

Women's Health  
Annual Visit®



# Bleeding Disorders and Female Patients: Collaborative Care in the Women's Health Setting

Sanjay P. Ahuja, MD, MSc, MBA

Dominic Piunno Endowed Chair in Hemophilia & Bleeding Disorders  
Director, UH Rainbow Hemostasis & Thrombosis Center



Identified or perceived conflict of interest has been resolved  
in accordance with ACCME guidelines.

# Faculty Disclosures

Dr. Ahuja has the following disclosures:

**Consulting Fees:** HEMA Biologics, Sanofi, XaTek, Inc.

**Contracted Research:** XaTek, Inc.



# Objectives

1. Identify signs and symptoms that raise suspicion of a bleeding disorder to promptly refer for, or implement, management strategies
2. Incorporate evidence-based, multi-disciplinary co-management and patient-centric management strategies for female patients with bleeding disorders, particularly with menorrhagia and during pregnancy and childbirth to optimize safety
3. Describe the mechanism of action of new and emerging treatment options in rebalancing hemostasis



# Screening Tool

Q1. How many days did your period usually last, from the time bleeding began until it completely stopped?
Q2. How often did you experience a sensation of “flooding” or “gushing” during your period?
Q3. During your period did you ever have bleeding where you would bleed through a tampon or napkin in $\leq 2$ hours?
Q4. Have you ever been treated for anemia?
Q5. Has anyone in your family ever been diagnosed with a bleeding disorder?
Q6. Have you ever had a tooth extracted or had dental surgery?
Q6a. Did you have problem with bleeding after tooth extraction or dental surgery?
Q7. Have you ever had surgery other than dental surgery?
Q7a. Did you have bleeding problem after surgery?
Q8. Have you ever been pregnant?
Q8a. Have you ever had bleeding problem after delivery or after a miscarriage?





**Table 1. Differential Diagnosis and Evaluation of Abnormal Uterine Bleeding**

<i>Category</i>	<i>Characteristics</i>	<i>Differential diagnosis</i>	<i>Evaluation</i>
Anovulatory	<p>Irregular, often infrequent periods<sup>4</sup></p> <p>Progesterone-deficient/estrogen-dominant state<sup>2</sup></p> <p>Flow ranges from absent or minimal to excessive<sup>4</sup></p> <p>14 percent of women with recurrent anovulatory cycles develop cancer or hyperplasia<sup>7</sup></p>	<p>Adolescence<sup>4,6</sup></p> <p>Diabetes mellitus, uncontrolled<sup>6</sup></p> <p>Eating disorder<sup>6</sup></p> <p>Hyper- or hypothyroidism<sup>8,9</sup></p> <p>Hyperprolactinemia<sup>4,9</sup></p> <p>Medication effects</p> <p>Antiepileptics<sup>10</sup></p> <p>Antipsychotics<sup>11</sup></p> <p>Perimenopause<sup>4</sup></p> <p>Polycystic ovary syndrome<sup>4,6</sup></p> <p>Pregnancy<sup>4</sup></p>	<p>Laboratory tests for pregnancy, TSH and prolactin levels<sup>4,8,9</sup></p> <p>Endometrial biopsy in the following persons at-risk of cancer:</p> <p>Adolescents who are obese and have two to three years of untreated anovulatory bleeding<sup>4</sup></p> <p>Women 35 years or younger with one or more of the following risk factors: chronic anovulation,<sup>4</sup> diabetes,<sup>12,13</sup> family history of colon cancer,<sup>12,13</sup> infertility,<sup>12,13</sup> nulliparity,<sup>12,13</sup> obesity,<sup>12,13</sup> tamoxifen use<sup>13,14</sup></p> <p>Women older than 35 years with suspected anovulatory bleeding<sup>4</sup></p> <p>Women with bleeding not responsive to medical therapy<sup>4</sup></p> <p>Imaging (transvaginal ultrasonography or saline infusion sonohysterography) if bleeding does not respond to medical therapy<sup>9</sup></p>
Ovulatory	<p>Regular intervals (every 24 to 35 days) with excessive bleeding or duration greater than seven days<sup>2</sup></p> <p>Less than 1 percent of women develop cancer or hyperplasia if they have no more than one risk factor for endometrial cancer<sup>7</sup></p>	<p>Bleeding disorder<sup>4,15</sup></p> <p>Factor deficiency</p> <p>Leukemia</p> <p>Platelet disorder</p> <p>von Willebrand disease</p> <p>Hypothyroidism<sup>8,9</sup></p> <p>Liver disease, advanced<sup>6</sup></p> <p>Structural lesions</p> <p>Fibroids<sup>16</sup></p> <p>Polyps<sup>17</sup></p>	<p>Laboratory tests for pregnancy, complete blood count,<sup>9</sup> TSH level<sup>8,9</sup></p> <p>Test for bleeding disorder in adolescents<sup>4,6</sup> and in women with one or more of the following risk factors<sup>19,20</sup>: family history of bleeding disorder; menses lasting seven days or more with flooding or impairment of activities with most periods; history of treatment for anemia; history of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery</p> <p>Imaging* (transvaginal ultrasonography or saline infusion sonohysterography) to rule out structural abnormality<sup>21,22</sup></p> <p>Endometrial biopsy in women 35 years or younger with normal laboratory and imaging results and bleeding unresponsive to therapy, and in women older than 35 years with multiple risk factors for cancer<sup>4,12,13</sup></p>

TSH = thyroid-stimulating hormone.

