
- Subcutaneous Injection
- Given Monthly
- Still in Phase 2/3 trials at this time
- Can be used for both factor VIII and IX deficiency as well as rare bleeding disorders

Chuckles

- Chuckles was started on emicizumab and has tolerated this well
- Has not been having any bleeding symptoms
- Has moved to every other week therapy

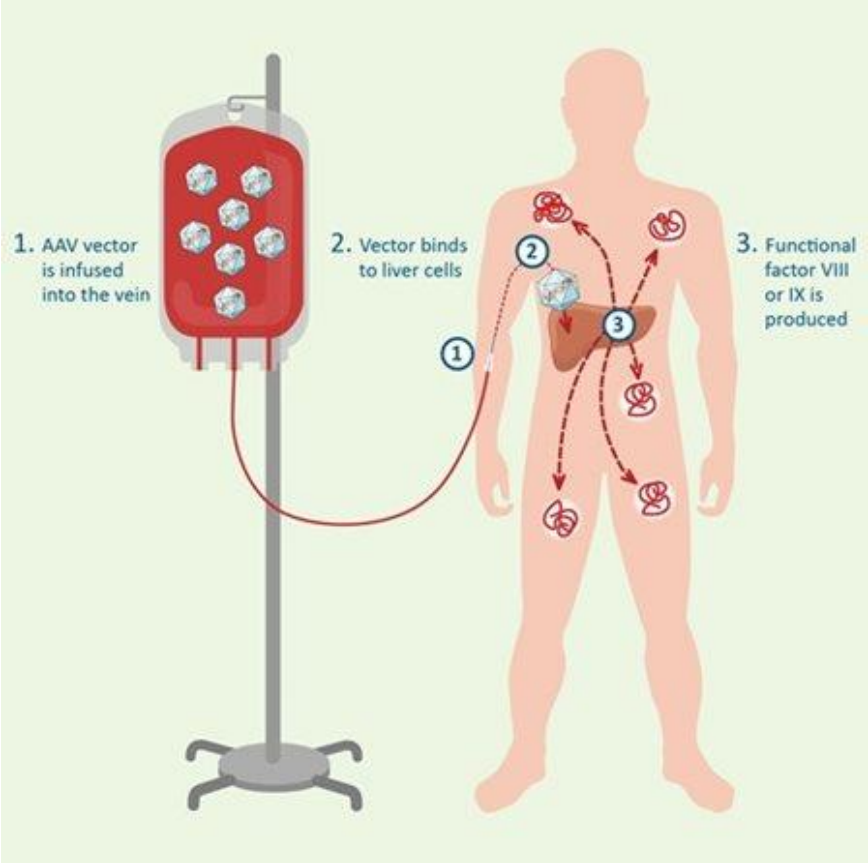
Chuckles

- Chuckles is now in college and is tired of having to take medicines
- Has been doing a lot of online research
- Would like to discuss possibilities of gene therapy



Gene Therapy

- Place factor VIII/IX transgene within an engineered AAV vector
- Give AAV vector molecules to patient through an IV
- Vectors infect hepatocytes
- Hepatocytes would then produce factor protein



Factor VIII gene therapy

- Long term data published on 15 patients recently
- Received varied doses of AAV vector
  - 1pt received $6x10^{12}$ viral genomes per kg→ 3 year data reported
  - 1pt received $2x10^{13}$ viral genomes per kg→ 3 year data reported
  - 7pts received $6x10^{13}$ viral genomes per kg→ 3 year data reported (cohort 3)
  - 6pts received $4x10^{13}$ viral genomes per kg→ 2 year data reported (cohort 4)

Pasi, et al. N Eng J Med. 2020;382:29-40

Factor VIII gene therapy

- Pts 1 and 2 had factor expression <1IU/dL
- Cohort 3 had median factor expression of 20IU/dL
- Cohort 4 had median factor expression of 13IU/dL

