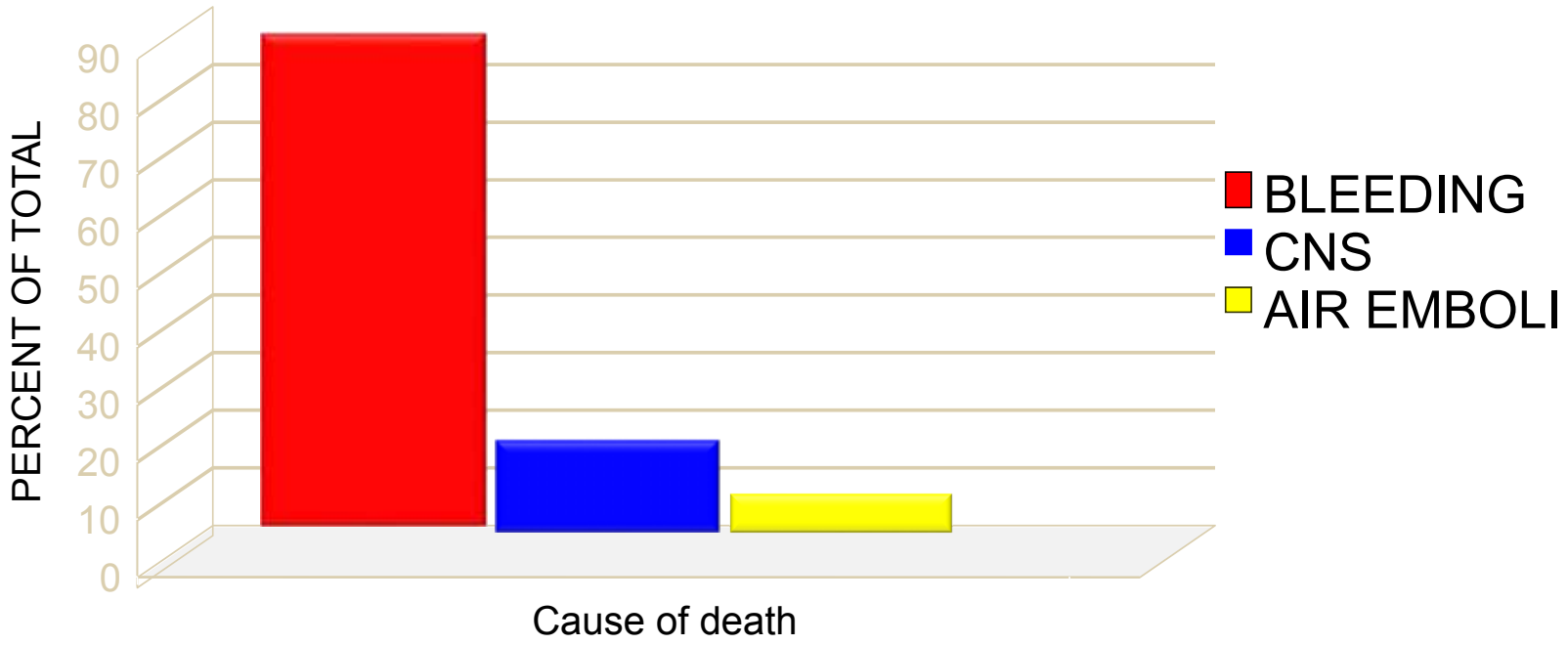
An Approach to bleeding

Johnny Mahlangu
Haemophilia Comprehensive Care Centre
Charlotte Maxeke Johannesburg Hospital and
Department of Molecular Medicine and Haematology
NHLS and University of the Witwatersrand, Johannesburg

Death in the Emergency



Hoyt *et al*. J Trauma *1994;37:426*.

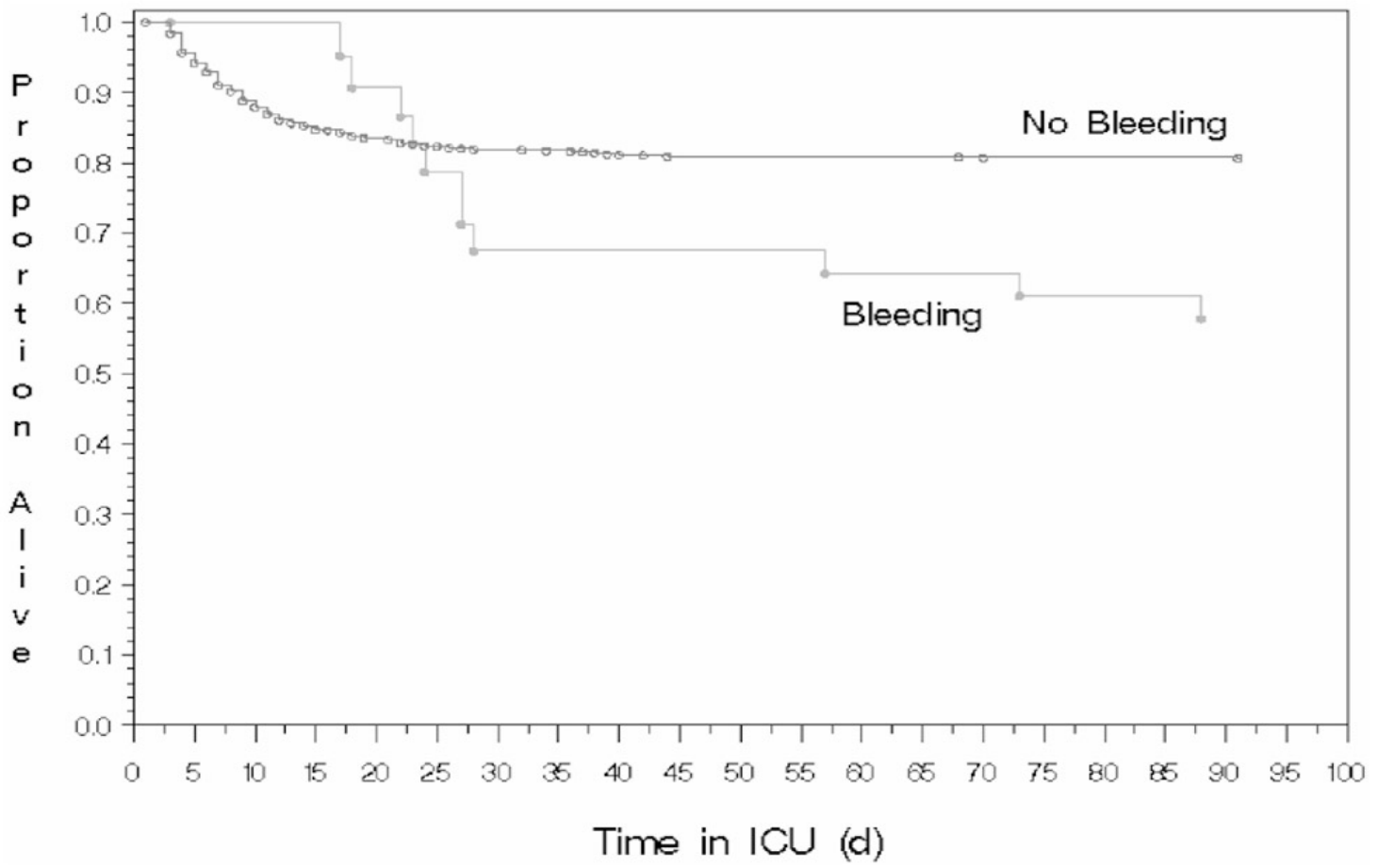
First 24 hr bleeding is an Independent Predictor

- Mortality
- ICU Admission
- ICU LOSS

(After Controlling for ISS;GCS; Age; Gender; Anemia ;Shock ,Lactate; Base Deficit; Shock Index HR/SBP>0.6)

Malone L *et al. J Trauma 2003;54:898-907*

ICU mortality



Cook *etal Critical care 2001; 5(6):368-375*

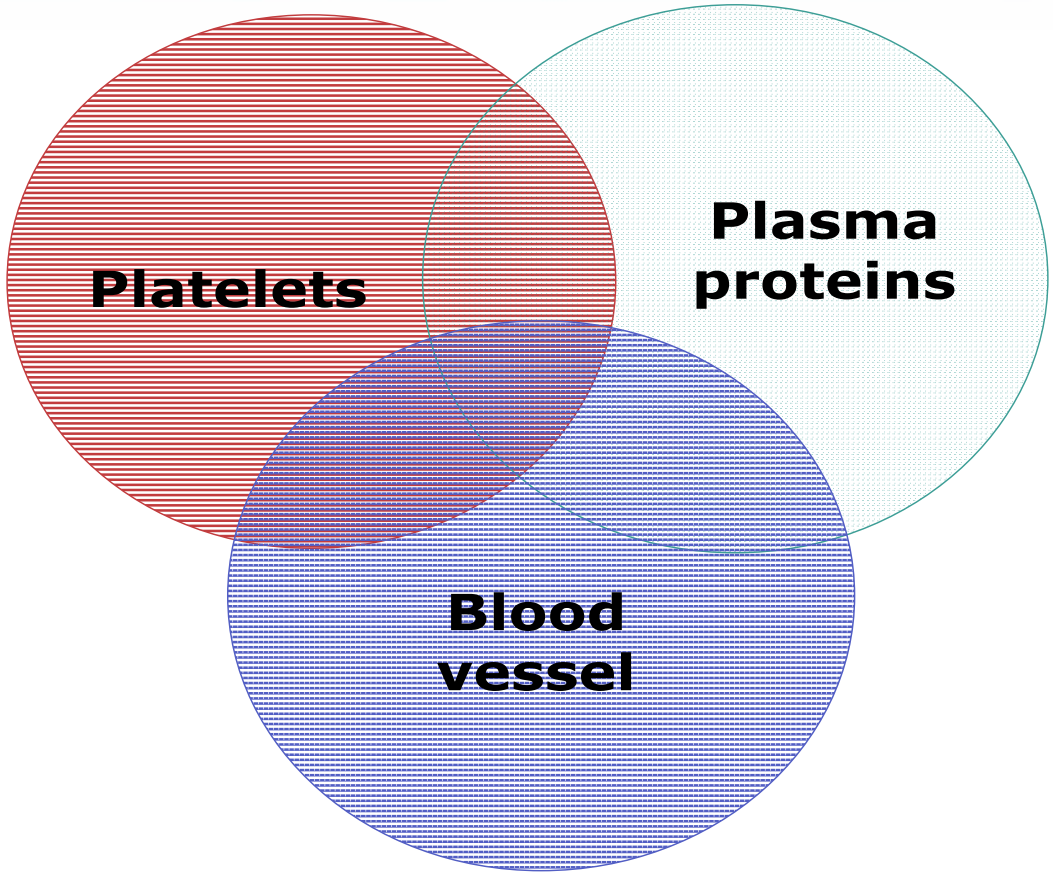
Which bleeding disorders?

Bleeding frequency and bleeding recurrence is more common in inherited bleeding disorders than acquired bleeding disorders

In this talk….

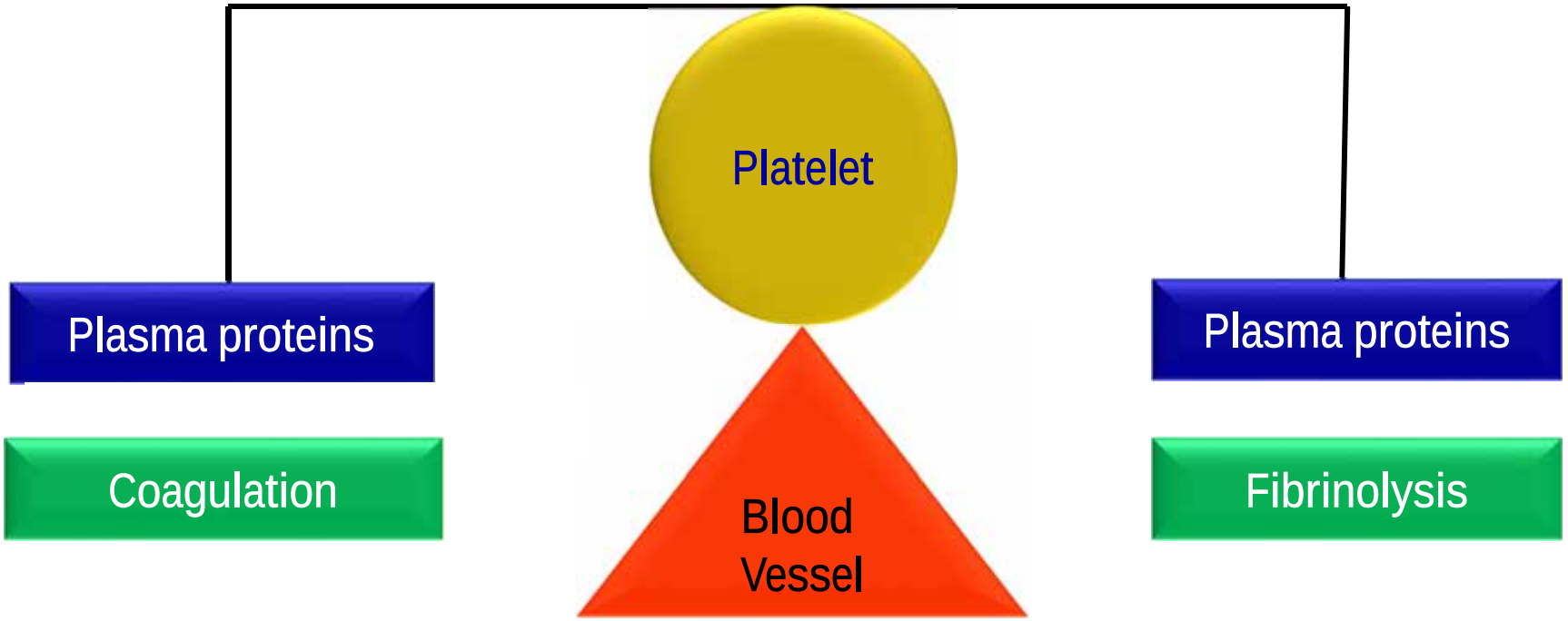
- Mechanism of haemostasis
- Aetiology of inherited bleeding
- Evaluation of inherited bleeding
- Principles of management of bleeding

