Basics of Factor VII Deficiency

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Disclosures

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Vignette 1

A 7-year-old female c/o bilateral ankle “pain and swelling
ballet dancer - had X- rays done by Ortho documented – bony changes

Now presents with
- Oozing after dental extraction for 2 days despite pressure with gauze and ice

Family history
- 10 -year-old brother had 1episode of severe joint pain and swelling while playing soccer
- Previously, he had one episode of severe nosebleed lasting 30 mins – went to the ED to get packing of nostril
- Parents first cousins

http://reddymed.com/hdbc/

With permission from Drs Usha Reddy and Roshni Kulkarni

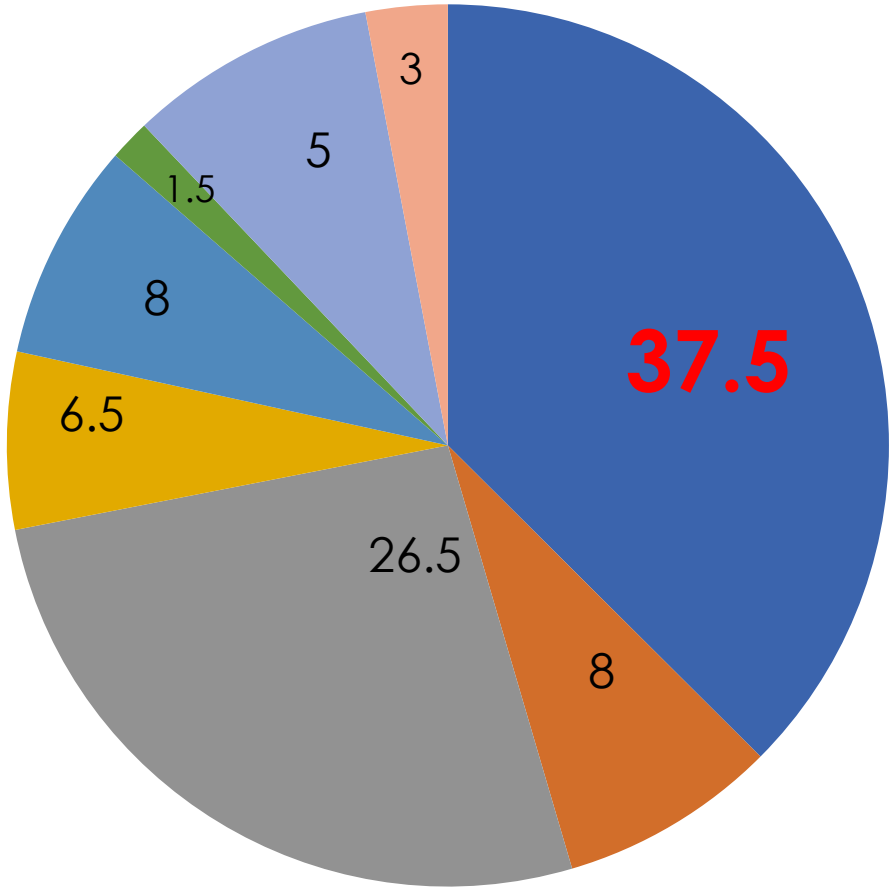
Prevalence of RBDs

Defect	Iran	Italy	UK
Fibrinogen	70 (1.5%)	10 (0.2%)	11 (0.2%)
Prothrombin	15 (0.3%)	7 (0.02%)	1 (0.02%)
FV	70 (1.5%)	21 (0.5%)	28 (0.6%)
FVII	300 (6.6%)	58 (1.3%)	62 (1.3 %)
FV + FVIII	80 (1.7%)	29 (0.7%)	18 (0.3%)
FVIII	**3000 (65.4%)**	**3428 (79.9%)**	**3554 (77.2%)**
FIX	**900 (19.6%)**	**626 (15.0%)**	**762 (16.1%)**
FX	60 (1.3%)	16 (0.4%)	25 (0.5%)
FXI	20 (0.4%)	60 (1.3%)	150 (3.3%)
FXIII	80 (1.7%)	31 (0.7%)	26 (0.5%)