\*—Not usually needed in adolescents.

Information from references 2, 4, and 6 through 22.





# Bleeding Disorders in Women

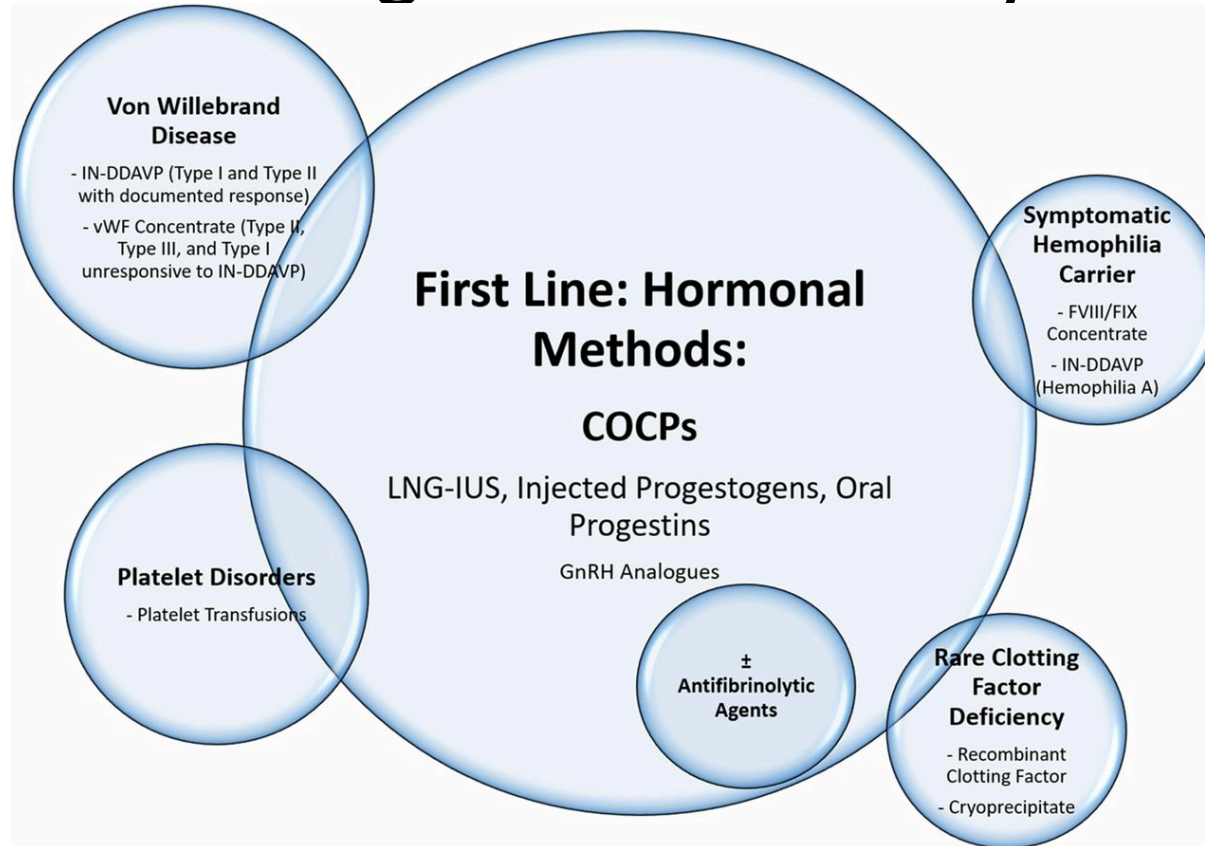
Women's Health



Annual Visit<sup>®</sup>



# Approach to the Management of Heavy Menstrual Bleeding



Rudi-Ann Graham et al. Pediatrics in Review 2018;39:588-600.



# Bleeding Disorders in Women

Women's Health









Annual Visit<sup>®</sup>





# Pictorial Bleeding Assessment Calendar (PBAC)

Surname, First Name	Start Date:		Total:					
Towel	Day							
	1	2	3	4	5	6	7	8
								
								
								
Clots/Overflow								
Tampon	Day							
	1	2	3	4	5	6	7	8
								
								
								
