FOUNDATION FOR
Women & Girls
with Blood Disorders

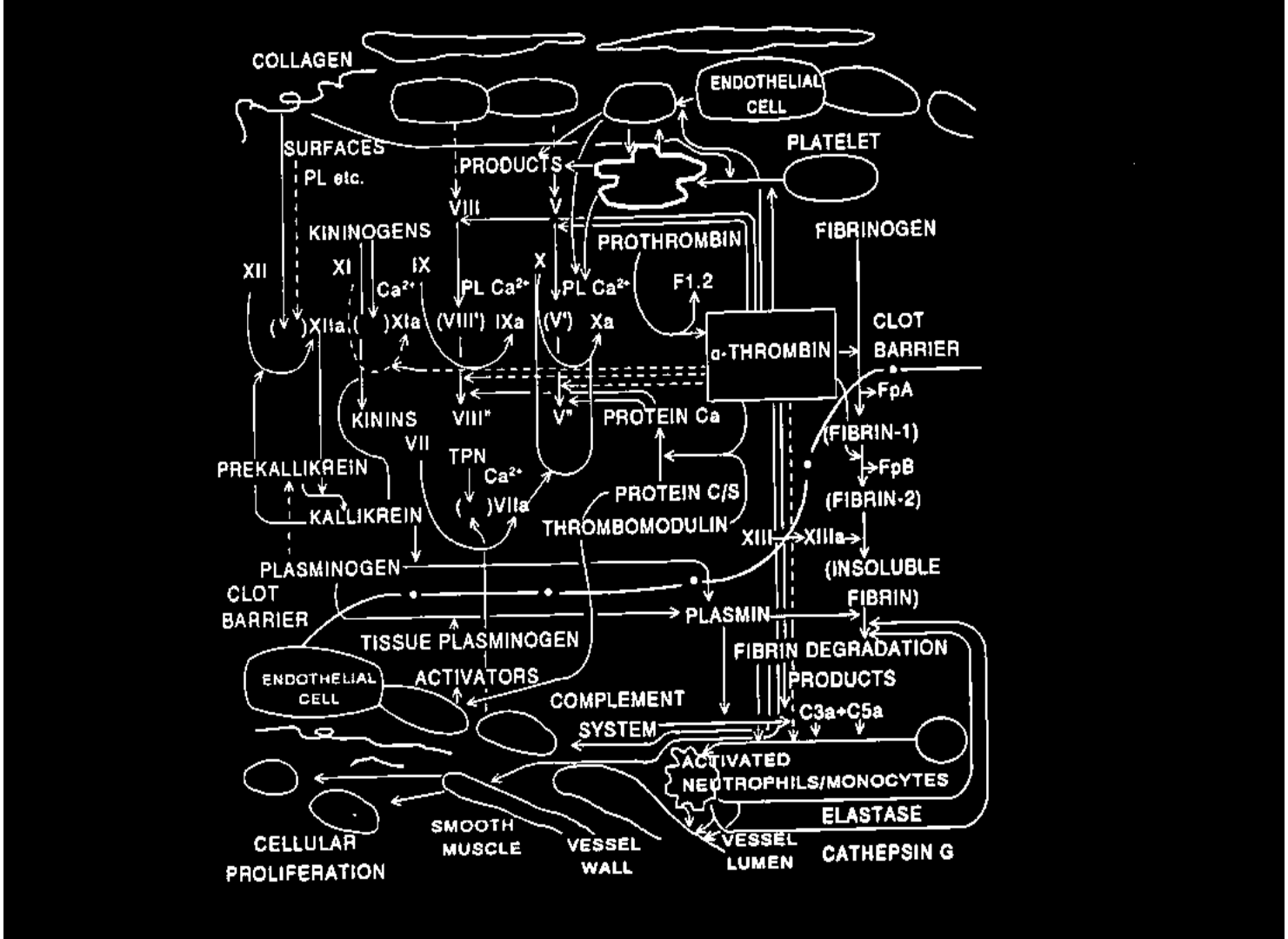
Hemostatic Options for Heavy Menstrual Bleeding

Peter A. Kouides M.D.
Medical and Research Director, Mary M. Gooley Hemophilia Center
Clinical Professor of Medicine, University of Rochester School of Medicine
Attending Hematologist, Rochester General Hospital