3 - 5 fold higher prevalence in Iran

Mannucci PM , Blood 2004

Prevalence of RBDs - Clotting Factor Deficiencies (%)



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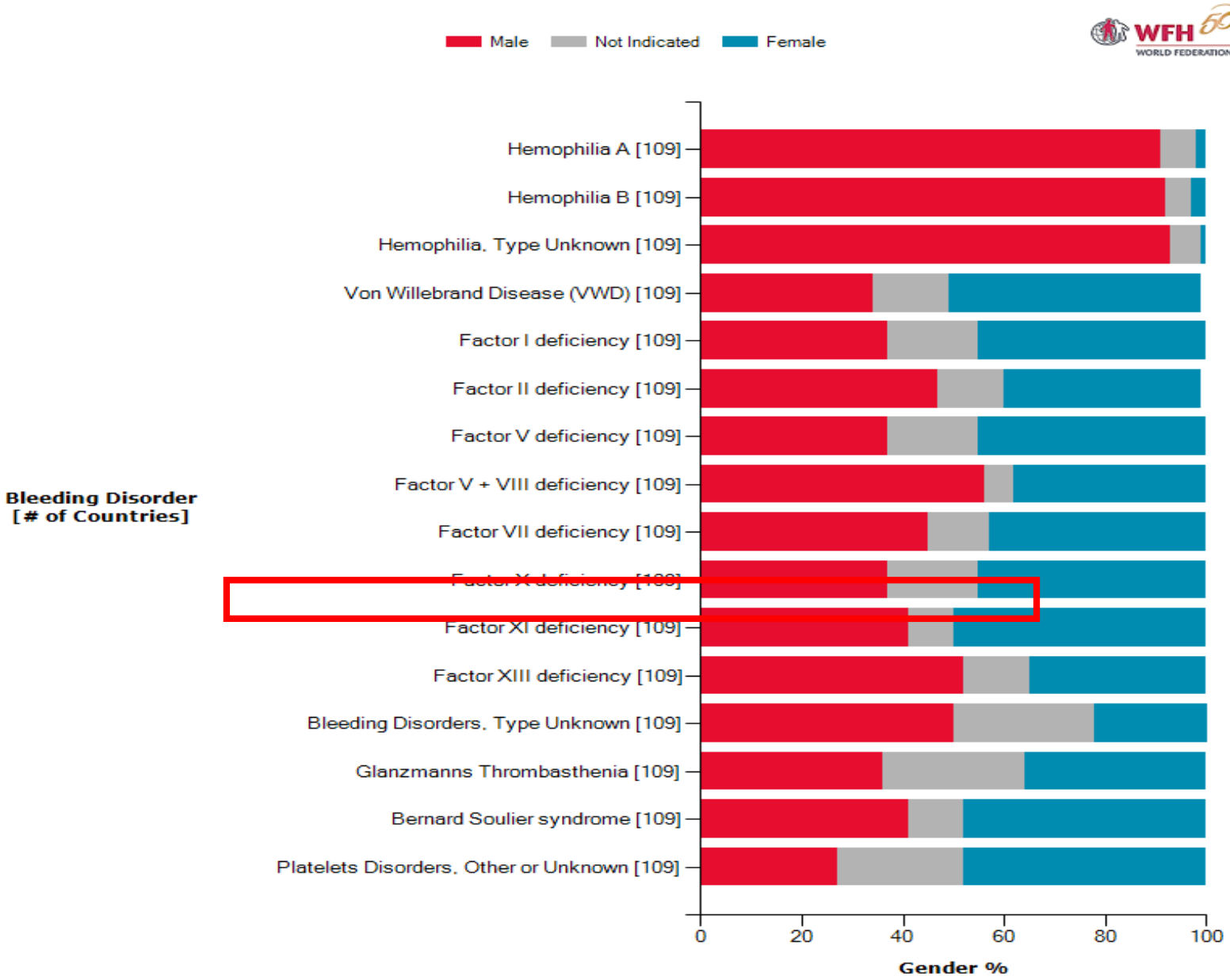
WFH: http://www.wfh.org/ ; EN-RBD: http://www.rbd.eu/