Clots/Overflow								

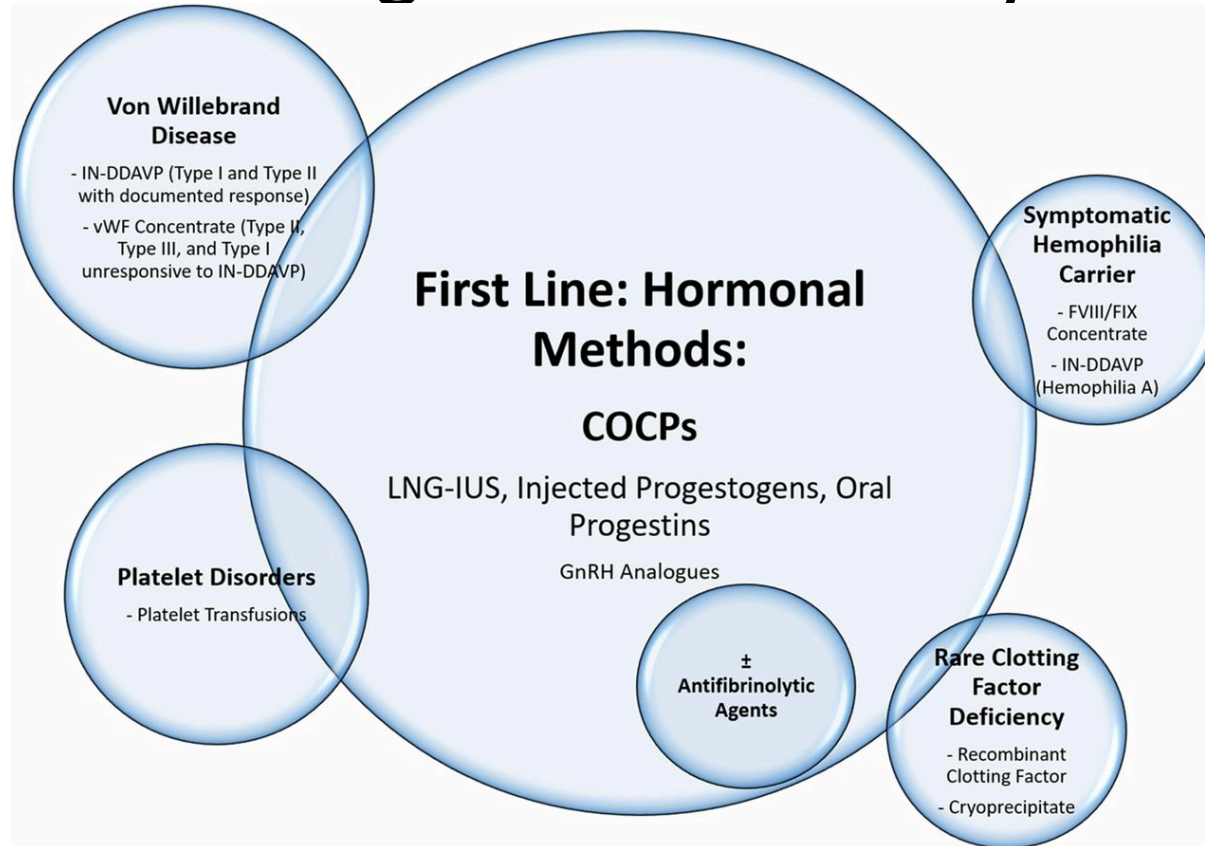
**Interpretation:**

A score of >100 points indicates menstrual loss >80ml/cycle

PADS	
Lightly Soaked	+1 Point
Moderately Soaked	+5 Points
Heavily Soaked	+20 Points
TAMPONS	
Lightly Soaked	+1 Point
Moderately Soaked	+5 Points
Heavily Soaked	+20 Points
CLOTS	
Small	+1 Point
Large	+5 Points
FLOODING	
Any	+5 Points