Pathophysiology of bleeding

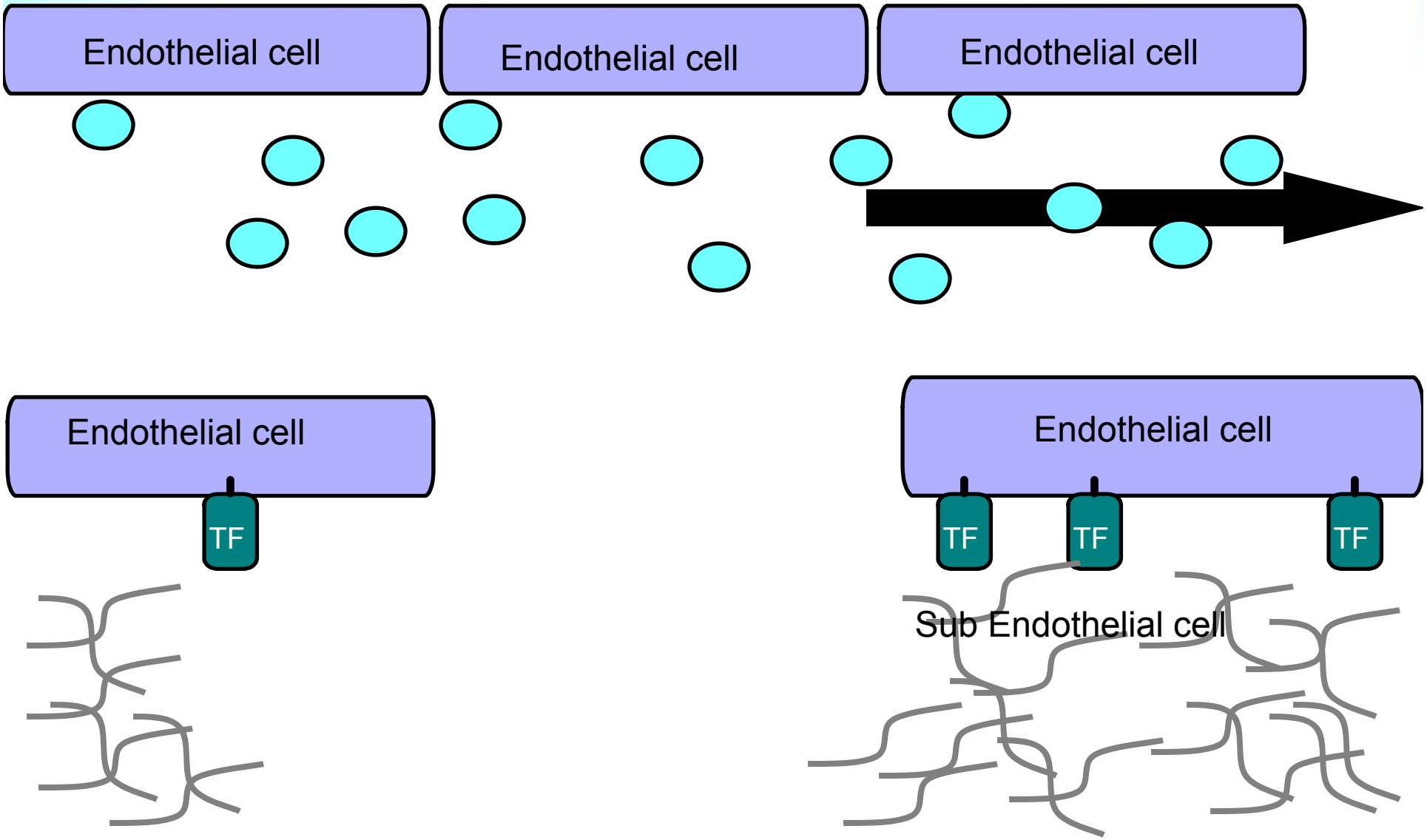


Any bleeding is a direct consequence of one or more of these three factors

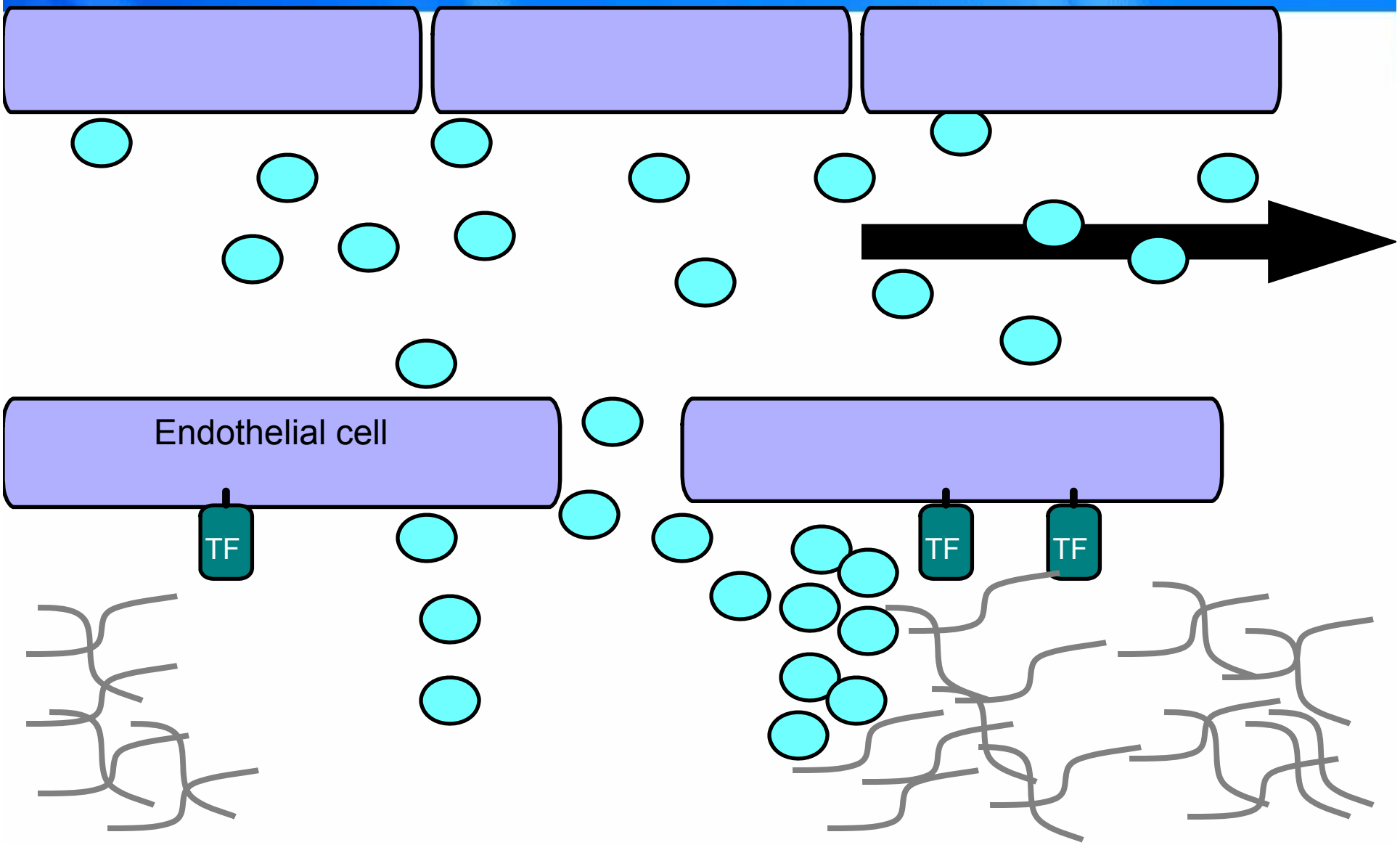
Haemostatic balance



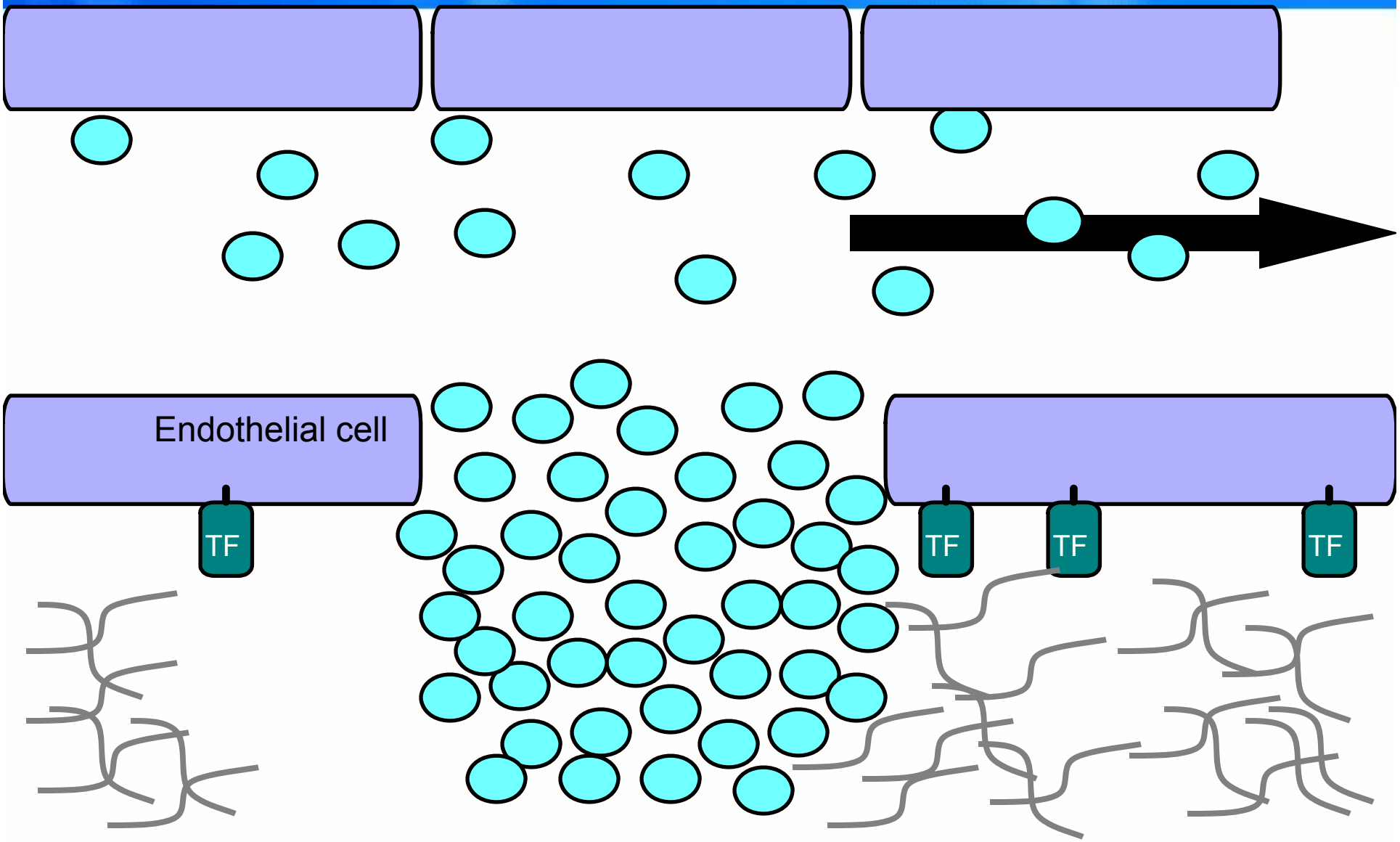
Vessel injury



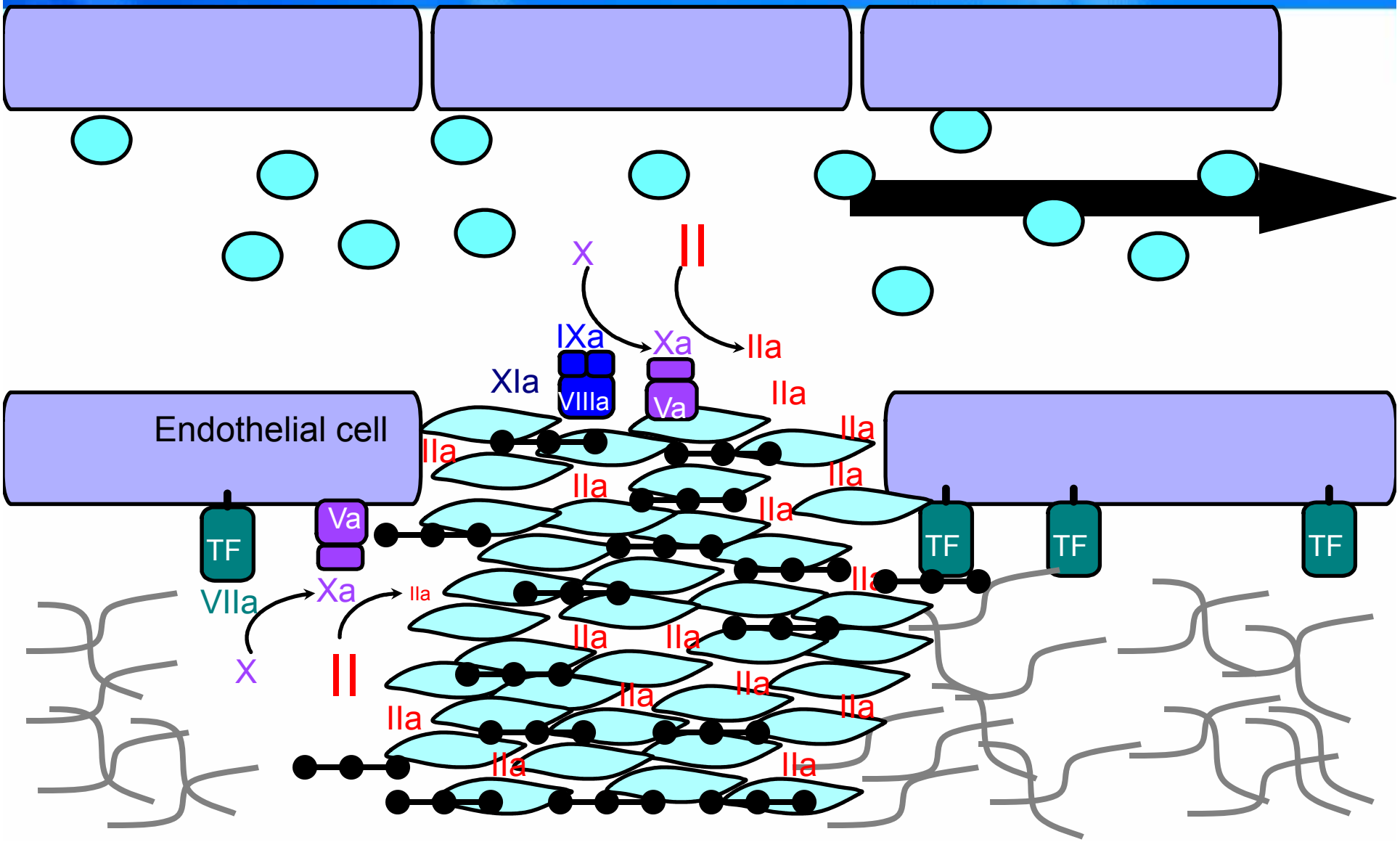
Vasoconstriction



Platelet plug



Blood Clot


X
II
IXa
Xa
IIa
XIa
VIIIa
Va
IIa
IIa
IIa
IIa
IIa
IIa
Endothelial cell
TF
Va
TF
TF
TF
VIIa
Xa
IIa
X
II
IIa
IIa
IIa
IIa
IIa
IIa
IIa

Outline

- Mechanism of haemostasis
- **Aetiology of bleeding**
- Evaluation of bleeding
- Management of bleeding patient

Blood vessel abnormalities

Altered vessel wall

- Kasabach Merrit
- Hereditary haemmorhagic telangiectasia

Connective tissue

- Marfan syndrome
- Ehlers Danlos
- Pseudoxanthoma
- Scleroderma

Congenital blood vessel abnormalities are very rare

Inherited platelet disorders

- Adhesion
- Aggregation
- Signal transduction
- Granular secretion
- Cytoskeletal changes