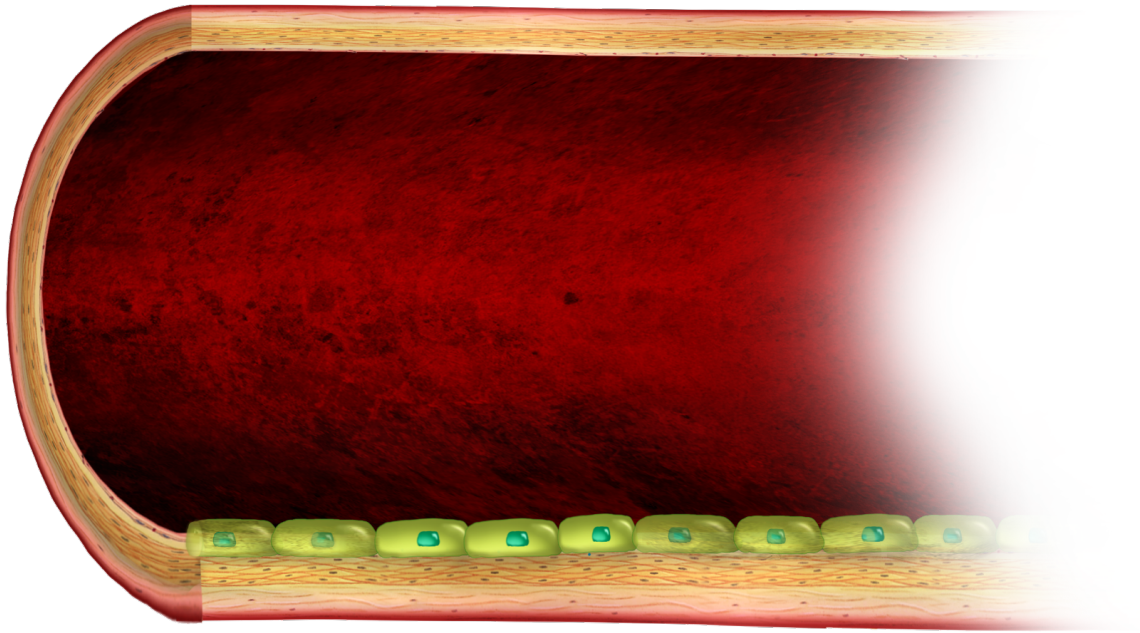
Vision: All women and girls with blood disorders are correctly diagnosed and optimally treated and managed at every life stage

OBJECTIVES

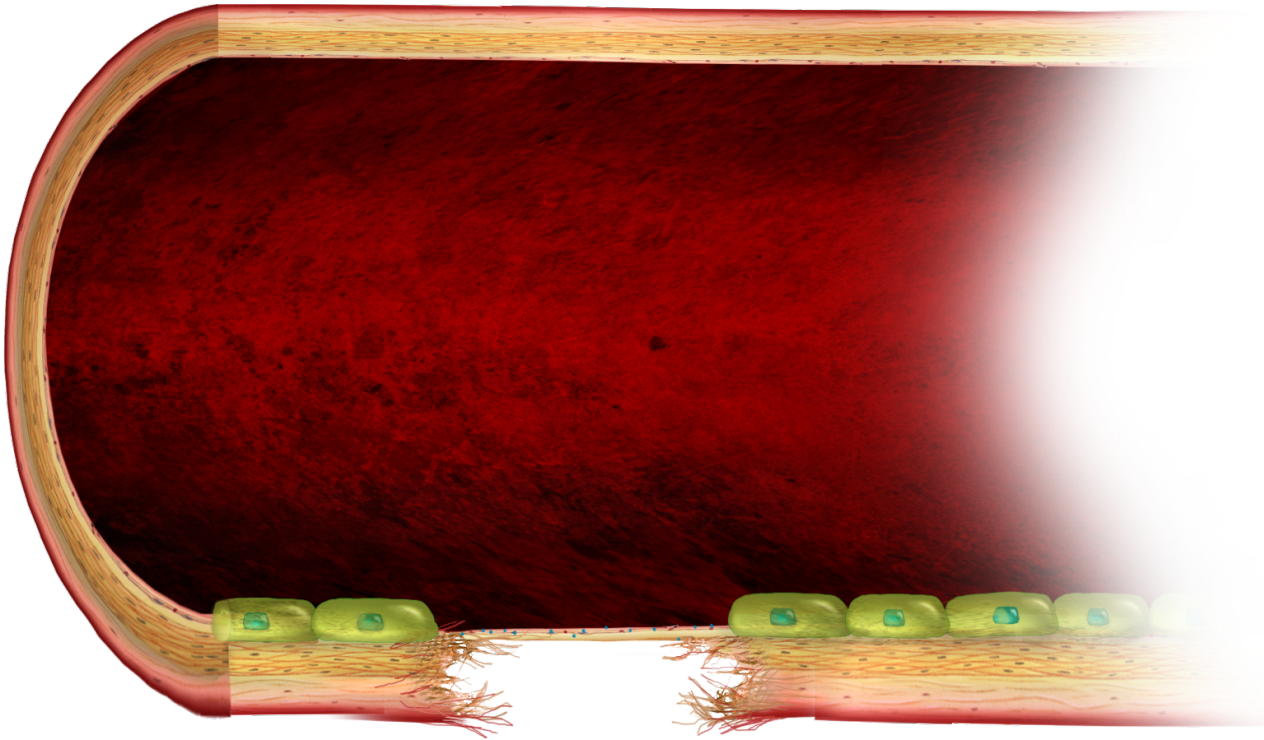
- Review the hemostasis of mensturation
- Identify therapeutic targets
- Therapuetic options for heavy menses in general
- Therapeutic options for inherited bleeding disorders
- Focus on therapeutics in von Willebrand disease