# Approach to the Management of Heavy Menstrual Bleeding

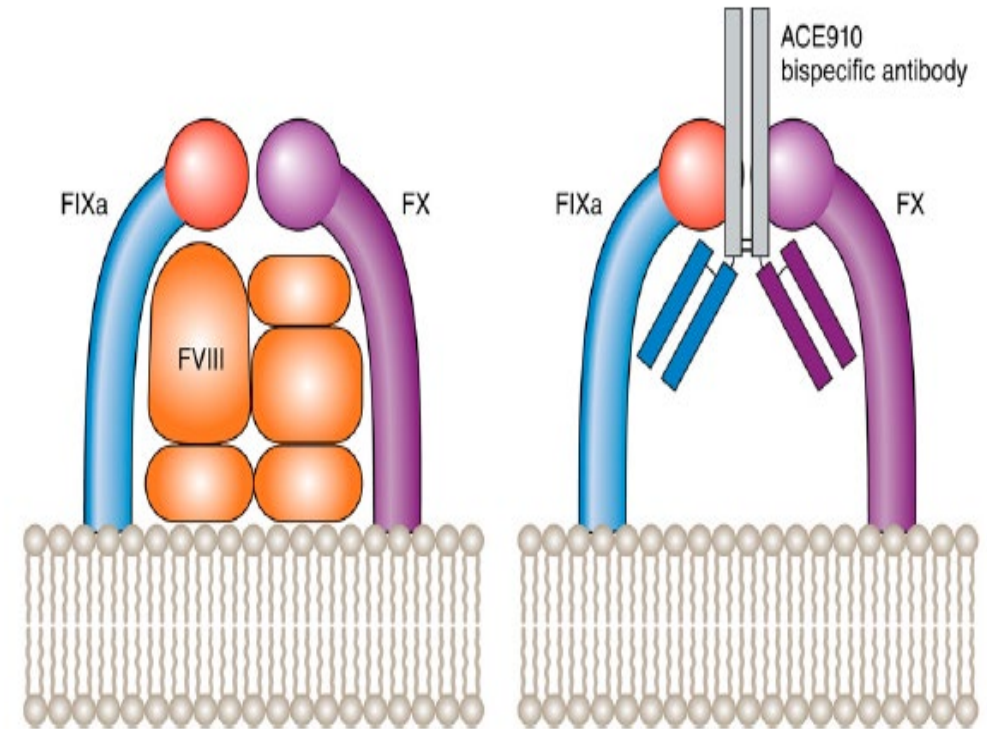


Rudi-Ann Graham et al. Pediatrics in Review 2018;39:588-600.



# Emicizumab

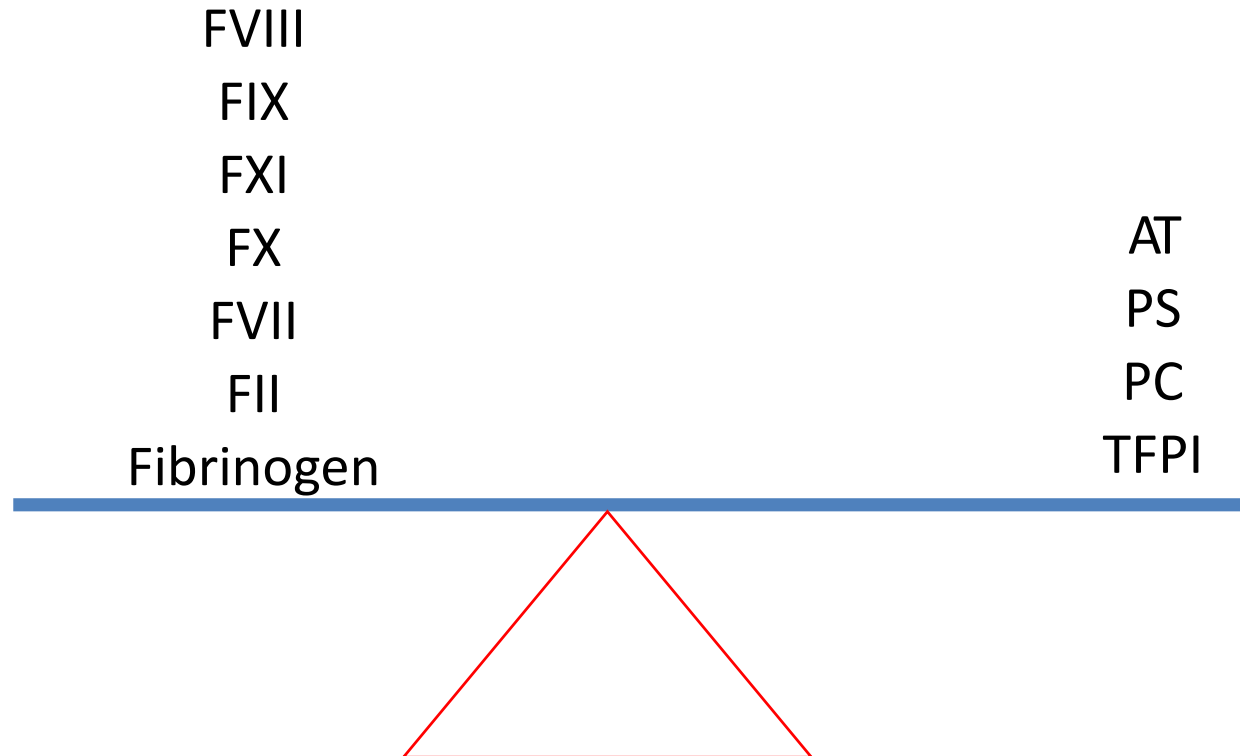
- Humanized therapeutic bispecific antibody that bridges FIXa and FX, replacing the function of FVIIIa
- With a half-life of 4 to 5 weeks, can be administered once a week or longer
- Dosed the same way (by weight) in children, adolescents, and adults
- Once weekly subcutaneous injection



FVIII brings together FIXa and FX, allowing FXa and, ultimately, thrombin generation to proceed. The ACE910 bispecific antibody (against FIXa and FX) achieves the same action in the absence of FVIII. Professional illustration by Patrick Lane, ScEYence Studios.