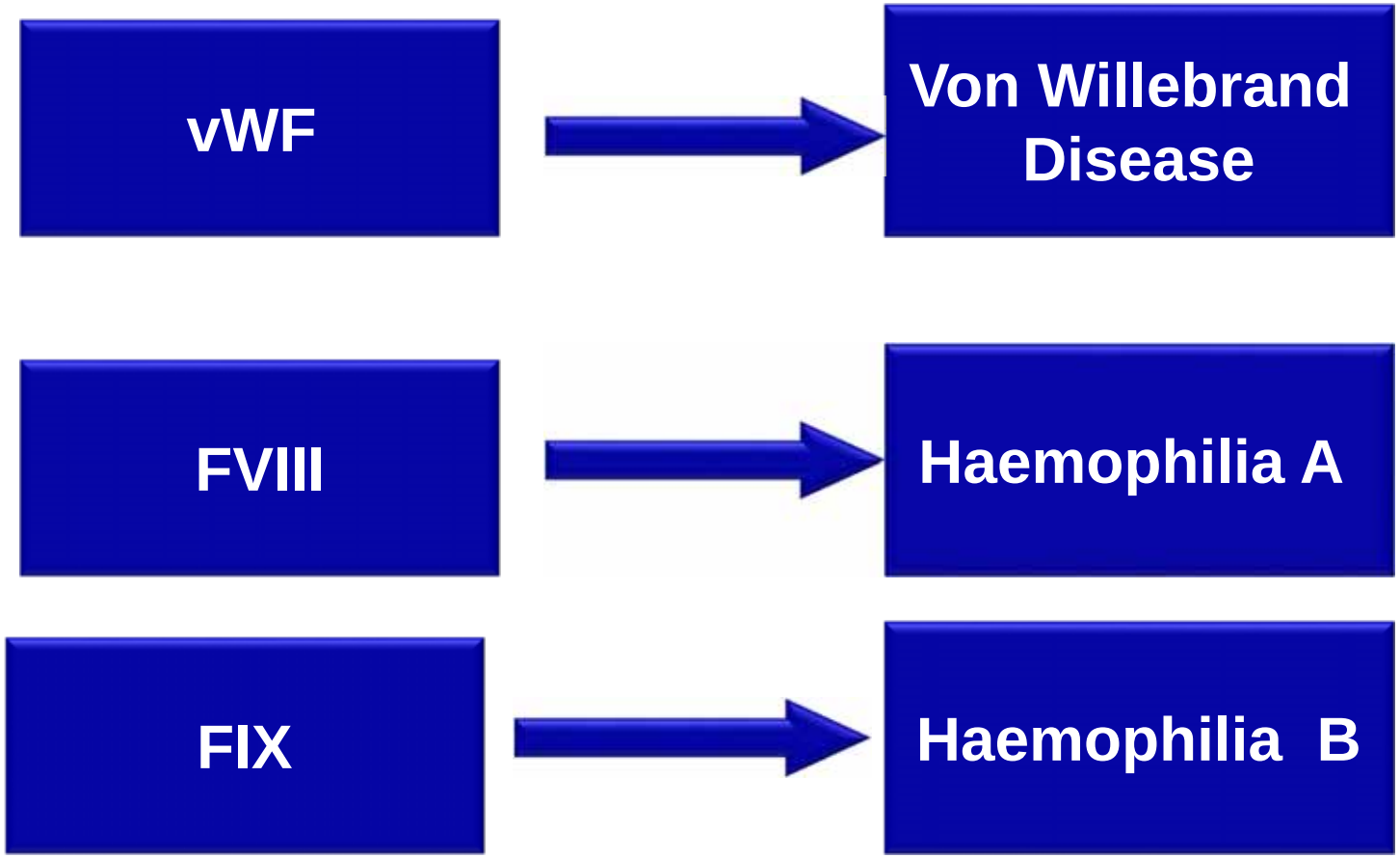
Inherited platelet disorders

Adhesion	• Bernard Soulier
Aggregation	• Glanzman's thrombasthenia
Signal transduction	• TS deficiency, cyclooxygenase
Granules	• Hemansky pudlac; GPS
Cytoskeletal	• Wiskott Aldrich
Primary secretion	• TVA2, ADP, Epinephrine
Production	• MYH9; TWAR

Congenital Plasma proteins

Plasma protein	Inheritance	Prevalence
Factor I	AR/AD	Rare
Factor II	AD	Rare (extremely)
Factor V	AR	1 /1000 000 births
Factor FVII	AR	1/500 000 births
Factor FVIII	X linked	1/10 000 male births
Factor IX	X linked	1/60 000 male births
Factor X	AR	1/500 000 births
Factor XI	AD	4% AJ, rare otherwise
Factor XIII	AR/AD	Rare
vWF	AR/AD	1/100

Congenital Plasma proteins



Outline

- Pathophysiology of haemostasis
- Aetiology of bleeding
- **Evaluation of bleeding**
- Management of bleeding

Bleeding evaluation

- History
- Physical examination
- Screening tests
- Confirmatory tests

Bleeding evaluation

History

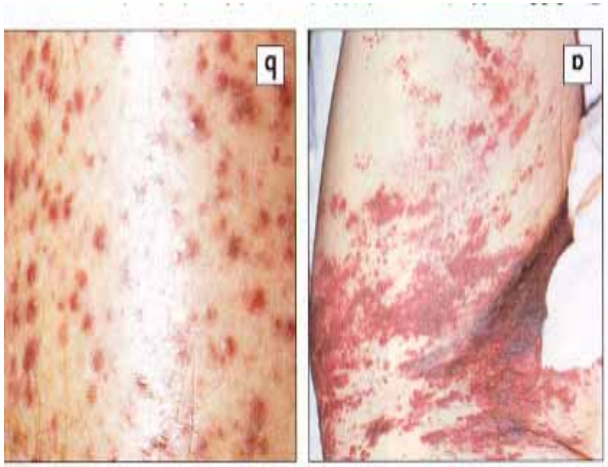
- Main differential diagnosis
- Congenital or acquired
- Drugs

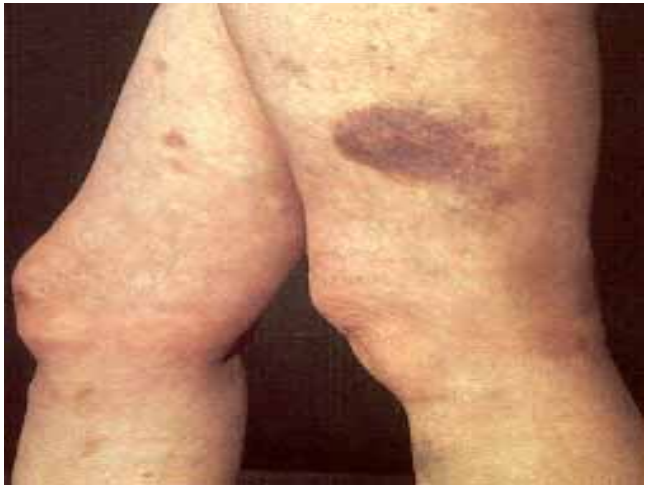
Bleeding evaluation

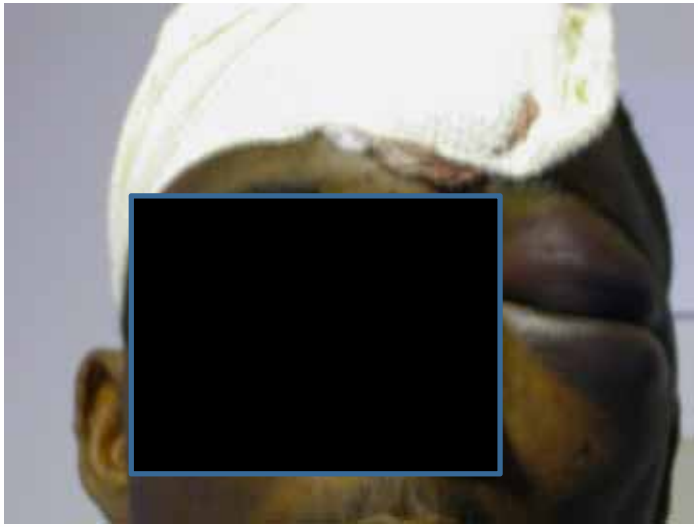
History

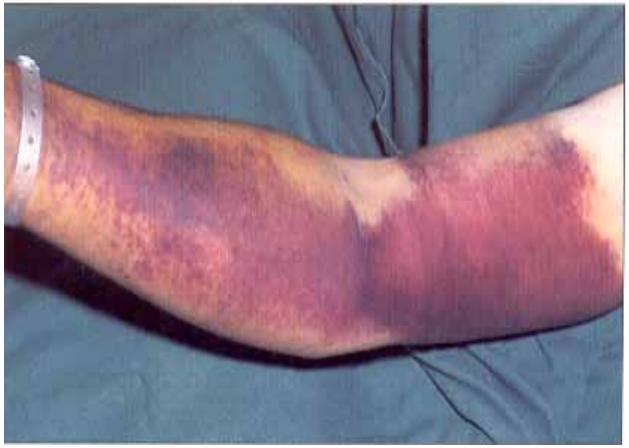
- Type of bleed
- Extent of bleed
- Site
- Amount
- Spontaneous or induced
- Immediate or delayed

Skin bleed

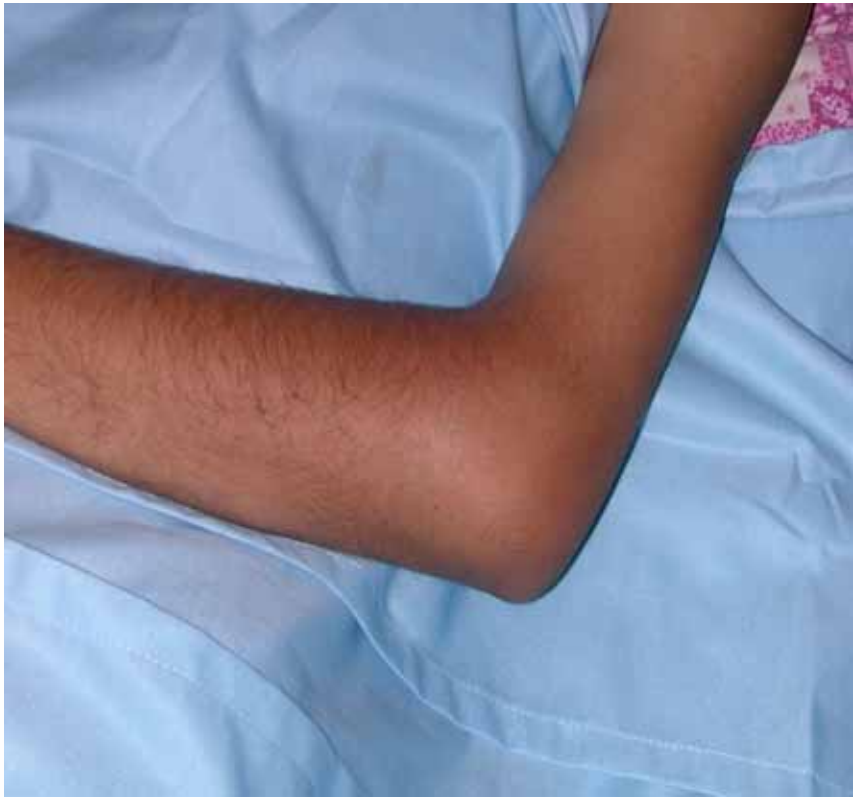




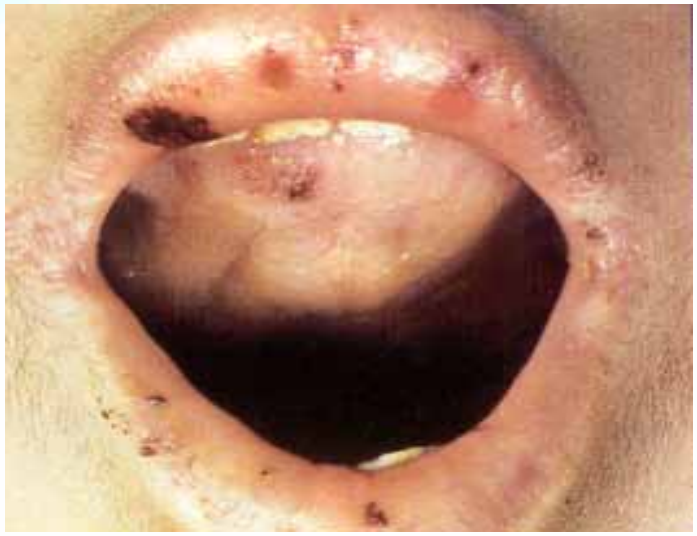


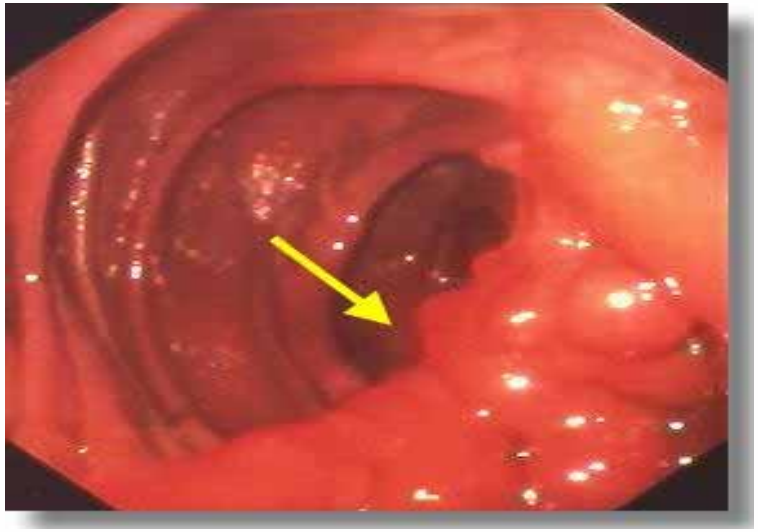


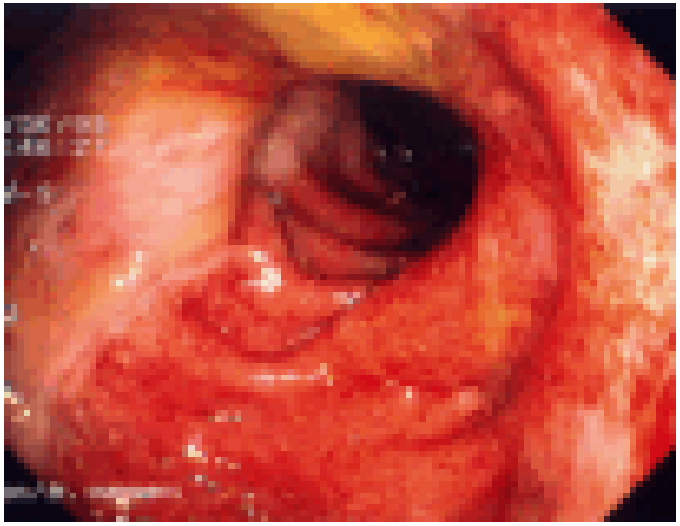
Joint bleed

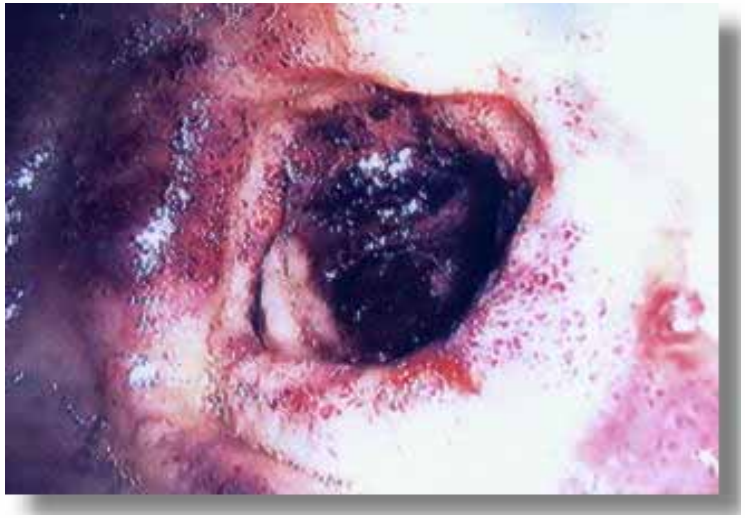


Mucous membrane bleed

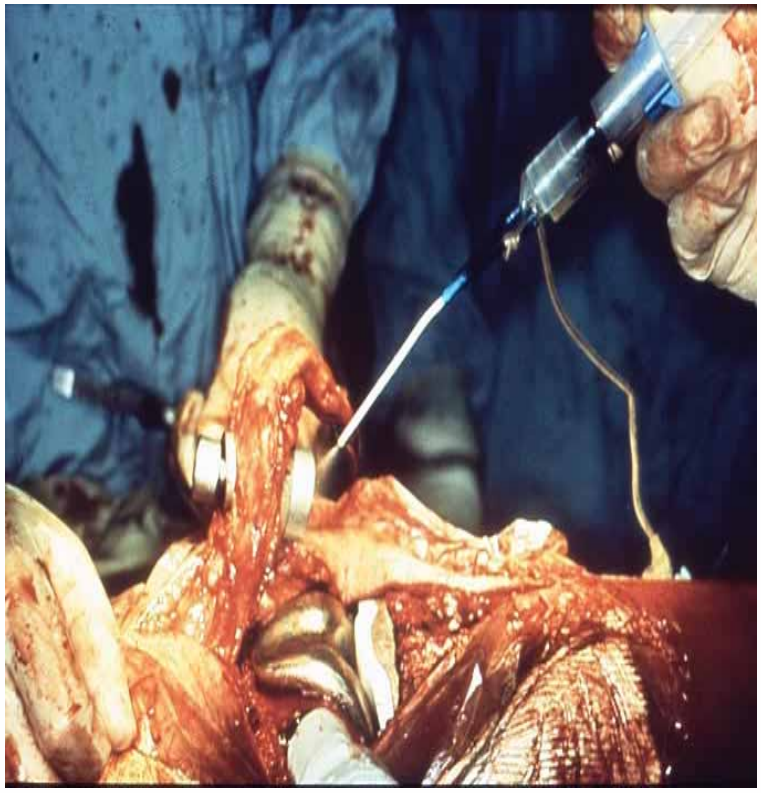








Traumatic bleed



Bleeding evaluation

Examination

- Pallor , jaundice
- Petechaie, purpura, ecchymoses,
- Haemarthrosis, haematomas
- Melaena, haematochezia
- Neuropathy, blindness, respiratory compromise

Who to test?