Pasi, et al. N Eng J Med. 2020;382:29-40

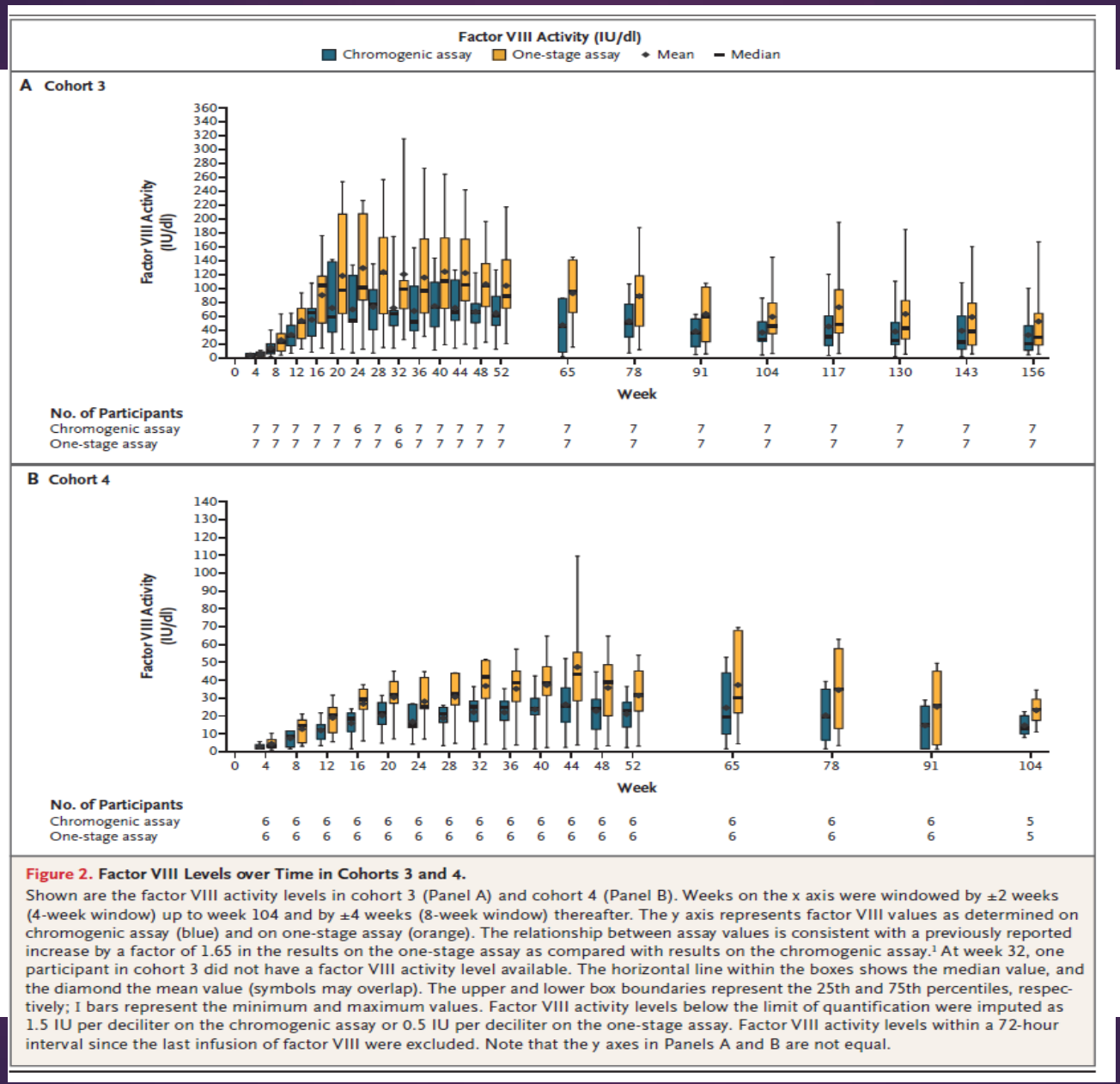
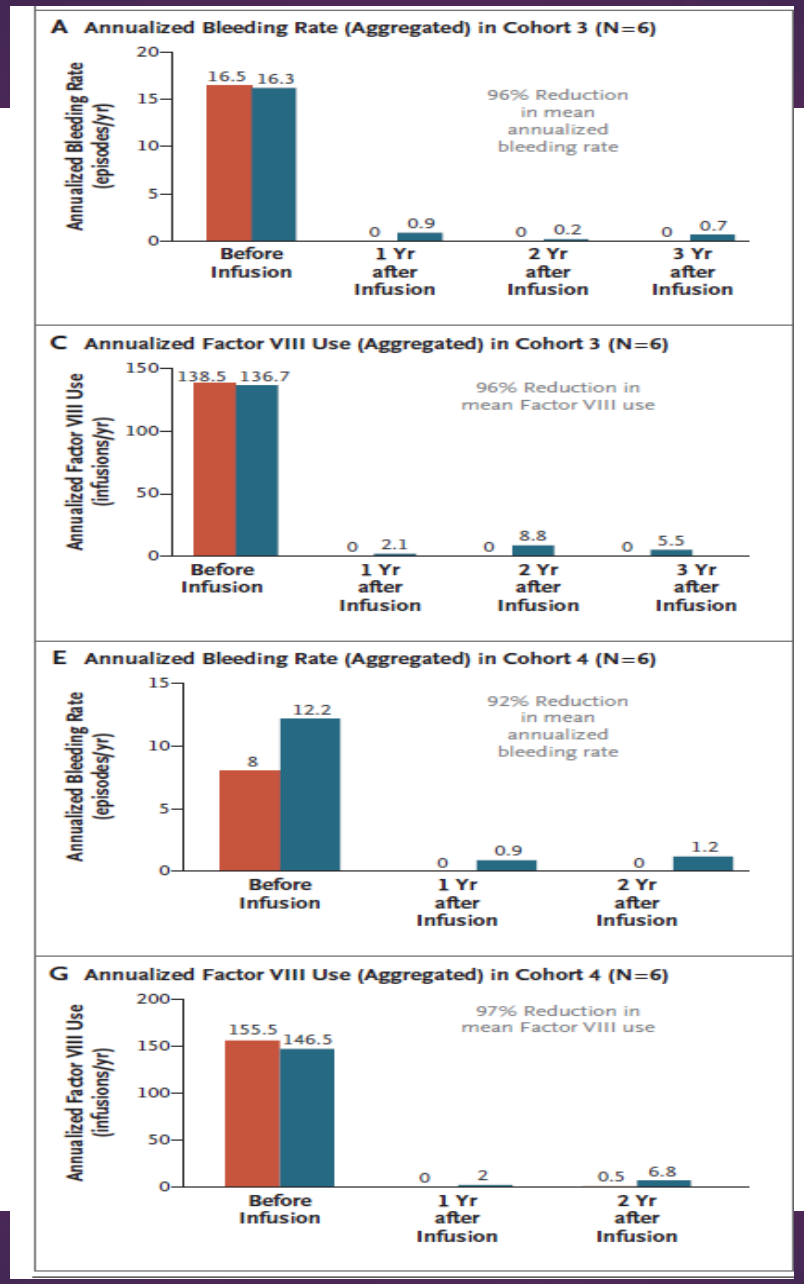