WFH Annual Global Survey Data : Bleeding Disorders by Gender (%) in 2012



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Rate of Consanguinity

1- 40-70%

2 - 50%

3 - 85%

4 - 49%

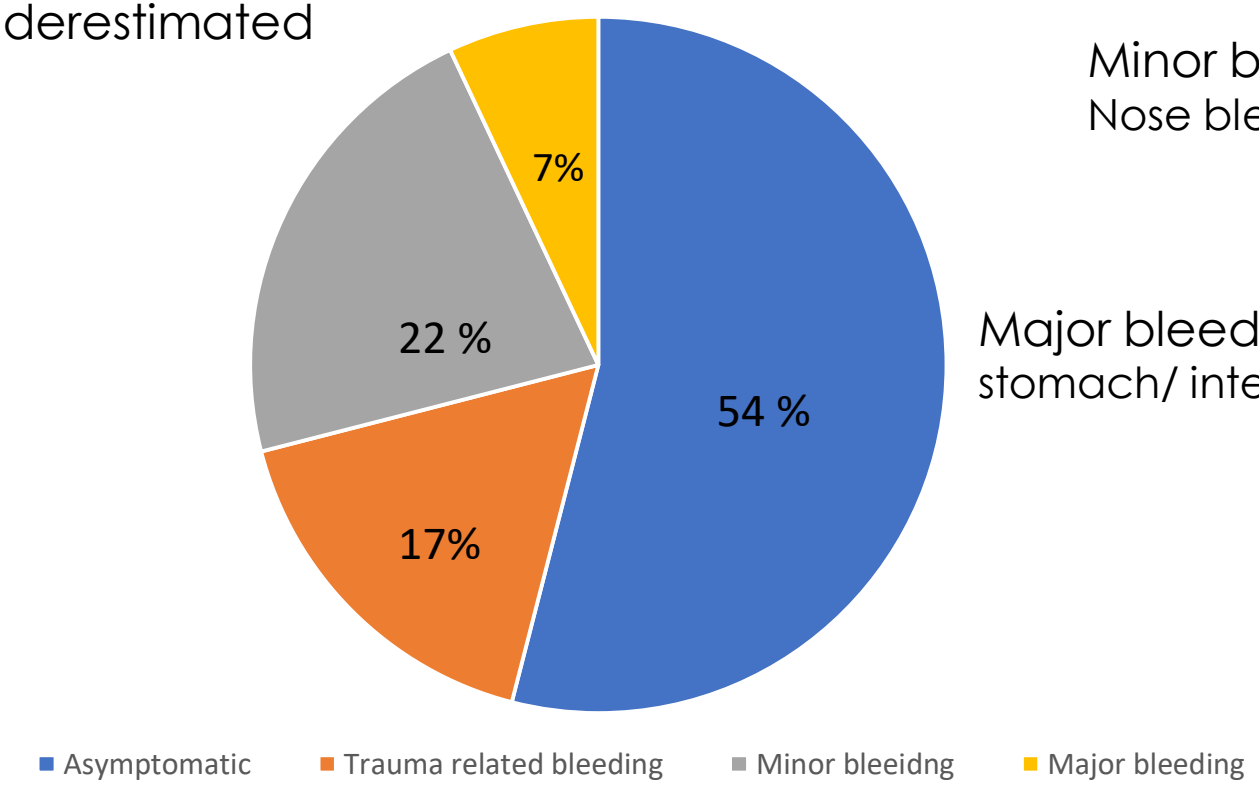
5 - 40%

6 - 60%

RBDs – 3-7 -fold higher in the Middle East and SE Asia than developed countries

How Symptomatic are FVII deficiency patients?

Prevalence is underestimated



Minor bleeding = mild spontaneous bleeds, Nose bleeds, bruising, heavy menses

Major bleeding = joint bleeds, brain bleeds, stomach/ intestinal bleeds, umbilical cord bleeding