- Definite family history
- Spontaneous bleeding
- Induced uncontrolled bleeding
- Life threatening bleed
- Minor recurrent bleed
- Prior to major surgery
- Prior to biopsy or invasive procedure

Von Willebrand Disease

Von Willebrand disease(vWD)

Definition

- Commonest inherited heterogeneous group of bleeding disorders
- Due to mutation in vWF gene
- Resulting in qualitative and/or quantitative deficiency of Von Willebrand factor
- May or may not present with bleeding

vWD - Prevalence

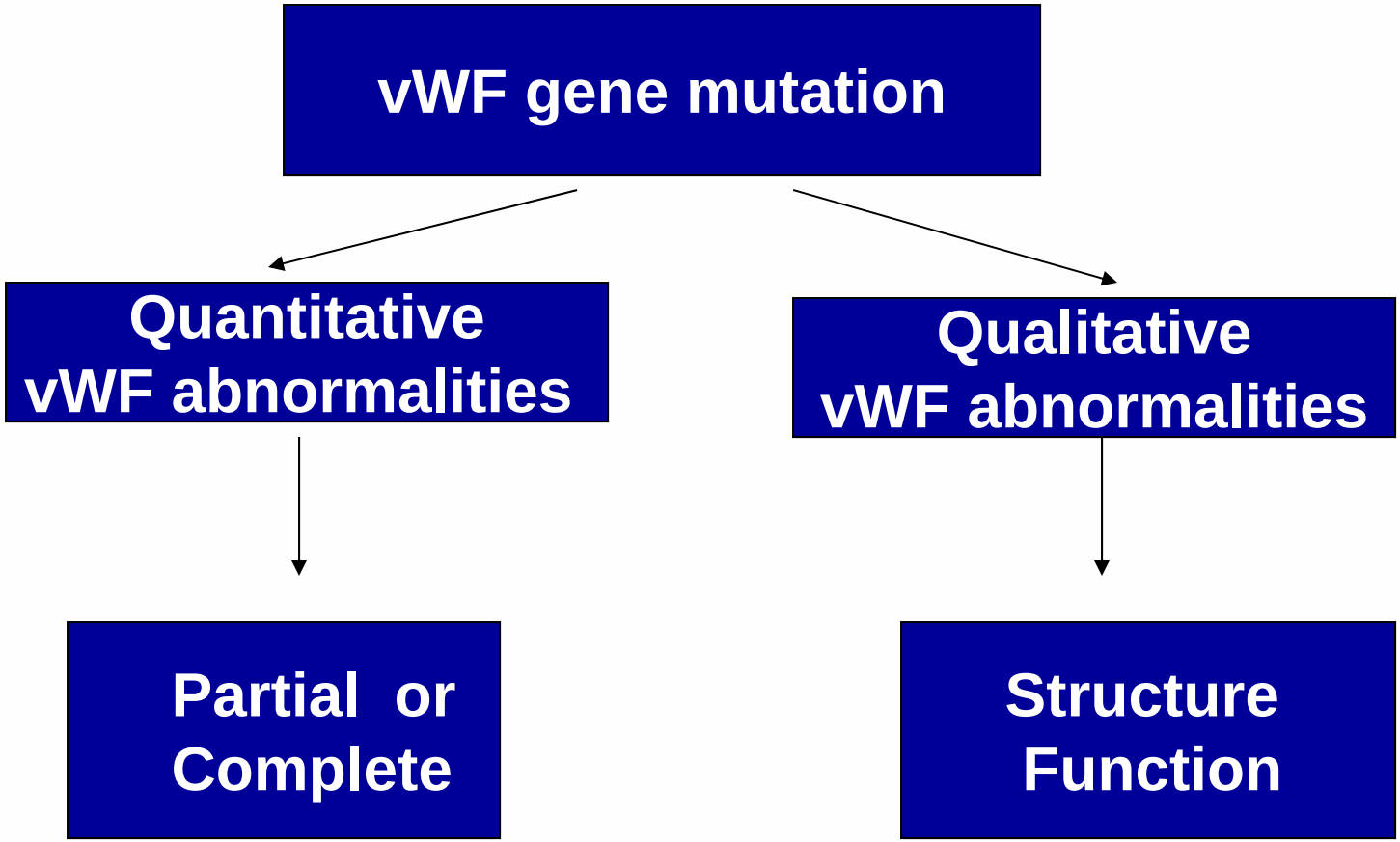
Estimated frequency

- 1 in 100
- No race, sex or age predilection

Accurate prevalence estimation precluded

- Variable expressivity
- Reduced penetrance
- New mutations

vWD -Aetiology



vWD - Classification

	Abnormality	vWD Type
Quantitative	Partial absence	1
	Total absence	3
Structure	Abn assembly/secretion	2A1
	Multimer proteolysis	2A2
Function	↑binding to platelets	2B
	↓binding to platelets	2M
	↓binding to FVIII	2N

vWD – frequency

	Frequency	Inheritance mode
Type 1	70-80%	AD
Type 2	20-30%	AD/AR
Type 3	<5%	AR

vWD- clinical features

Mucocutaneous bleeding

Symptom	Frequency(%)
Epistaxis	60
Dental surgery	50
Easy bruising	40
Menorrhagia	35
Gum bleeding	35
Post[artum	25
Postoperative	20
GIT bleeding	10

Diagnostic Testing

Tests to establish the diagnosis

1-vWF antigen

2- vWF:R:Co

3- Factor VIII

4-PTT

5-Bleeding time

Tests to subtype vWD

1- RIPA

2-Multimer analysis

3-vWF- Factor VIII binding (Type 2N)

Diagnostic Typing

	Type 1	Type 2	Type 3
vWF-Ag	40-60	N	0
vWF-Activity	decreased	N	decreased
Factor VIII	40-60	N	2-3%
PTT	Normal	N	Prolonged
Bleeding time	Prolonged	N	Prolonged

Diagnostic subtyping

	HMW MULTIMER	RIPA	FVIII
2A	Absent	Decreased	Normal
2B	Normal	Increased	Normal
2M	Normal	Decreased	Normal
2N	Normal	Normal	Reduced

Treatment of vWD

Non replacement therapy

- DDAVP
- Antifibrinolytic therapy
- Oestrogen therapy

Replacement therapy

- vWF plasma concentrate
- Cryoprecipitate
- Recombinant vWF

The Haemophilias

Classification

Factor level

- Factor <1% -Severe
- Factor 2-5% -Moderate
- Factor >5-50% -Mild
- Factor >50% -Normal

Note

- Biochemical-clinical phenotypic discrepancy

Clinical features

Haemmorrhagic manifestation

- Severe -Bleed spontaneously
- Moderate -Bleed with minor trauma
- Mild -Bleed with surgery or trauma

Sites of bleeding

- Joints - knees > ankles > elbows >shoulder > wrist > hips
- Muscles - Psoas muscle, quadratus,
- Mucous membranes- oral, nasal, GIT, GUT
- Organ systems – GUT, GIT, CNS,

Laboratory Diagnosis

Screening tests

- INR
- PTT
- Platelet count
- Hess test /bleeding time

Confirmatory tests

- Correction studies
- Factor assay
- Inhibitor assay
- Genetic family studies

Differential diagnosis

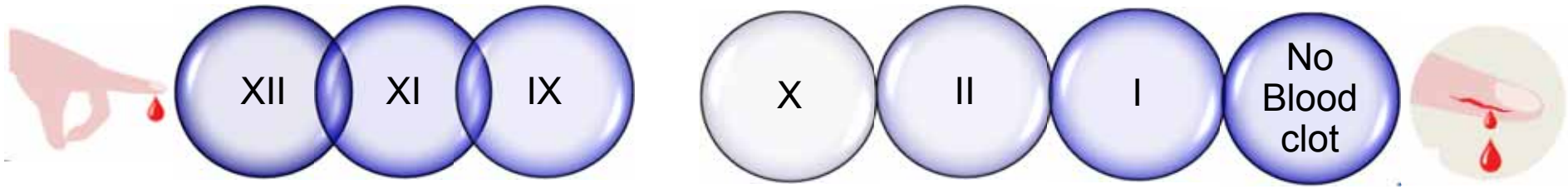
	Coagulation defect	Plt / capillary defect
Bleeding onset	Spontaneous	Induced
Site of bleeding	Joints/muscles	Skin/ mucous
Type of bleeding	Haemarthrosis/ haematoma	Petechiae/echymoses/ purpura
Time to onset	Delayed	Immediate
INR/PTT	Prolonged	Normal
Bleeding time	Normal	Prolonged
Platelet count/fx	Normal	Abnormal

Principles of Management

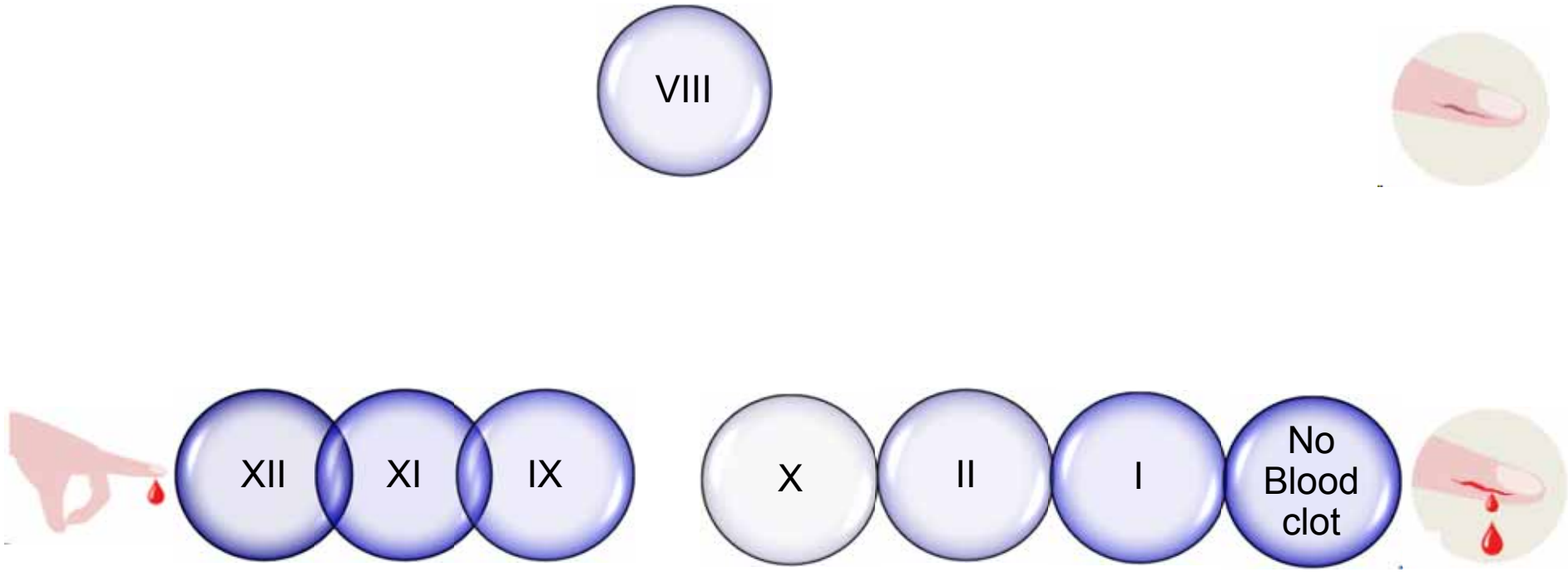
- Treat bleeds with specific product
- Treat bleeds early
- If in doubt, treat
- Treat veins with care
- Avoid product causing platelet dysfunction
- Avoid intramuscular injections
- Do not aspirate joints before treatment
- Apply local measures
- Multidisciplinary approach

Advances in management of bleeding disorders

Standard of care is replacement of missing clotting factor



Standard of care in haemophilia is replacement of missing clotting factor



Remarkable progress in haemophilia bleed management therapies

1944	• 1st use of whole blood
1955	• 1st use of Fresh Frozen Plasma used
1964	• 1st use of Cryoprecipitate used
1980	• 1st use of Plasma derived Clotting factor
1990	• 1st use of recombinant Clotting Factor
1998	• 1st use of extended half life clotting factors
2014	• 1st use of non-replacement therapies

CFC replacement approaches

New CFC replacement therapies

- Fusion technology
- PEGylation technology
- Sequence modification CFC

Non CFC replacement therapies

- Anti-TFPI
- AT3 RNAi
- Anti IXa/X
- Gene therapy

CFC- Clotting factor concentrate; AT3- antithrombin 3; TFPI-tissue factor pathway inhibitor; RNAi – interfering ribonucleic acid

CFC replacement technologies

Fusion technology	**1.FC fusion** **2. Albumin fusion** **3. CTP fusion** **4 PSA fusion**	**FVIII-FC** **FIX-FC** **FVIII-FP** **FIX-FP** **FVII-FP** **FVII-CTP** **Bax-826**	Mahlangu etal 2014 Powell etal 2013 FVIII-FP Santogostino 2016 Ongoing Ongoing Ongoing
PEGylation technology	**1. Site directed** **2. Random** **3. GlycoPEGylation**	**Bay-94 9027** **Bax-855** **N8-GP** **N9-GP**	**Shah etal 2016** **Konkle etal 2015** **Giangrande 2016** **Young etal 2016**
Sequence modification	**1. Heavy+light chain fusion**	**SingleChain FVIII**	**Mahlangu 2016**