Figure 2. Factor VIII Levels over Time in Cohorts 3 and 4.

Shown are the factor VIII activity levels in cohort 3 (Panel A) and cohort 4 (Panel B). Weeks on the x axis were windowed by ±2 weeks (4-week window) up to week 104 and by ±4 weeks (8-week window) thereafter. The y axis represents factor VIII values as determined on chromogenic assay (blue) and on one-stage assay (orange). The relationship between assay values is consistent with a previously reported increase by a factor of 1.65 in the results on the one-stage assay as compared with results on the chromogenic assay.[1] At week 32, one participant in cohort 3 did not have a factor VIII activity level available. The horizontal line within the boxes shows the median value, and the diamond the mean value (symbols may overlap). The upper and lower box boundaries represent the 25th and 75th percentiles, respectively; I bars represent the minimum and maximum values. Factor VIII activity levels below the limit of quantification were imputed as 1.5 IU per deciliter on the chromogenic assay or 0.5 IU per deciliter on the one-stage assay. Factor VIII activity levels within a 72-hour interval since the last infusion of factor VIII were excluded. Note that the y axes in Panels A and B are not equal.

Pasi, et al. N Eng J Med. 2020;382:29-40



Pasi, et al. N Eng J Med. 2020;382:29-40

Factor IX gene therapy

- AAV viral vector used
- Factor IX transcript used is from highly active variant
  - Factor IX padua
- IV infusion of $5x10^{11}$ viral genomes per kg
- Followed for 52 weeks

George, et al. N Eng J Med 2017;377:2215-27.

Factor IX gene therapy

- Factor IX activity was observed within 1wk of infusion
- Steady state factor expression reached within 14wks of infusion
- Mean factor IX activity was 33.7% +/- 18.5%

George, et al. N Eng J Med 2017;377:2215-27.