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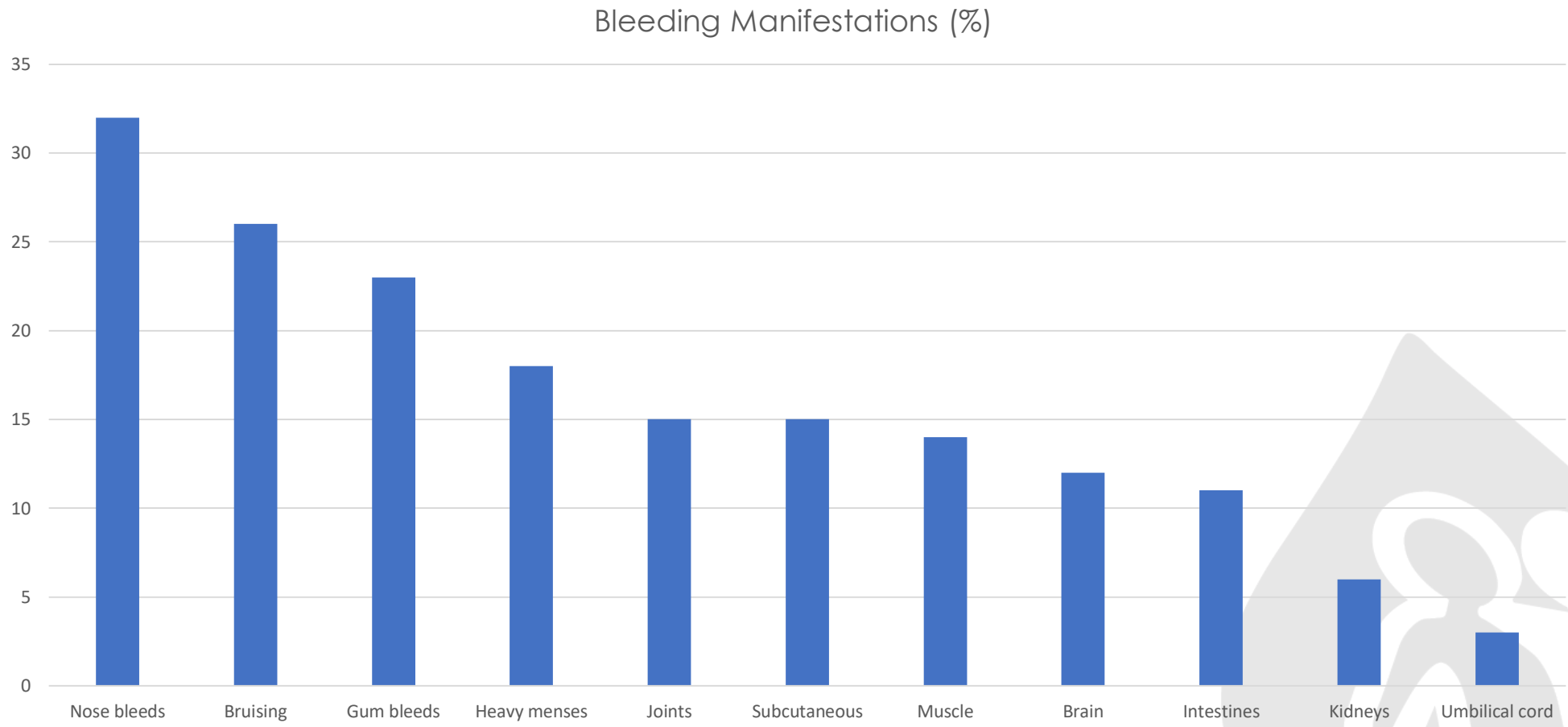
STER Data, Mariani G, 2007



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Data from STER Registry - Mariani et al

FVII Deficiency: Clinical Phenotypes

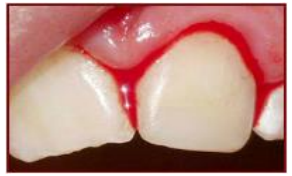
- *Asymptomatic individuals* (ASY): Diagnosed during hemostatic screening for surgery or FH

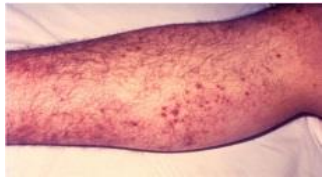
- *Platelet-like* type of symptoms (PLT): Epistaxis, easy bruising, gum bleeding, menorrhagia, hematuria,

- *Hemophilia-like* type of symptoms (HLT): Hemarthrosis, CNS, GI, cord stump bleeding, hematomas (muscle and subcutaneous)