Non-replacement therapies in haemophilia

Non CFC replacement therapies

- **Anti-TFPI**
- **AT3 RNAi**
- **Anti IXa/X**
- **Gene therapy**

Non-replacement therapies in haemophilia

Non CFC replacement therapies

- **Anti-TFPI**
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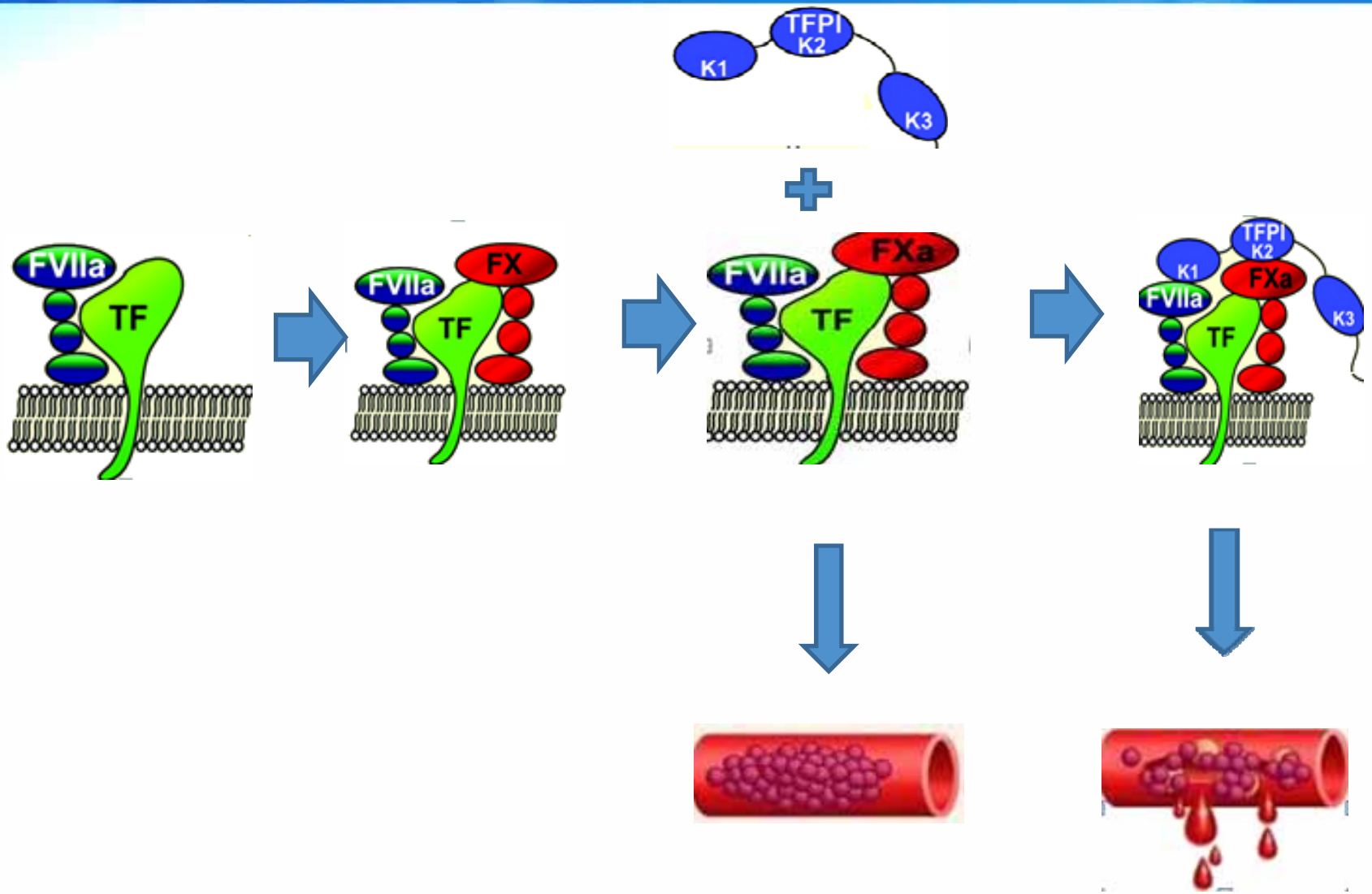
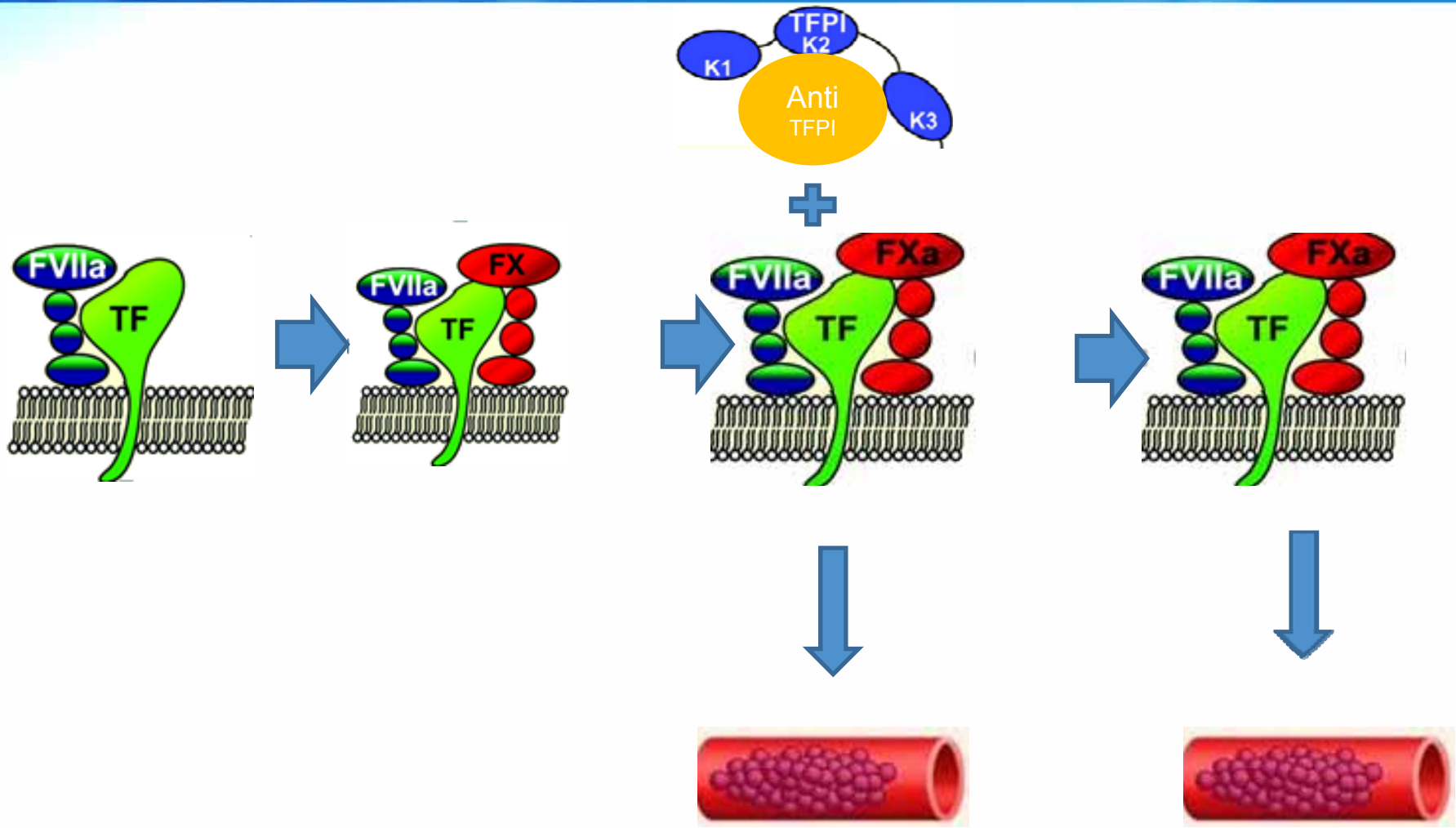
Rationale for anti-TFPI use in haemophilia



Broze GJ, Jr., Girad TJ. *Front Biosci (Landmark Ed)* 2012; **17:** 262–80.

Rationale for anti-TFPI use in haemophilia

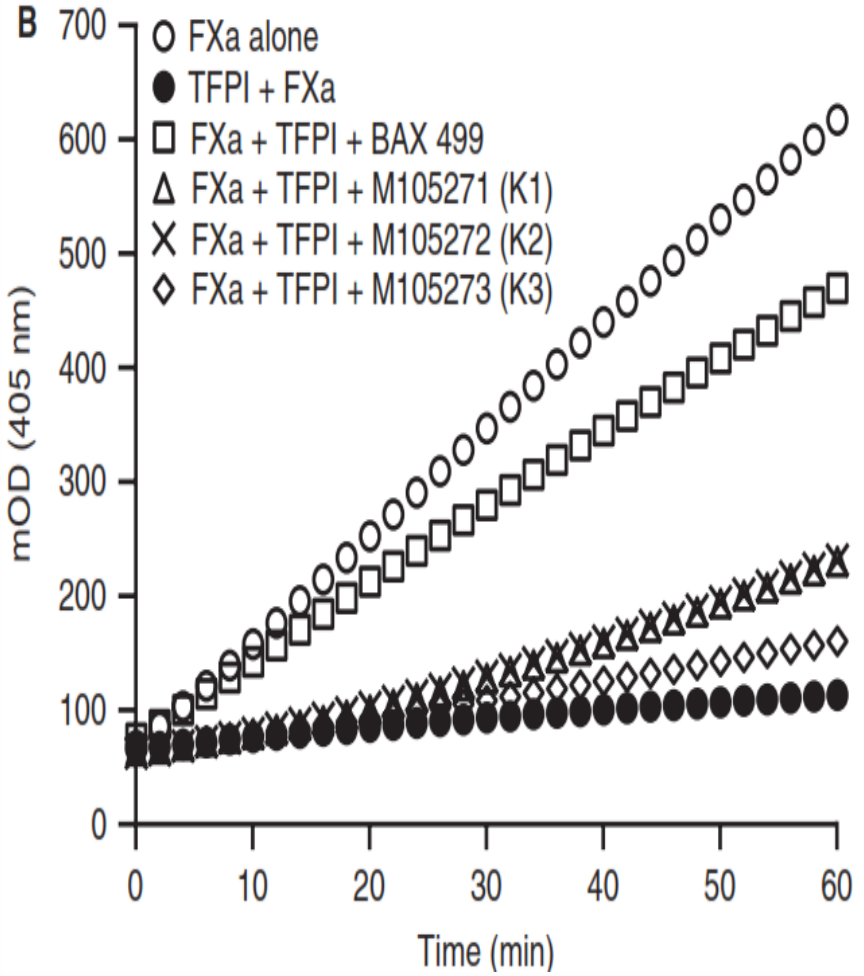


Broze GJ, Jr., Girad TJ. *Front Biosci (Landmark Ed)* 2012; **17:** 262–80.]

Anti-TFPI Clinical studies

PEG-Aptamer

- Bax 499
- Phase I/II
- Increased TFPI level and decreased thrombin
- Stopped due to excessive bleeding



Phase 1 anti-TFPI study

Journal of Thrombosis and Haemostasis, **13**: 743–754 DOI: 10.1111/jth.12864

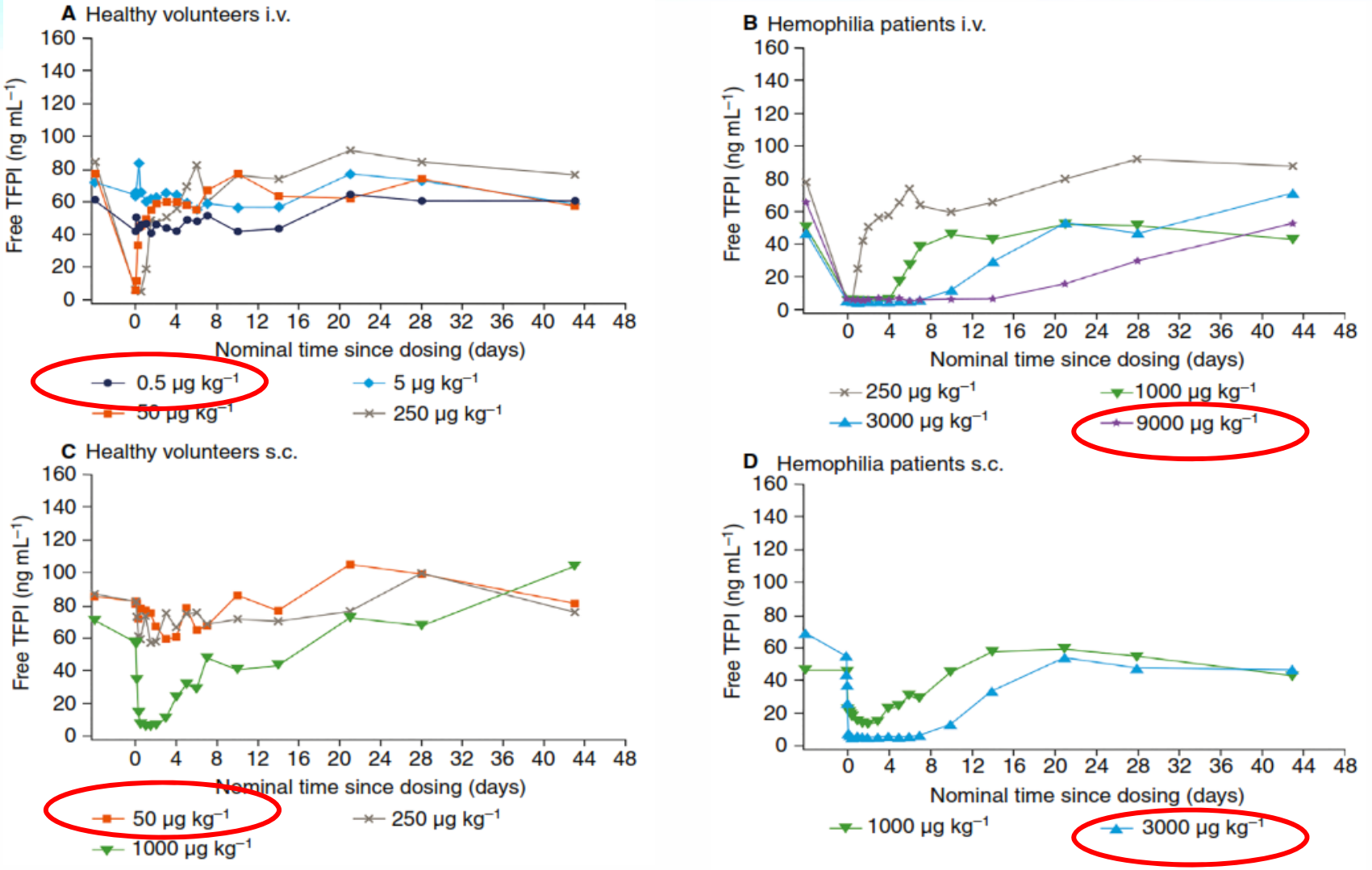
ORIGINAL ARTICLE

Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial

P. CHOWDARY,* S. LETHAGEN,†‡ U. FRIEDRICH,† B. BRAND,§ C. HAY,¶ F. ABDUL KARIM,** R. KLAMROTH,†† P. KNOEBL,‡‡ M. LAFFAN,§§ J. MAHLANGU,¶¶ W. MIESBACH,*** J. DALSGAARD NIELSEN,††† M. MARTÍN-SALCES‡‡‡ AND P. ANGCHAISUKSIRI§§§

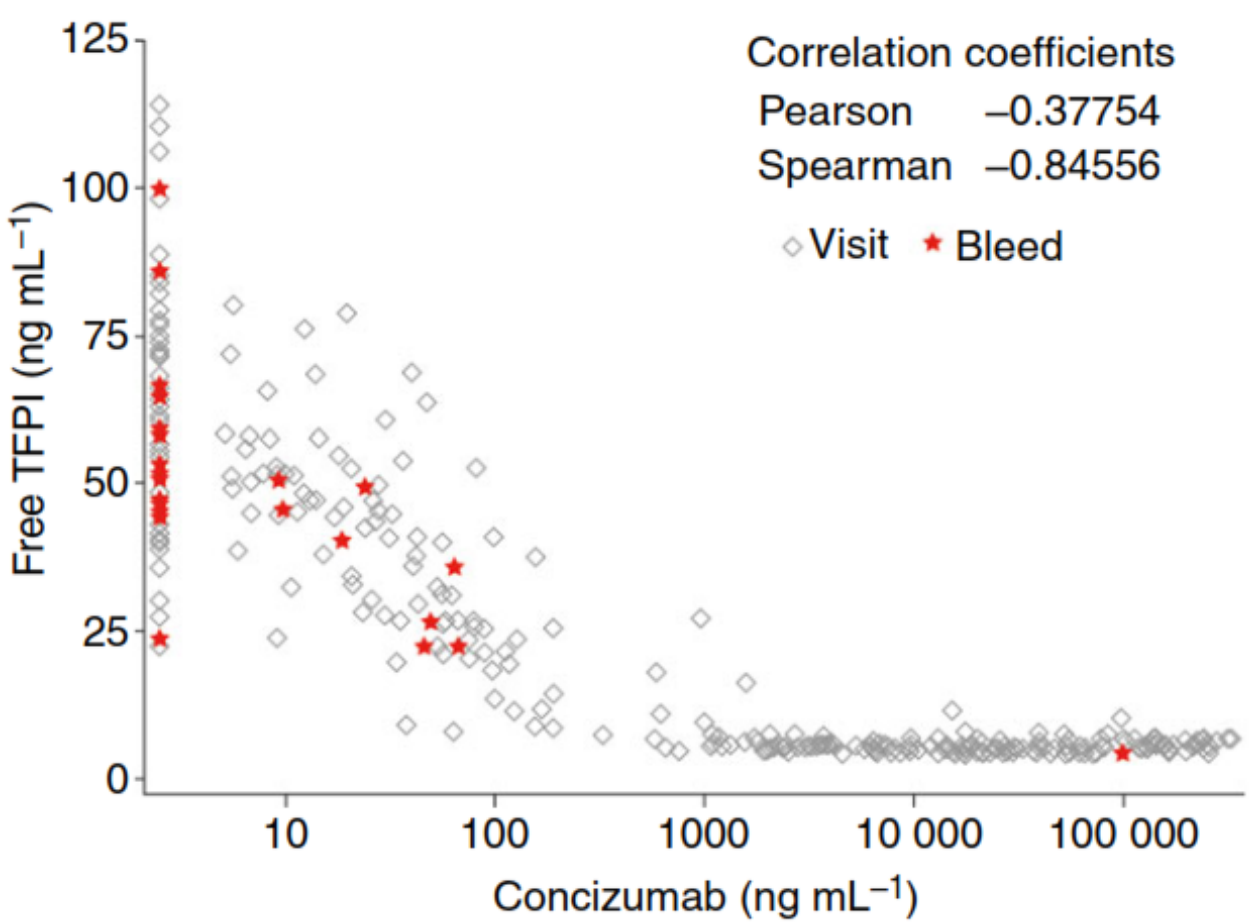
**Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free Hospital, London, UK; †Novo Nordisk A/S, Søborg, Denmark; ‡Copenhagen University, Copenhagen, Denmark; §Division of Hematology, University Hospital, Zurich, Switzerland; ¶University Department of Haematology, Manchester Royal Infirmary, Manchester, UK; **Haemophilia Centre, National Blood Centre, Kuala Lumpur, Malaysia; ††Department of Internal Medicine—Angiology, Haemostasis and Coagulation disorders, Vivantes Hospital im Friedrichshain, Berlin, Germany; ‡‡Division of Haematology and Haemostasis, Department of Medicine 1, Medical University of Vienna, Vienna, Austria; §§Imperial College London, Hammersmith Hospital, London, UK; ¶¶Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa; ***Zentrum für Innere Medizin, Med. Klinik III, Hämophilie-Zentrum, Frankfurt/M, Germany; †††Thrombosis and Haemostasis Unit, Department of Haematology, Rigshospitalet, Copenhagen, Denmark; ‡‡‡Haematology Department, Hospital Universitario La Paz, Madrid, Spain; and §§§Division of Hematology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand*

Pharmacokinetics sc vs iv



Chowdary et al J Thromb Haemost 2015; 13: 743–54.