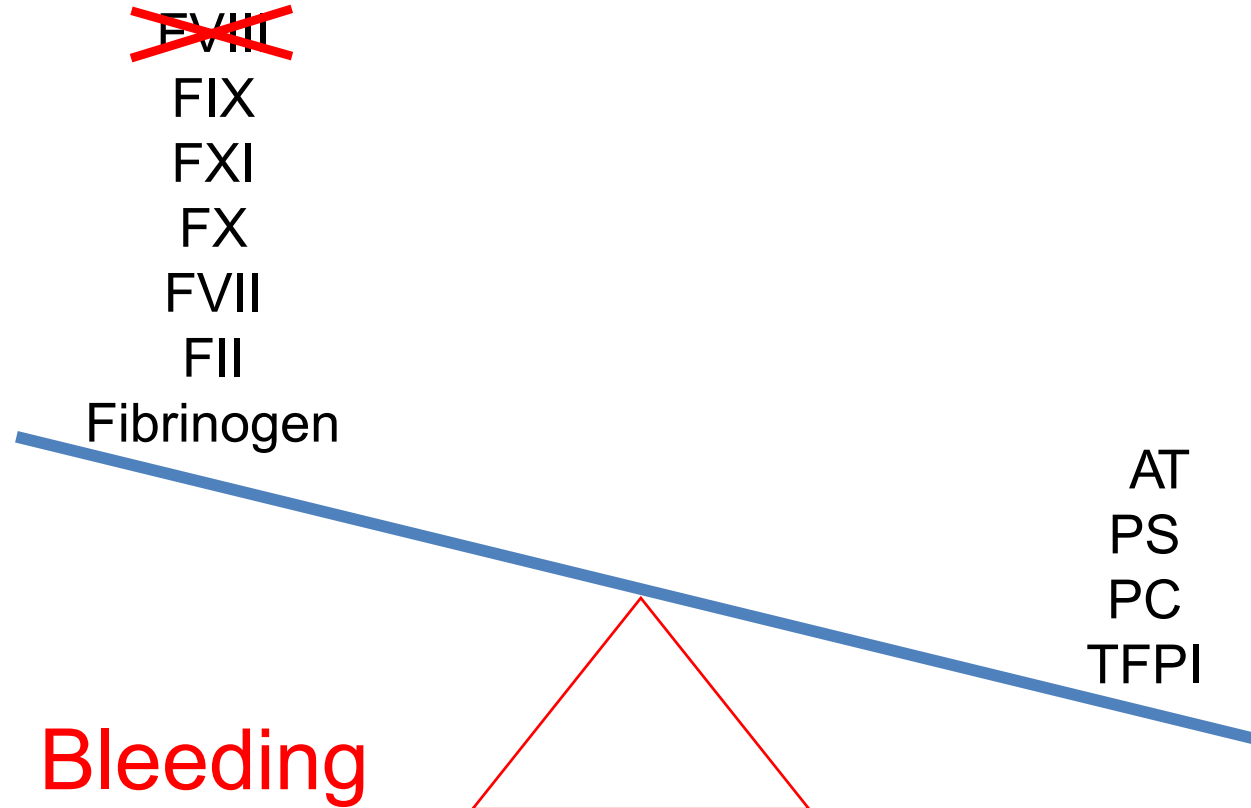


# “Balanced Hemostasis”

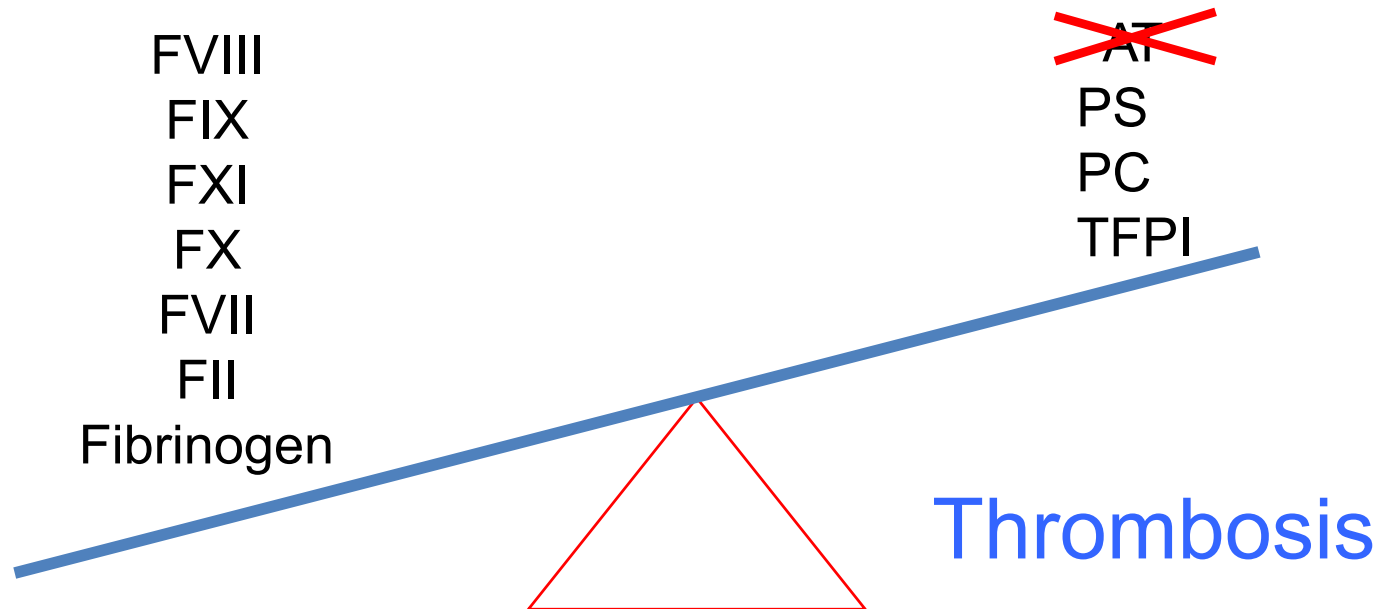




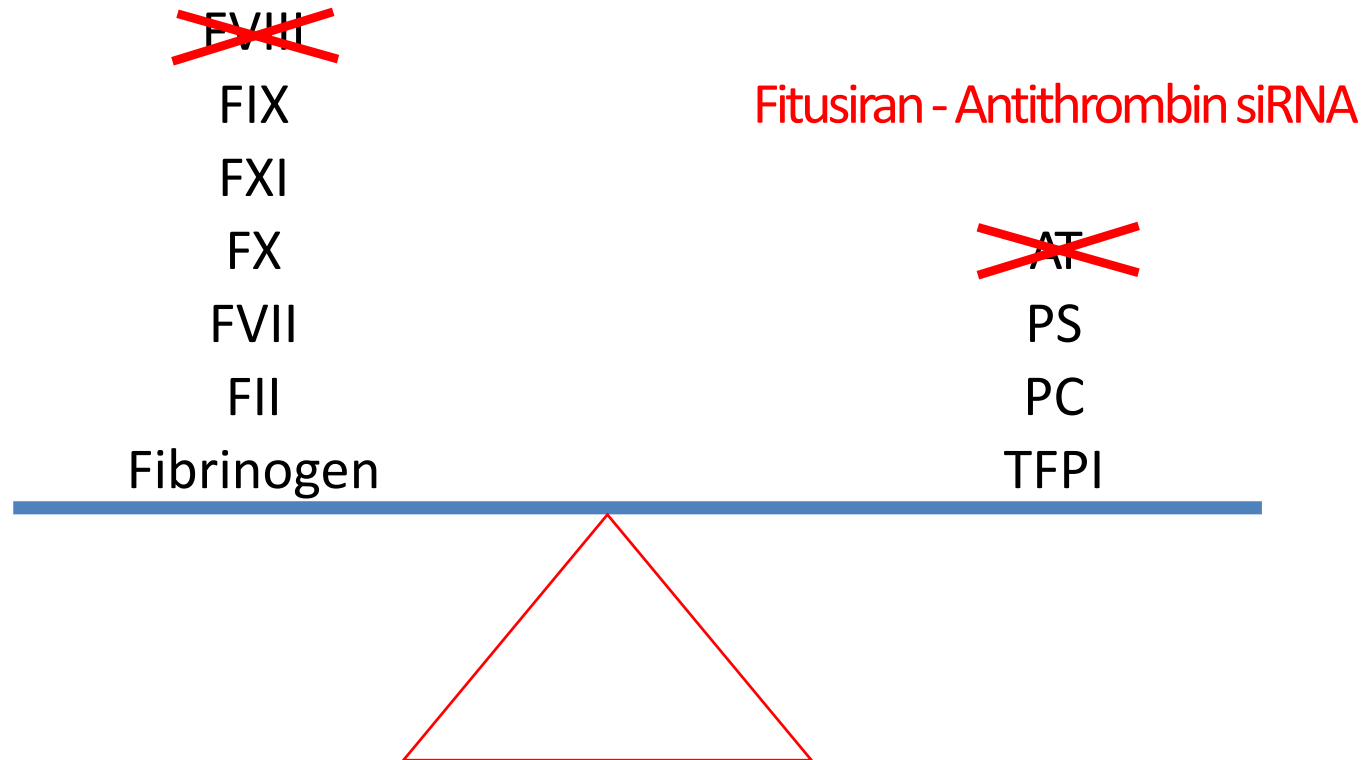
# Unbalanced Hemostasis Hemophilia A



# Unbalanced Hemostasis - Antithrombin Deficiency



# “Re-Balanced Hemostasis”



Ragni M. NEJM 2015; 373.





# Fitusiran

- Fitusiran (ALN-AT3SC), an investigational RNA interference (RNAi) therapy that specifically targets antithrombin messenger RNA (encoded by SERPINC1) to suppress the production of antithrombin in the liver
- Subcutaneous injection of fitusiran lowered antithrombin levels and increased thrombin generation in participants with hemophilia A or hemophilia B
- Subcutaneous administration monthly
- Currently being studied for both hemophilia A and B

Pasi, et.al. N Engl J Med 2017; 377:819-828.