Clinical Symptoms

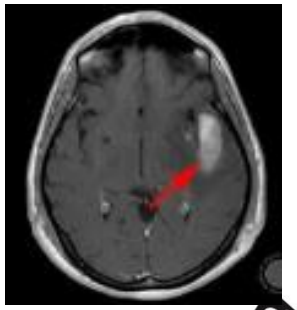
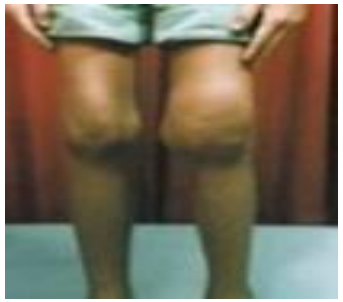
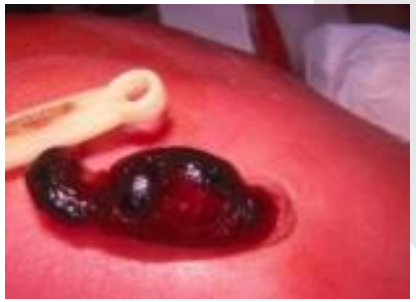
Highly variable bleeding tendency





- Most common symptoms
  - Skin and lining area bleeding
  - Heavy menses and prolonged bleeding at labor and delivery
  - Excessive bleeding with invasive procedures including circumcision

- Frequently in FVII deficiencies
  - CNS bleeding, umbilical cord bleeding, joint bleeds and soft tissue haematomas

Laboratory Diagnosis

- Prolonged PT and normal aPTT – repeat testing 1-2 weeks later to confirm
- Levels < 70% although symptomatic < 30 %
- PT can range from moderate elevation to prolonged elevation (> 20s)
- FVII:C assay ; FVII antigen
- Genotyping

Pitfalls of FVII: C assays

Treatment Options

- Substitution therapy with FVII concentrate mainstay of therapy in severe cases
- Effective for spontaneous bleeds, surgery, and for prophylaxis in children with severe deficiency
- rFVIIa replacement therapy
  - Most widely accepted option for spontaneous bleeds and in surgical setting
  - Recommended dosage 15-30 μg/kg q4-6h to maintain FVII levels above 15%-20%
  - Slight risk for inhibitor development

Additional Treatment Options

- Fresh Frozen Plasma(FFP)
  - Widely used in past; still used heavily in developing countries
  - Limited efficacy data; should only be used if no alternative
  - Risk of circulatory overload and transmission of blood-borne pathogens

- Prothrombin Complex Concentrates(PCCs)
  - Effective in securing hemostasis, with low volume infusion
  - Risk of thrombosis with repeated administration or perioperative use

FVII Deficiency and Prophylaxis

- Prophylaxis not a common practice, but feasible
  - Very short half-life of FVII in blood (1.5-3h)
- Infants prone to severe and frequent bleeding are main targets for prophylaxis
- Indicated for prophylaxis in severe disease characterized by CNS or GI bleeding, hemarthrosis, or menorrhagia associated with low to very low FVII:C levels

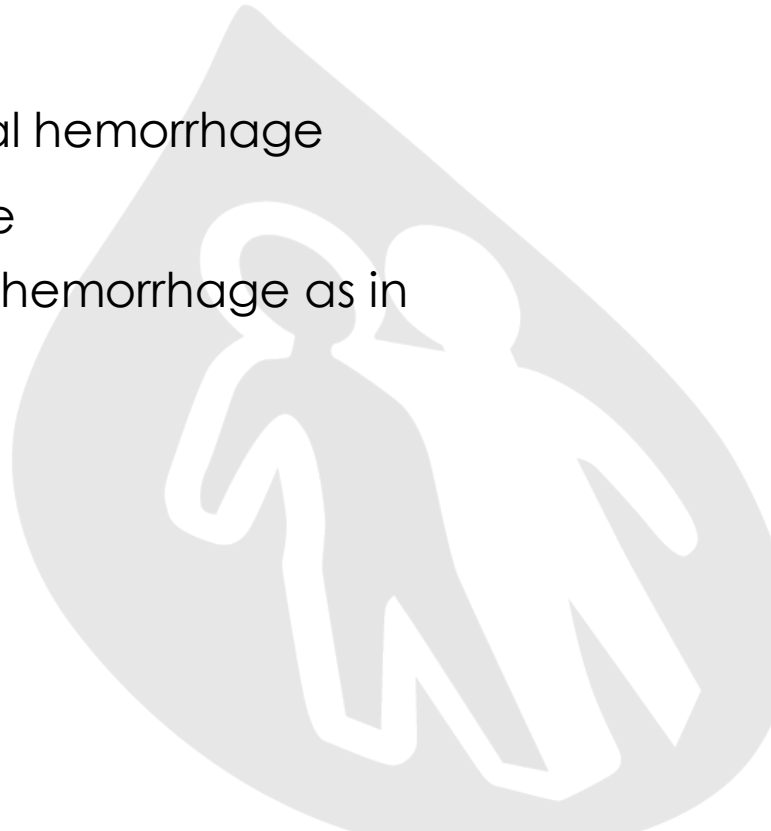
Role of Prophylaxis in FVII Deficiency ???