Non-linear pharmacokinetics



Chowdary et al J Thromb Haemost 2015; 13: 743–54.

Safety profile

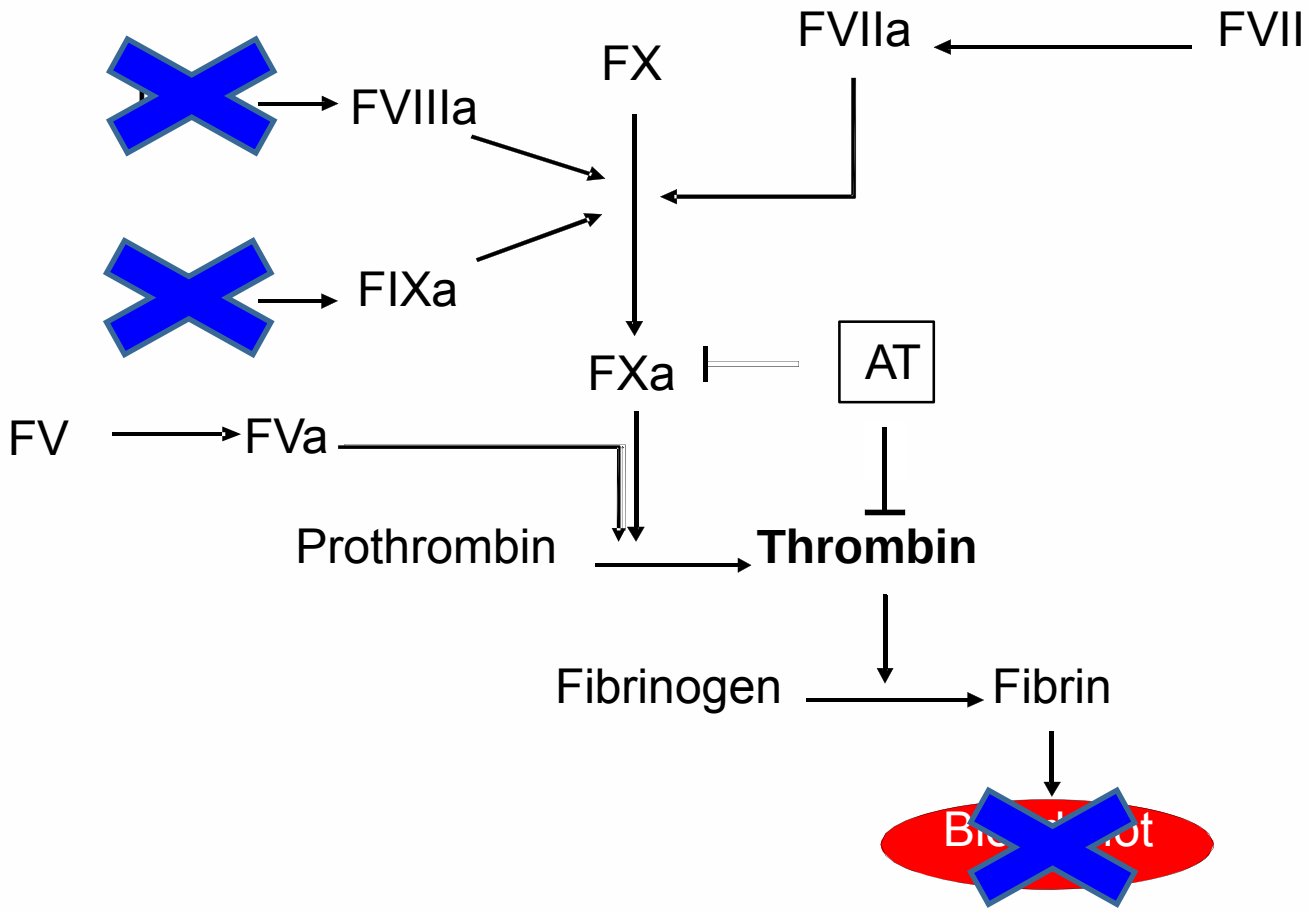
- No SAE
- No thrombosis or vascular events
- No allergy
- No anti-concizumab antibodies
- No inhibitors
- No clinically relevant changes in
  - TT, aPTT, fibrinogen, antithrombin
- Dose dependent changes in
  - Ddimers
  - Prothtombin fragment 1+2

Non-replacement therapies in haemophilia

Non CFC replacement therapies

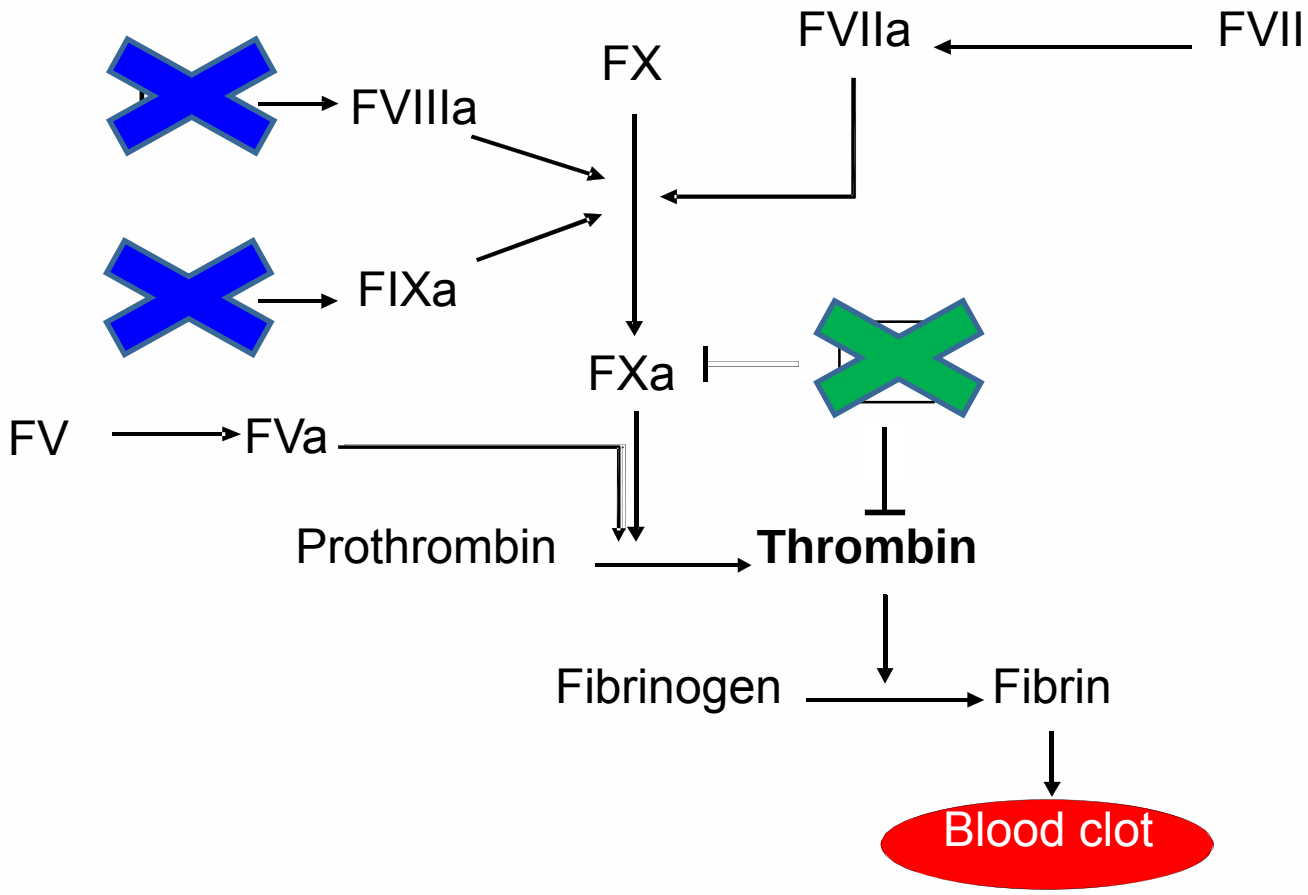
- Anti-TFPI
- **AT3 RNAi**
- Anti IXa/X
- Gene therapy

Haemostasis in normal and PWH



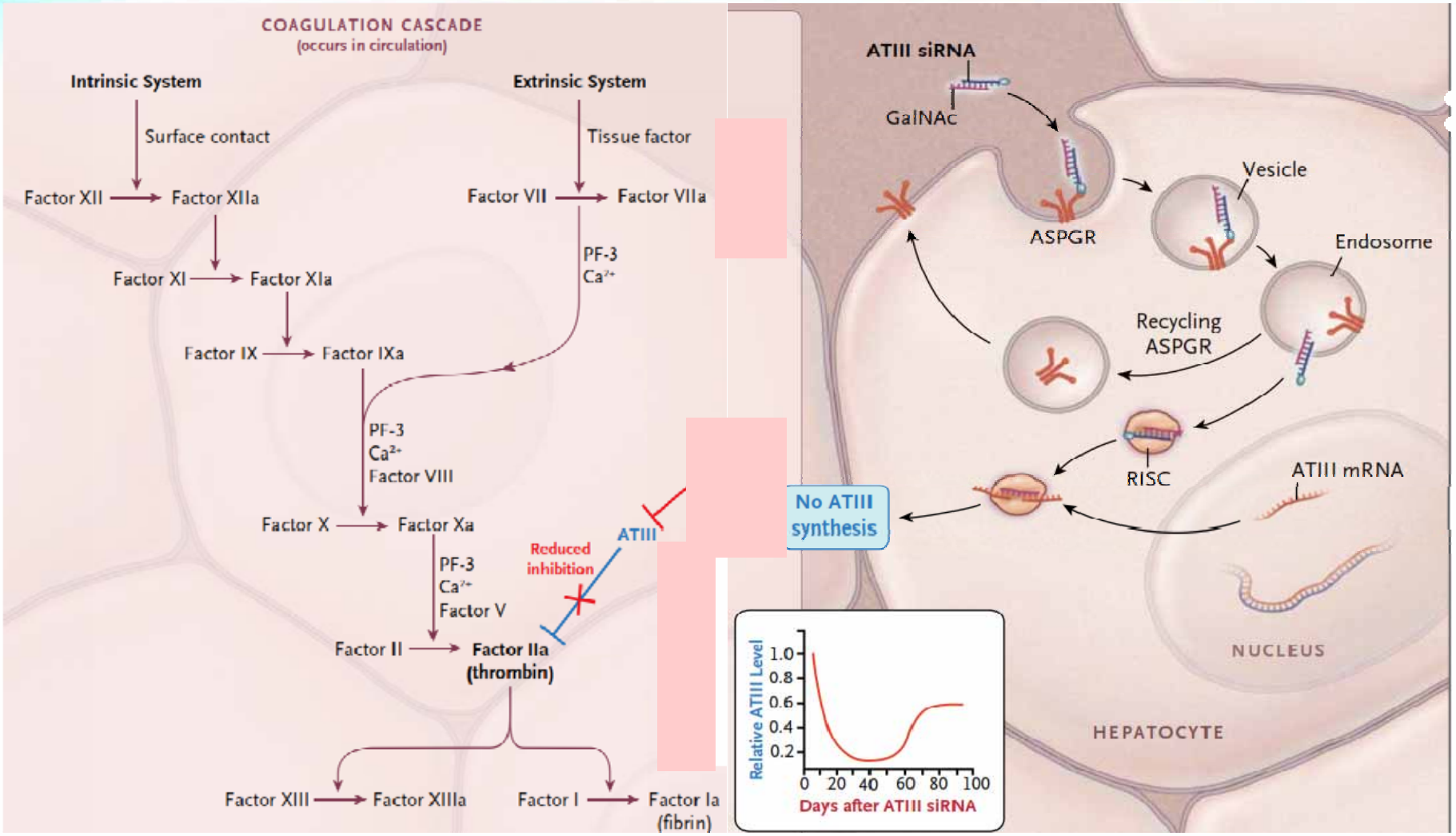
Sehgal et al Nature med 2015; 21(5) :492-497