Women's Health

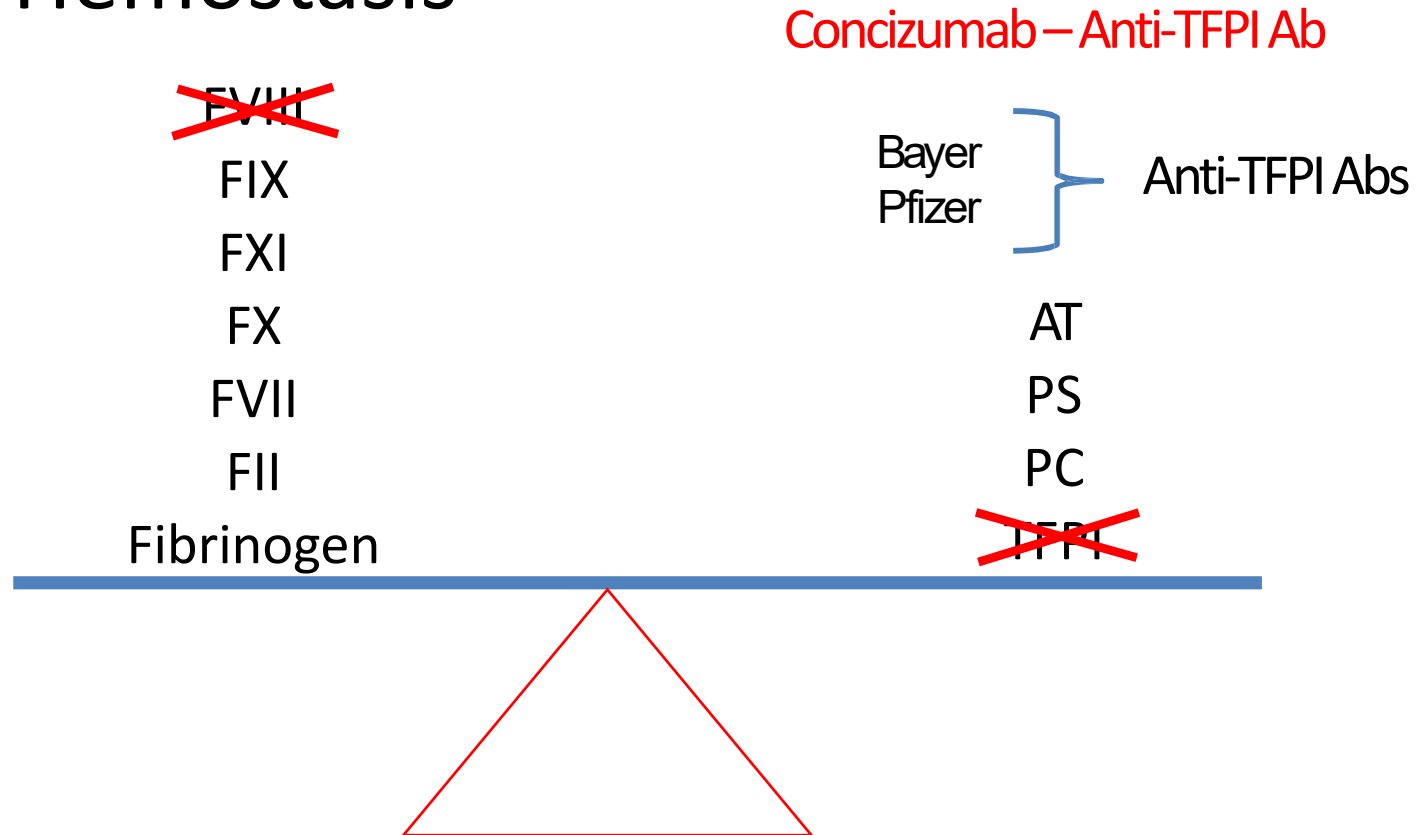


Annual Visit<sup>®</sup>





# “Re-Balanced Hemostasis”



Ragni M. NEJM 2015; 373.