- Prophylaxis need is related to
  - Bleeding frequency
  - Severity of spontaneous bleeding
  - Risk of long-term sequelae
- Types of prophylaxis in RBDs

Primary prophylaxis: Before any bleeding occurs - - risk for intracranial hemorrhage

Secondary prophylaxis: After a bleeding event, to prevent recurrence musculoskeletal bleeding or life-threatening hemorrhage as in severe FVII deficiency

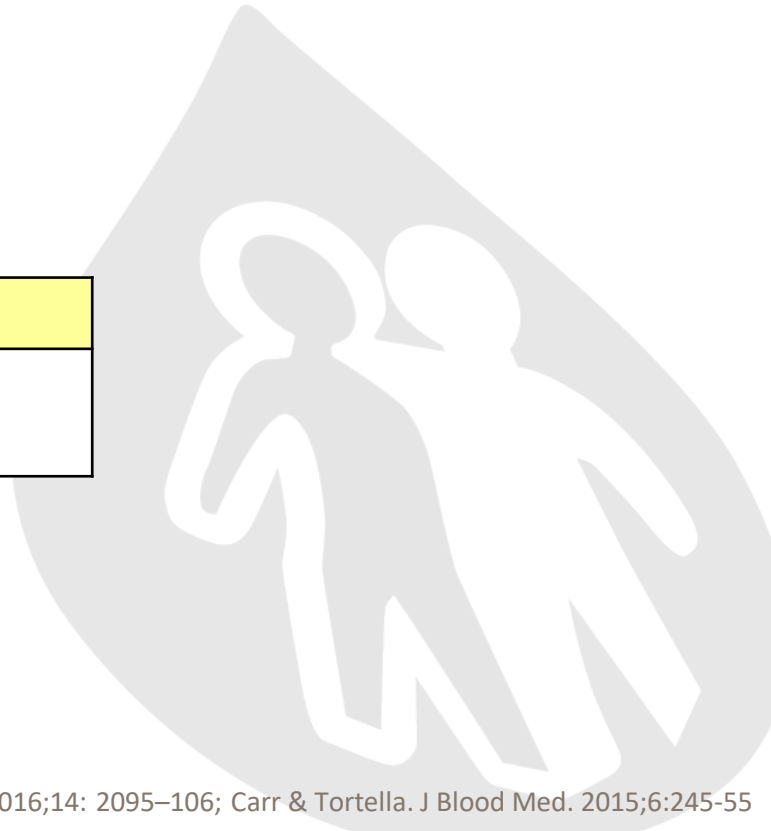
- Data regarding benefit of prophylaxis is sparse



Factor VII deficiency

- Most common RBD: 35-38% of cases
- Treatment
  - rFVIIa considered optimal therapy
  - Doses 15-30 µg/kg
  - Limitation is short half-life requiring at least 2-3 infusions per week
  - Longer-acting rFVIIa molecules have been generated
    - GlycoPEGylation or fusion protein technologies
    - Not studied in FVII deficiency

Factor	On demand dosages	Long term prophylaxis dosages
Factor VII	**rFVIIa 15–30 µg/kg every 4–6 hours**	**rFVIIa 20-40 µg/Kg 2-3 times/week**