AT role



Sehgal et al Nature med 2015; 21(5) :492-497

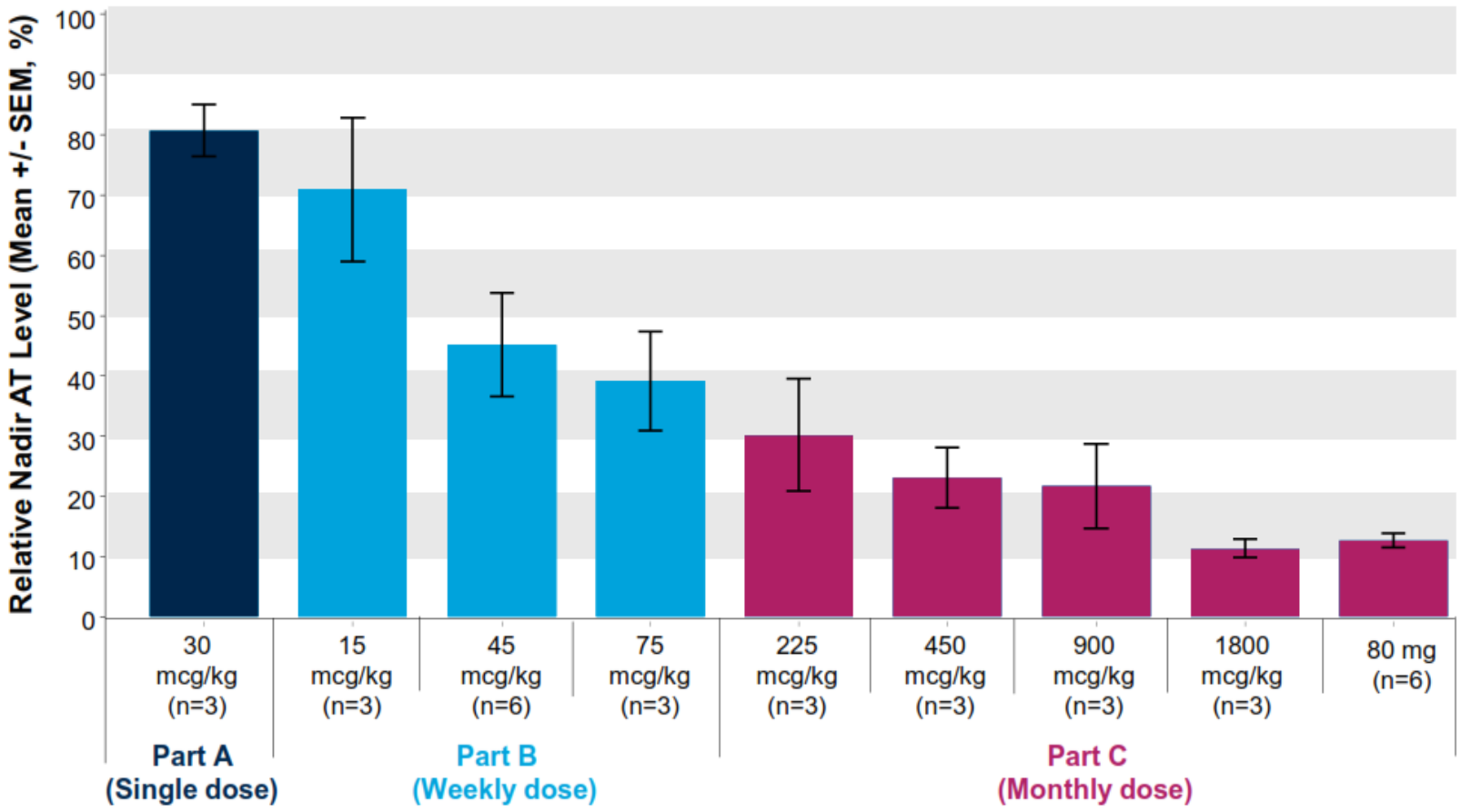
AT3 RNAi Mechanism of action



Ragni M NEJM 2015; 373(4): 389-390

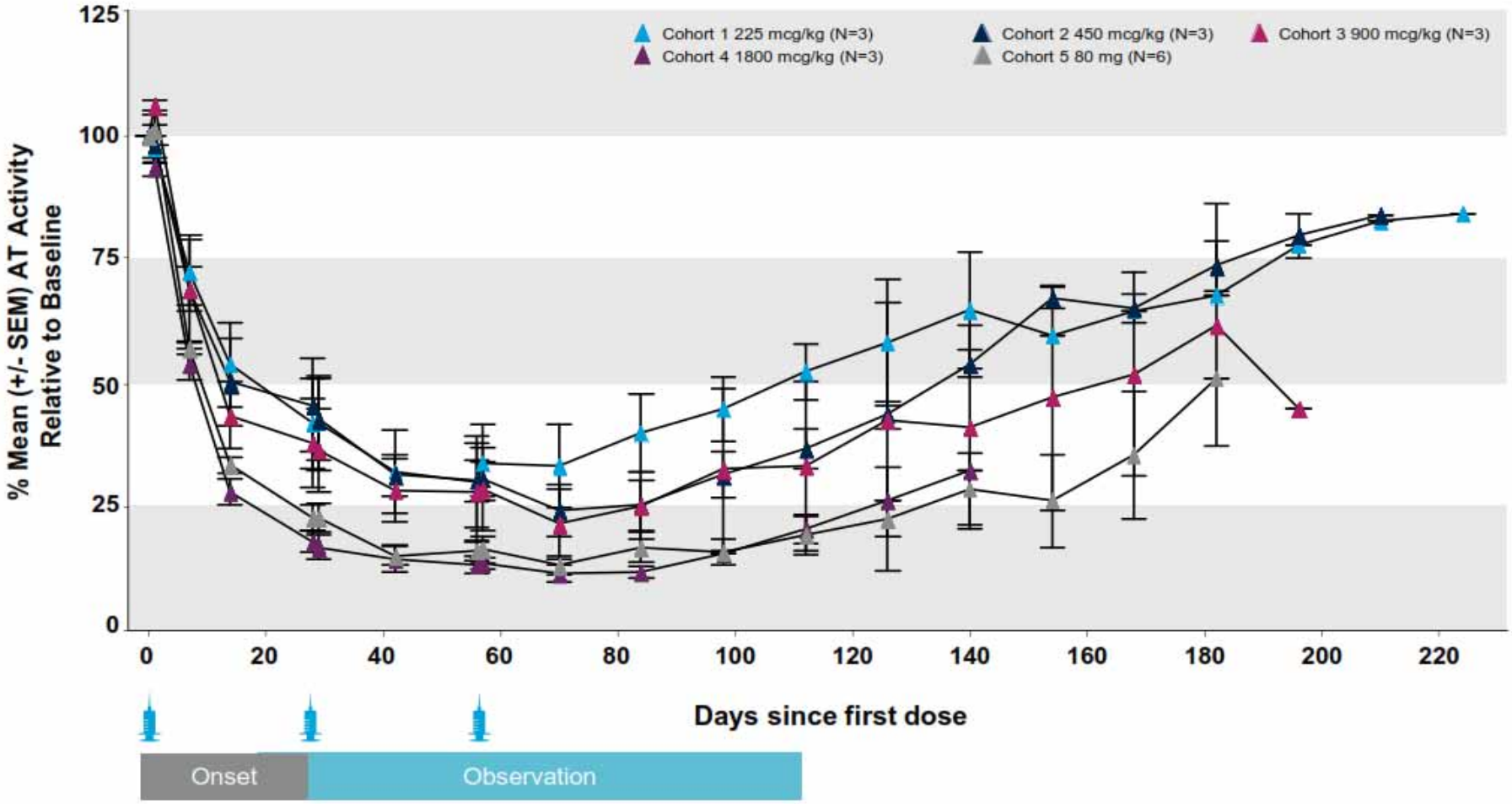
Phase 1 Results: Dose dependent response

Mean maximal AT lowering of 87 ± 1% at 80 mg fixed dose



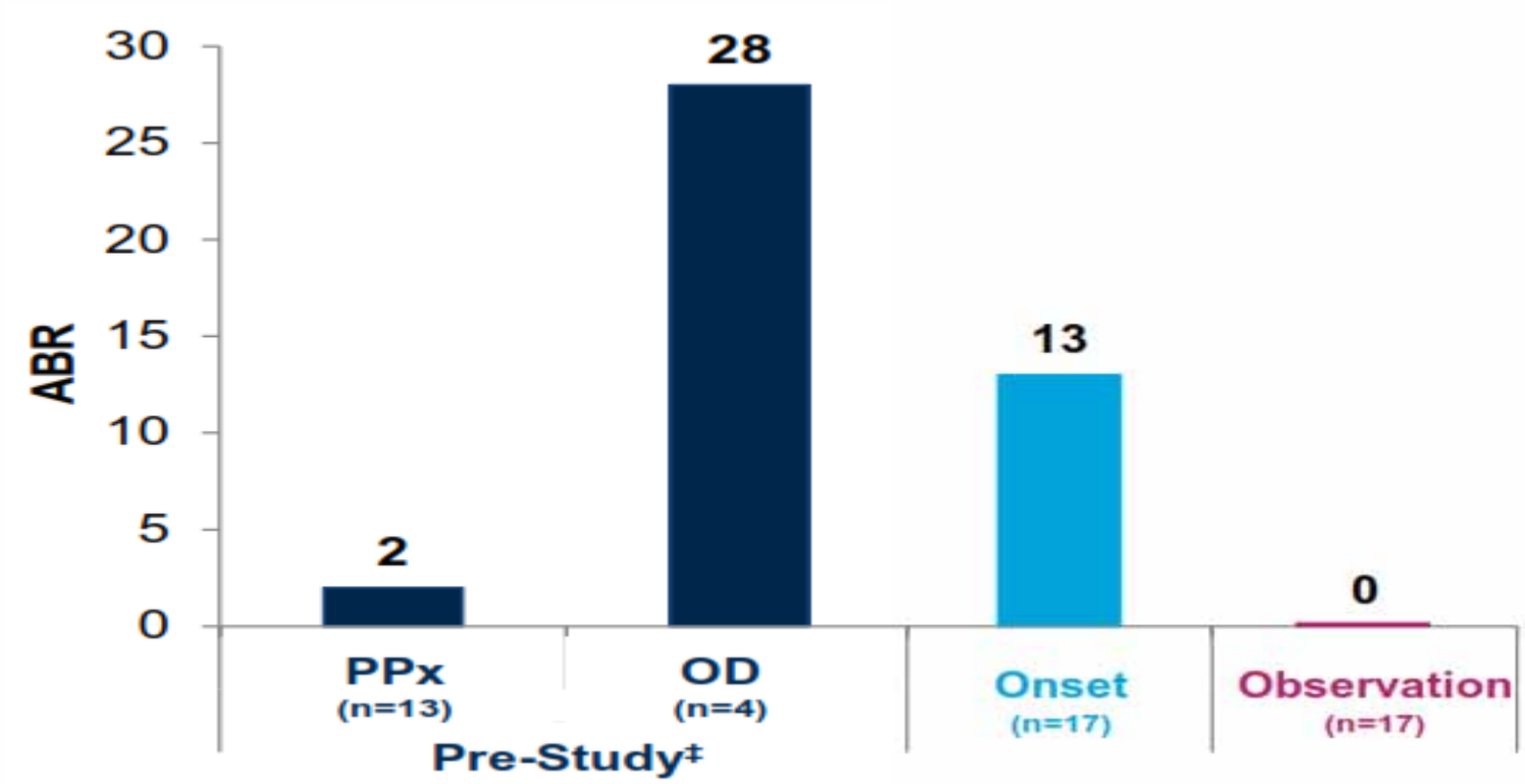
Sehgal et al Nature med 2015; 21(5) :492-497

AT after monthly dosing of ALN



Pasi etal WFH congress 2016, Orlando

Summary of Median ABR (All Cohorts, n=17)



Pasi etal WFH congress 2016, Orlando

Safety profile based on current data

- Fitusiran generally well tolerated in hemophilia A and B patients with and without inhibitor
- No SAEs related to study drug;
- No thromboembolic events
- 11 (35%) patients reported mild drug-related ISRs
  - Mostly pain and/or erythema at the injection site
- AEs (excluding injection site reactions(ISRs)) in ≥10% of patients:
  - upper respiratory tract infection (10%) and arthralgia (10%);
  - majority mild or moderate in severity
  - 1 discontinuation due to AE; event resolved in this patient with symptomatic management

Summary on ALN-RNAi

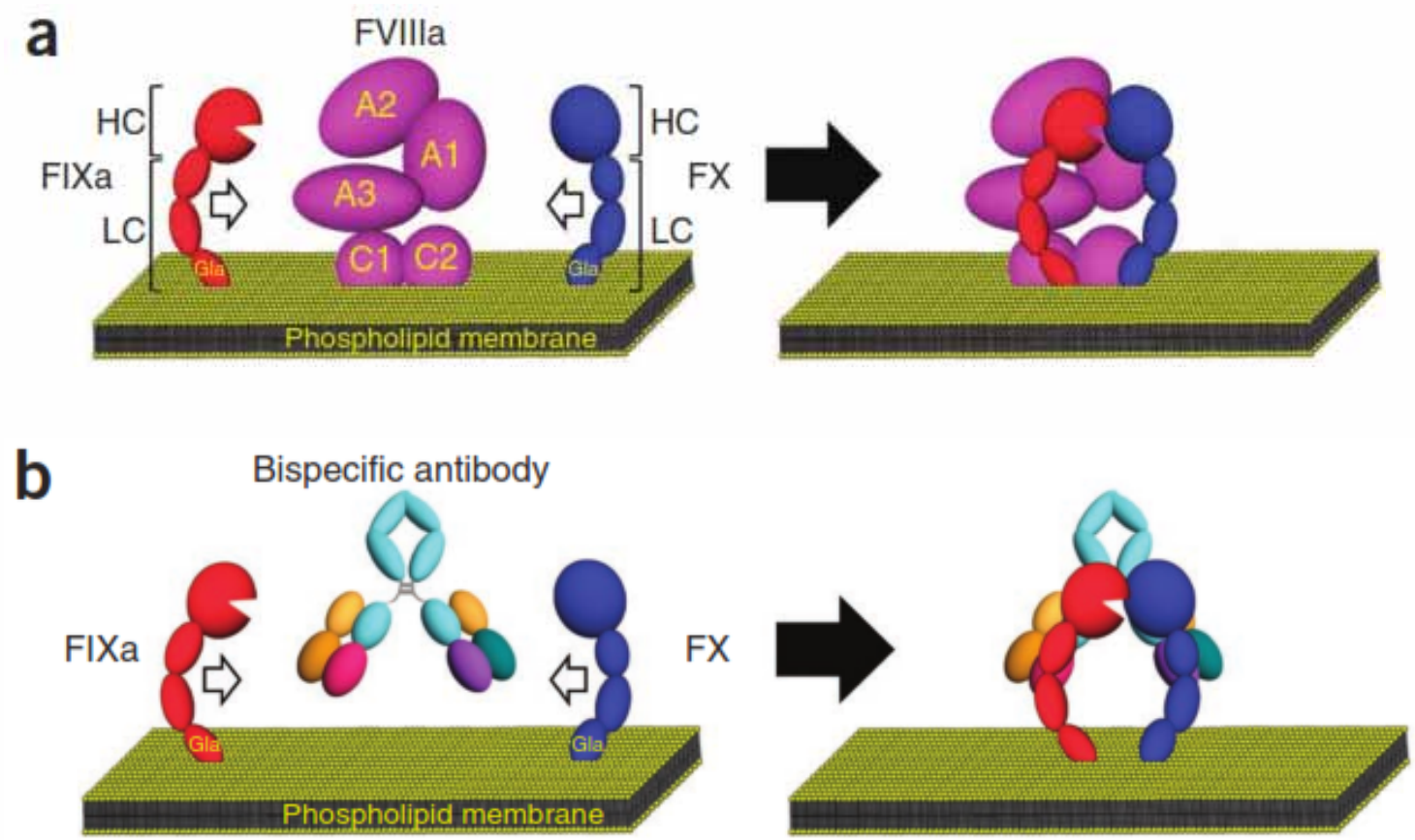
- Dose-dependent AT lowering and thrombin generation increase achieved, with once-monthly subcutaneous
- dose regimen; fixed 80 mg dose provides consistent AT lowering >75%
- Evidence of clinical activity and potential correction of hemophilia phenotype in non-inhibitor patients
- In exploratory post-hoc analysis in monthly dose cohorts, fitusiran achieved median ABR = 0, with
  - 53% patients bleed-free and
  - 82% patients experiencing zero spontaneous bleeds