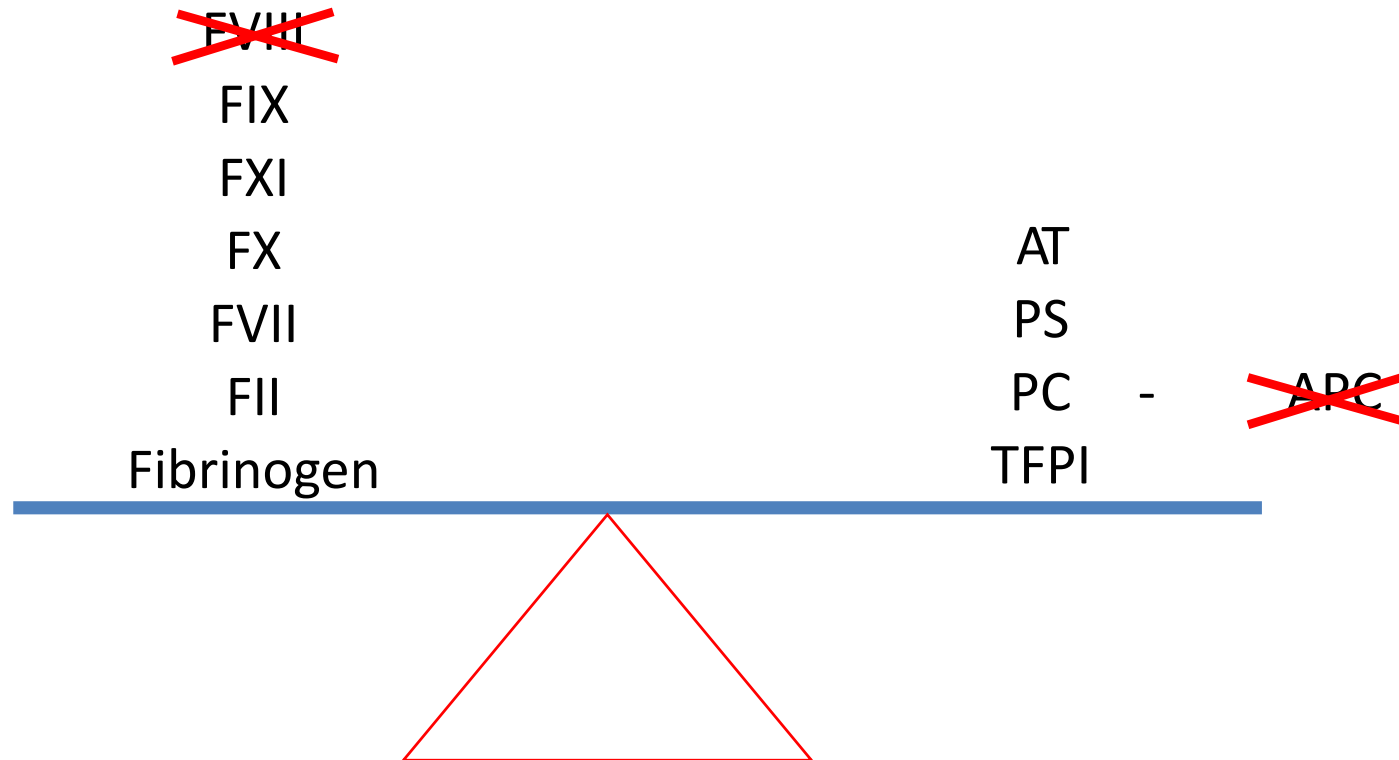


## Concizumab

- Concizumab is a high-affinity, humanized, mAb directed against the Kunitz-2 domain of human TFPI, designed to target and selectively block the FXa-binding site of TFPI
- Concizumab abolishes TFPI inhibition of the TF pathway, resulting in increased FXa production, thus allowing sufficient TG despite FVIII or FIX deficiency
- Concizumab has been shown to promote TF-induced TG by neutralizing TFPI in FVIII-deficient plasma



# “Re-Balanced Hemostasis”



Ragni M. NEJM 2015; 373.



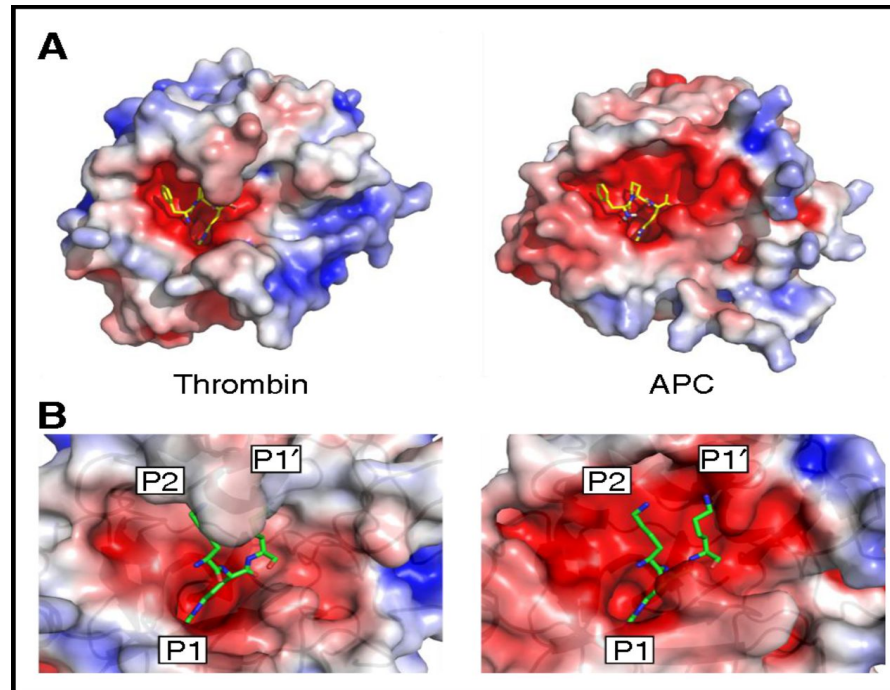
## THROMBOSIS AND HEMOSTASIS

# Design and characterization of an APC-specific serpin for the treatment of hemophilia

Stéphanie G. I. Polderdijk,<sup>1</sup> Ty E. Adams,<sup>1</sup> Lacramioara Ivanciu,<sup>2</sup> Rodney M. Camire,<sup>2</sup> Trevor P. Baglin,<sup>3</sup> and James A. Huntington<sup>1</sup>

### Key Points

- The endogenous inhibitors of APC also inhibit other coagulation proteases rendering them unacceptable for treatment of hemophilia.
- Rationally designed APC-specific serpins rescue thrombin generation in vitro and restore hemostasis in hemophilia mouse models.



Blood. 2017;129(1):105-113.





# Teamwork!





**omnia**<sup>SM</sup>  
EDUCATION