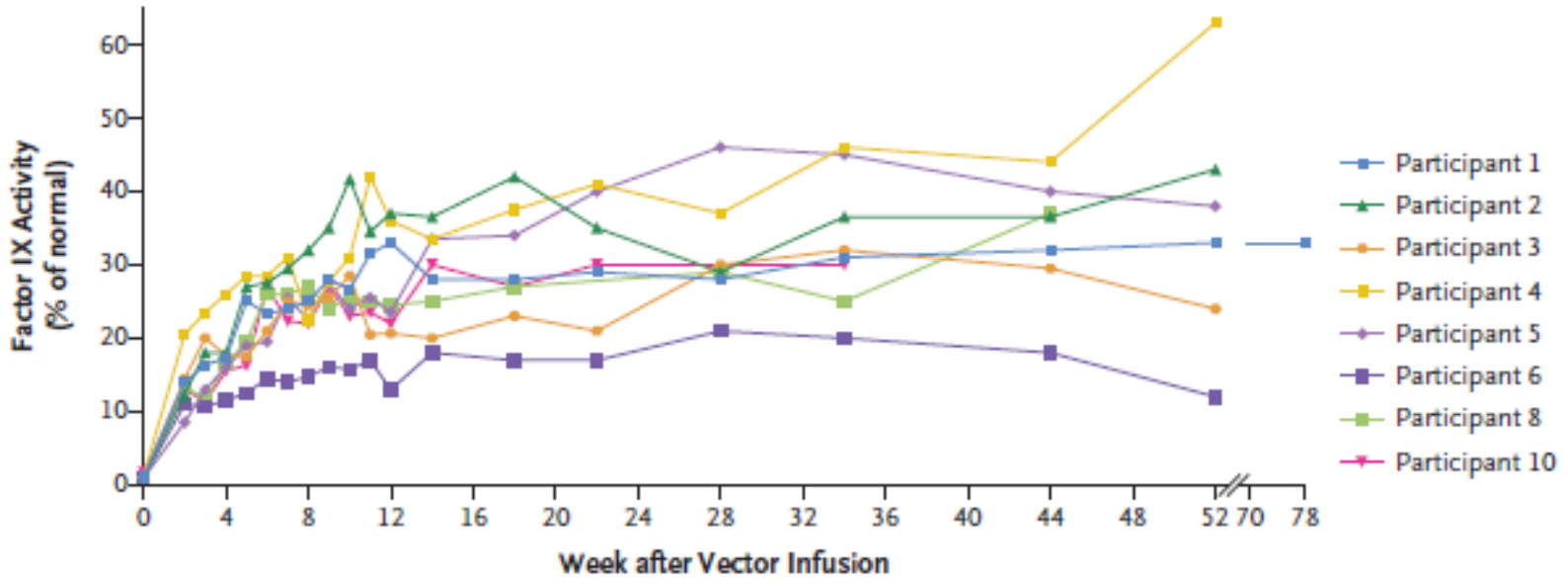
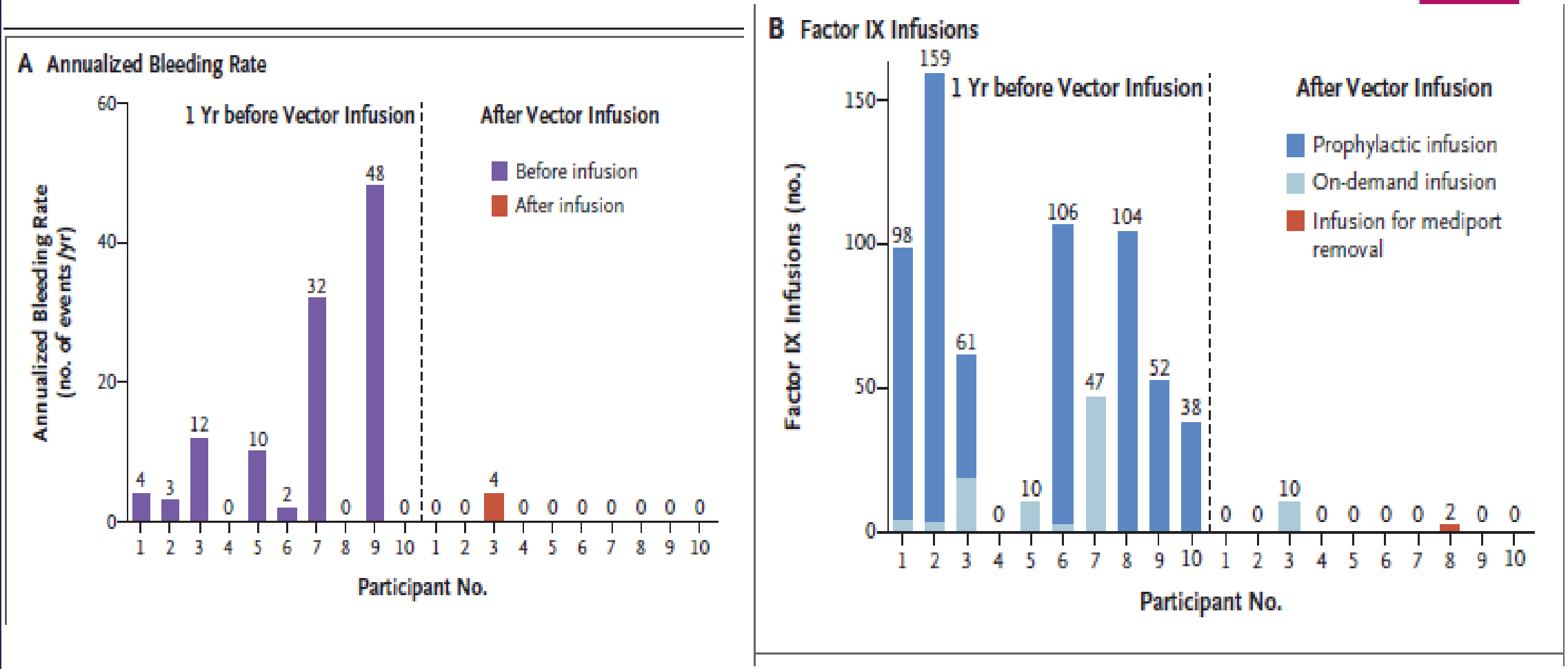