Non-replacement therapies in haemophilia

Non CFC replacement therapies

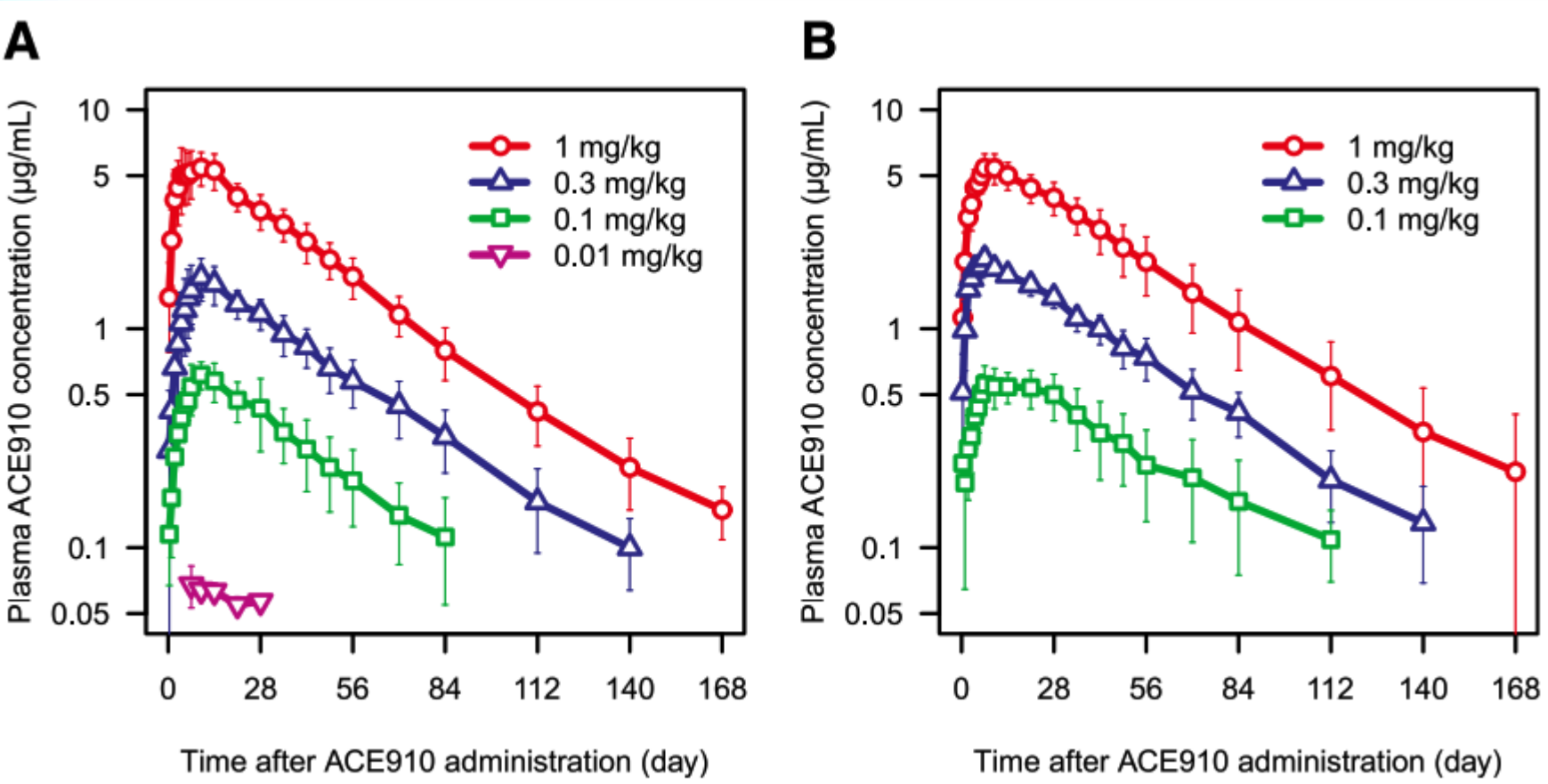
- Anti-TFPI
- AT3 RNAi
- **Anti IXa/X**
- Gene therapy

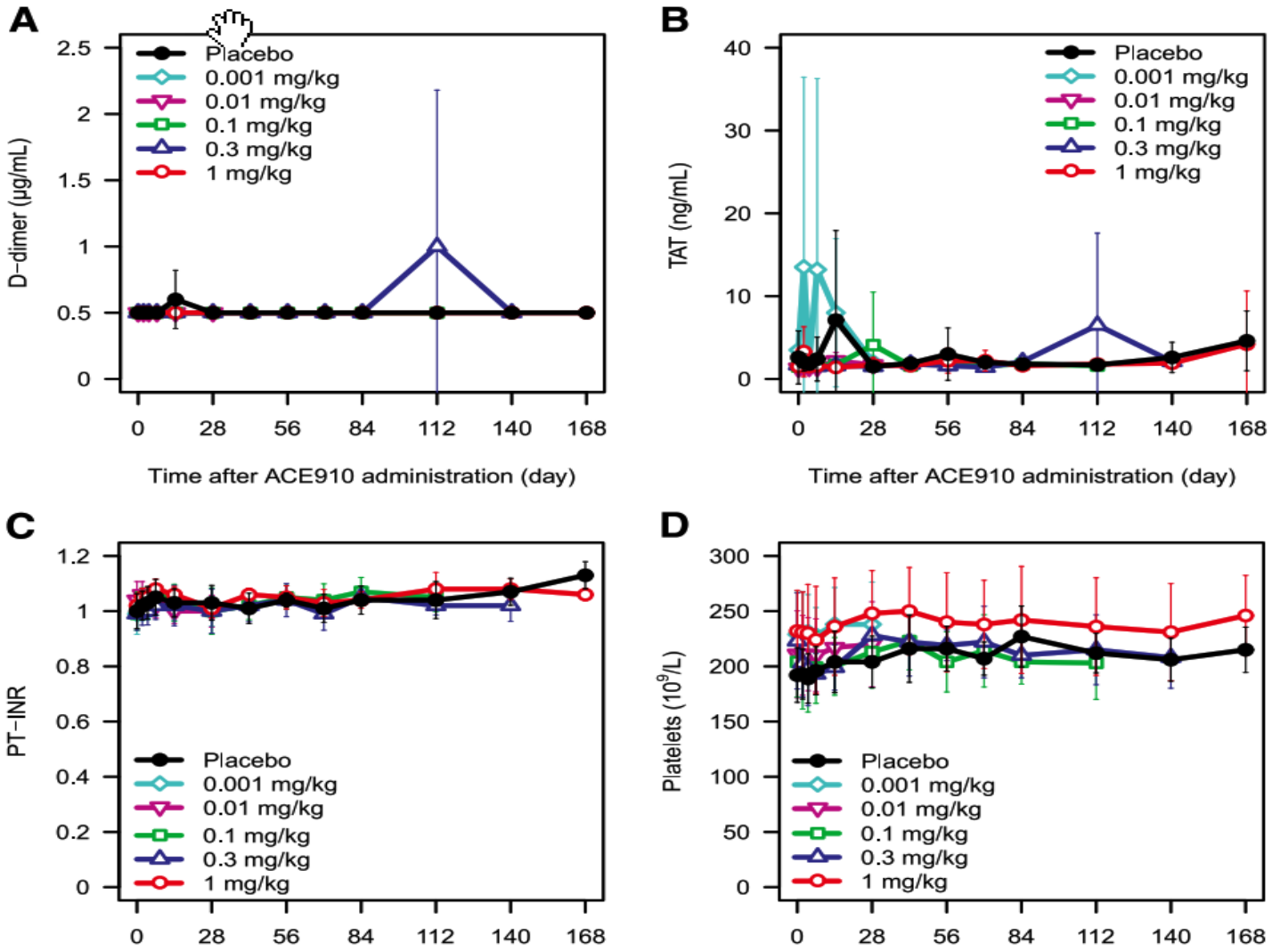
ACE910 Bispecific antibody



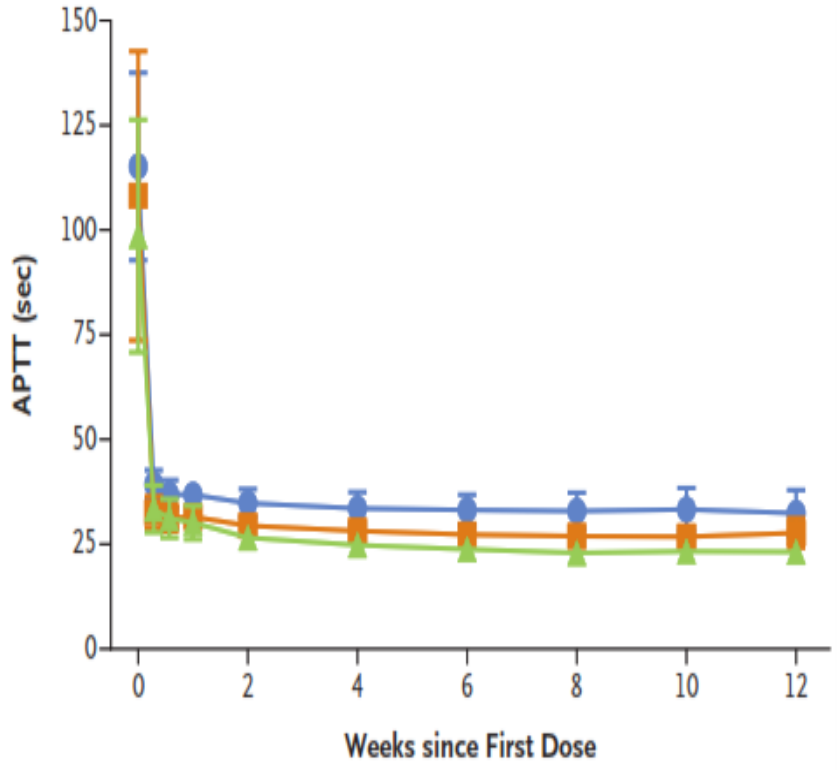
Kitazawa etal Nature Med 2012 ; 18(10): 1570-1574

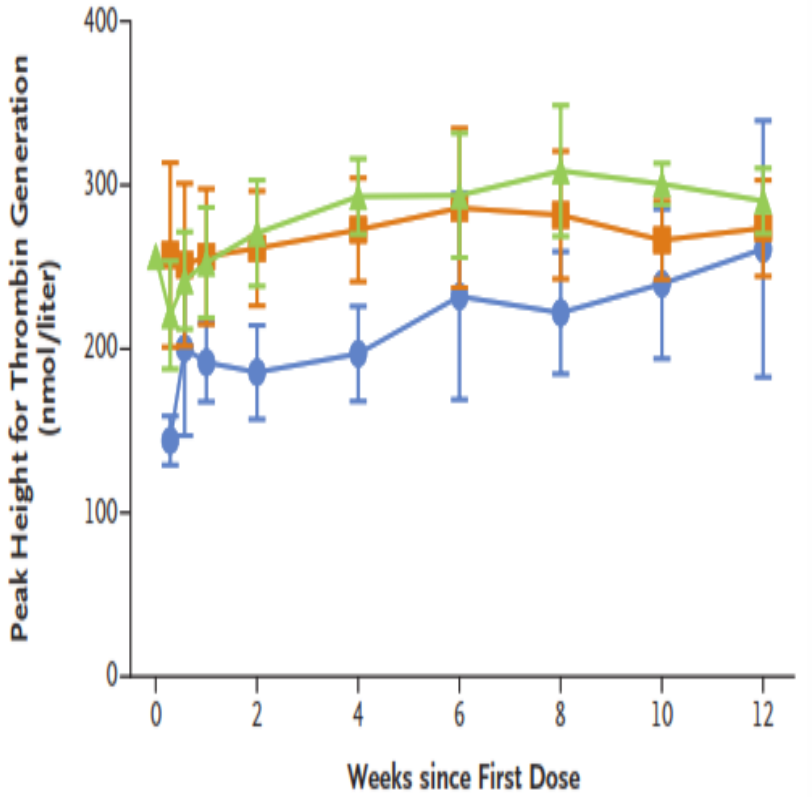
Plasma ACE910 concentration




A
D-dimer (μg/mL)
2.5
2
1.5
1
0.5
0
Placebo
0.001 mg/kg
0.01 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg
0
28
56
84
112
140
168
Time after ACE910 administration (day)
B
TAT (ng/mL)
40
30
20
10
0
Placebo
0.001 mg/kg
0.01 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg
0
28
56
84
112
140
168
Time after ACE910 administration (day)
C
PT-INR
1.2
1
0.8
0.6
0.4
0.2
0
Placebo
0.001 mg/kg
0.01 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg
0
28
56
84
112
140
168
D
Platelets (10^9/L)
300
250
200
150
100
50
0
Placebo
0.001 mg/kg
0.01 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg
0
28
56
84
112
140
168

Impact on aPTT and thrombin generation





Summary on Emicizumab

- Emicizumab was associated with neither serious adverse events nor clinically relevant coagulation abnormalities.
- Plasma concentrations of emicizumab increased in a dose-dependent manner.
- Activated partial-thromboplastin times remained short throughout the study.
- The median annualized bleeding rates in cohorts 1, 2, and 3 decreased from 32.5 to 4.4, 18.3 to 0.0, and 15.2 to 0.0, respectively.
  - There was no bleeding in 8 of 11 patients with factor VIII inhibitors (73%) and in 5 of 7 patients without factor VIII inhibitors (71%). Episodic use of clotting factors to control bleeding was reduced. Antibodies to emicizumab did not develop

Scepticism about gene therapy

nature

www.nature.com/nature

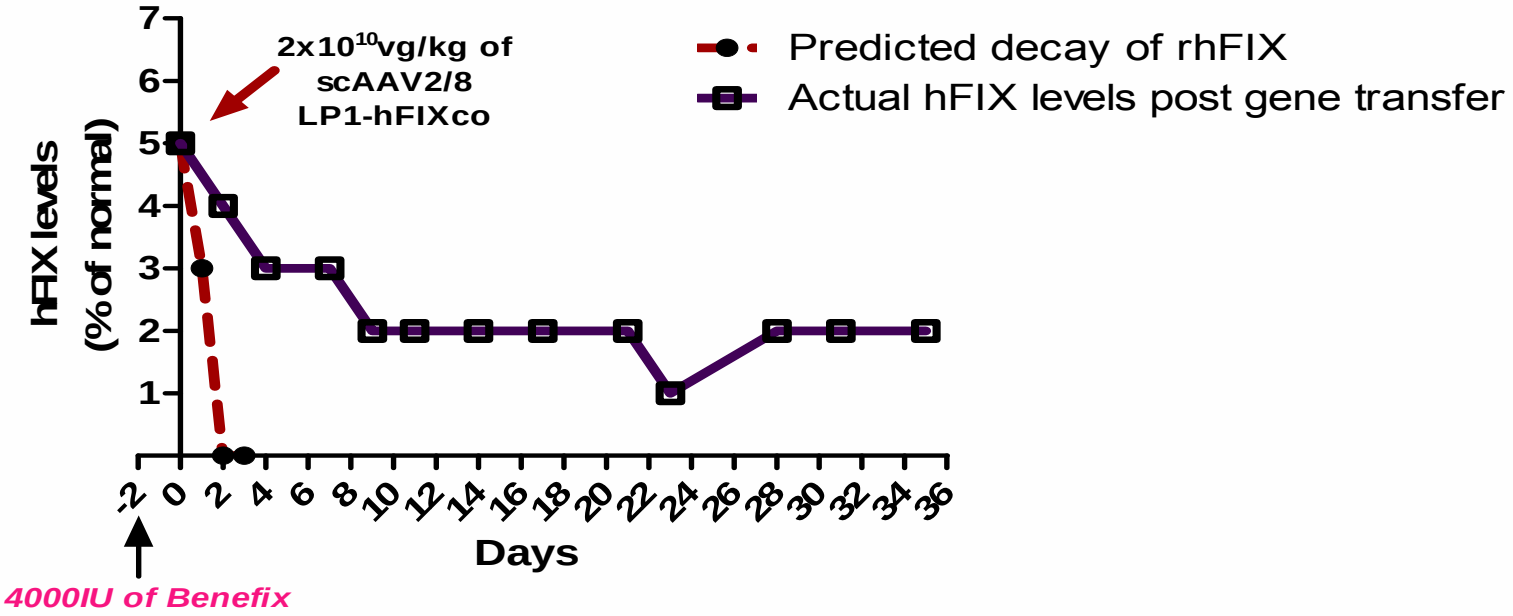
Vol 461 | Issue no. 7268 | 29 October 2009

Gene therapy deserves a fresh chance

Initial interest in gene therapy waned after the technology failed to live up to expectation. Progress made since has received little attention, but suggests that the pervading sense of disillusionment is misplaced.

First successful FIX gene therapy in man

- Phase 1
- 6 patients, 2 in each of 3 dose escalations
- Durable FIX levels 1–6%
- 2/6 transient ALT elevation



Nathwani, et al. NEJM 2011;365;2357

Haemophilia B longer term follow up data

- Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B.

- Long-term follow up of original 6 patients
  - Each of 3 dose escalations
- Plus 4 additional subjects
  - at high dose: 2 x 10^12 vector genomes/kg

- Long term FIX levels 1–6% – median 3.2 years follow up

Nathwani, et al. *NEJM* 2014;371:21

FVIII gene therapy?

- Bigger protein than FIX- Packaging more complex
- Platelet directed FVIII gene therapy
  - Animal model, lentiviral
- Hybrid porcine / human sequence
  - Lentiviral

Du, et al. *Nature Comm* 2013;4:2773

Johnston, et al. Gene Ther 2013;20(6):607–615

FVIII Clinical trials

- BMN 270: AAV 5-factor VIII vector
  - Trial due to start Q2/3 2015
  - First in man phase 1 FVIII trials
- UCL/St Jude (Nathwani/Davidoff)
  - Imminent

Summary

- Significant progress has been made in the development of therapies for haemophilia
- Extended half life products promise to make prophylaxis a reality
- Evolving alternative therapies are beginning to emerge
- All therapies have limitations in that they may not apply to all patients with haemophilia
- Gene therapy remains the choice option for cure of haemophilia


Thank
You!