Moss et al. JTH 2011;9:1368–74; Peyvandi et al. JTH 2016;14: 2095–106; Carr & Tortella. J Blood Med. 2015;6:245-55

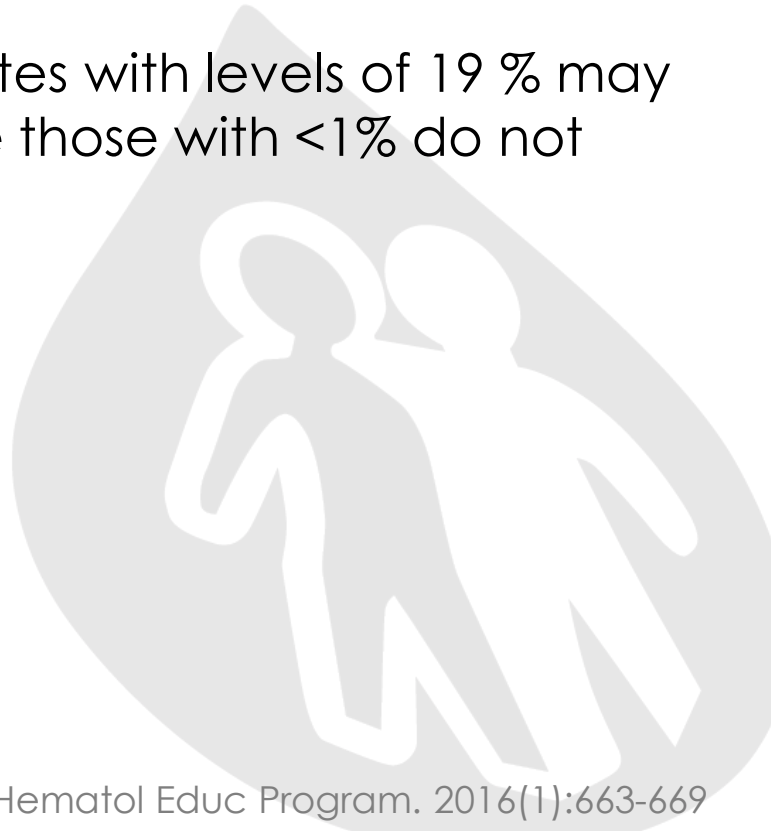
Treatment Strategy in Relation to Age and Type of Bleeding at Presentation

Bleeding Symptoms	Age	Clinical Picture	Treatment
CNS and GI	Newborns	Very Severe	Long-term Prophylaxis
Hemarthrosis and Hematomas	Toddlers	Severe	Prophylaxis/On demand
Menorrhagia	Teens/Adults	Severe or Mild	Prophylaxis/On demand
Mucocutaneous	Any	Mild	No Treatment/On demand

Defining Levels of Severity

Coagulant factor	Coagulant activity		
	Severe	**Moderate**	**Mild**
Fibrinogen	undetectable	0.1-1g/L	> 1g/L
FII	undetectable	< 10%	> 10%
FV	undetectable	< 10 %	>10%
FV +FVIII	< 20%	20-40%	> 40%
FVII	<10%	10-20%	> 20%
FX	< 10%	10-40%	> 40%
FXIII	undetectable	< 30%	> 30%

- **FVII**
  - Weak association between level and bleeding
  - heterozygotes with levels of 19 % may bleed while those with <1% do not



Peyvandi F & Menegatti M. Hematology Am Soc Hematol Educ Program. 2016(1):663-669

Registry Findings: Clinical Phenotype

IRF7-STER combined analysis indicates that bleeding symptom at disease presentation predicts subsequently developed bleeding phenotype

Di Minno MND, et al. *Blood*. 2011;118:abstract 30.

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Side Effects of Treatment

- Inhibitors (~ 2%)
- Thrombosis
  - 1/241 patients (trauma case)

STER Data – Mariani et al

Caregiver Resources

- Rare Coagulation Disorders Resource Room

  (www.rarecoagulationdisorders.org)

Session Evaluation

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- Learned new ideas/skills?
- Will implement new ideas/skills?

How could this session be improved?

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