Figure 1. Factor IX Activity after One Peripheral Infusion of SPK-9001 in the Eight Participants Who Did Not Have an Adeno-Associated Viral Capsid-Directed Immune Response.

The vector SPK-9001 was administered at a dose of 5×10^{11} vector genomes per kilogram of body weight.

George, et al. N Eng J Med 2017;377:2215-27.



George, et al. N Eng J Med 2017;377:2215-27.

Gene therapy questions

- Antibody to viral vector?
- Long term data regarding efficacy and safety
- Cost

End of the Journey(?)

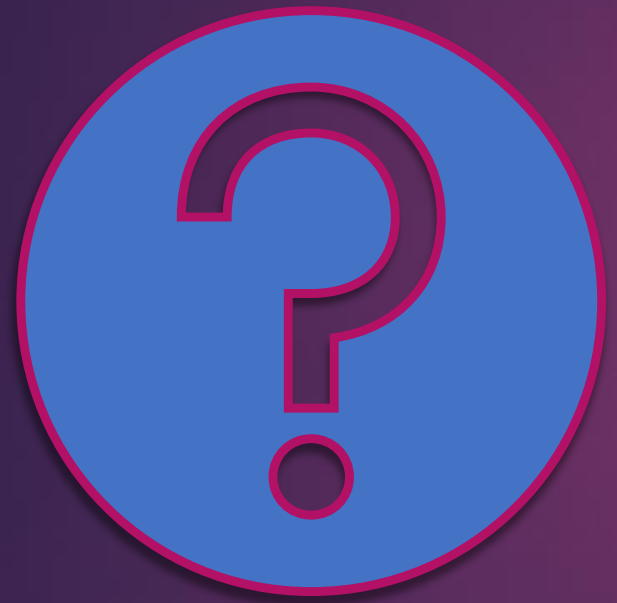
- Chuckles looking into joining a gene therapy trial in hopes of possibly curing his hemophilia
- Continues to travel the world

Conclusions

- Hemophilia therapy is rapidly evolving
- Factor replacement is still the mainstay of treatment, though changing
- Non-factor products playing an ever-growing role in treatment
- Gene therapy is right around the corner

Kansas City HTC

- ~800 pediatric and adult patients
- 4 Outreach clinic sites in addition to Adele Hall
  - Joplin, Wichita, Springfield, Dodge City
- Large staff
  - 5 physicians, 2 NPs, 2 RNs, social worker, data manager, program manager, admin assistant, and 3 research coordinators
- Multiple research studies



Questions