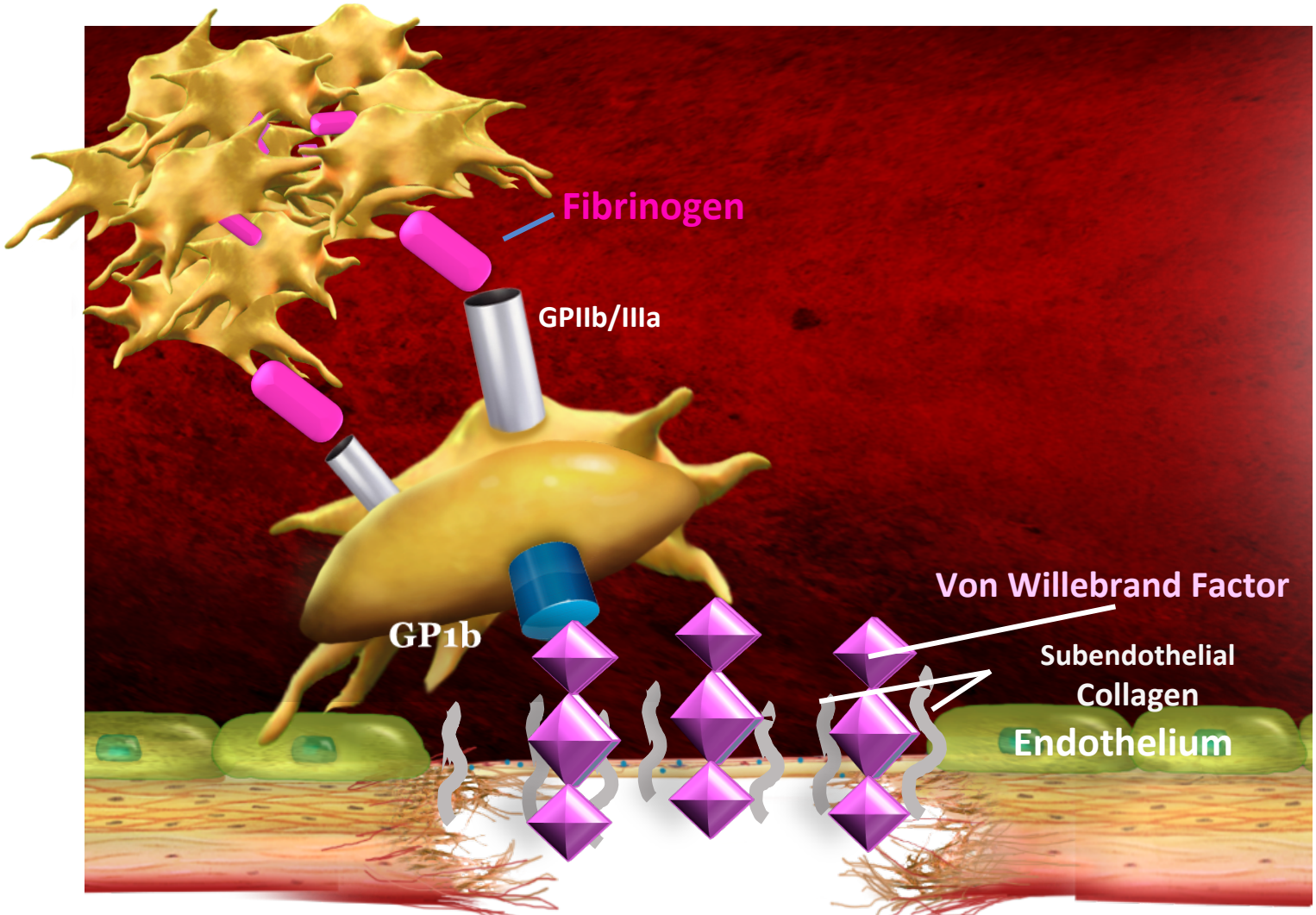

COLLAGEN
ENDOTHELIAL CELL
PLATELET
SURFACES
PL etc.
PRODUCTS
VIII
V
KININOGENS
PROTHROMBIN
FIBRINOGEN
XII
XI
IX
X
Ca2+
PL Ca2+
PL Ca2+
F1.2
(XIIa)
(XIa)
(VIII')
IXa
(V')
Xa
α-THROMBIN
CLOT BARRIER
FpA
KININS
VIII"
V"
PROTEIN Ca
(FIBRIN-1)
VII
TPN
Ca2+
PREKALLIKREIN
FpB
PROTEIN C/S
(FIBRIN-2)
(VIIa)
KALLIKREIN
THROMBOMODULIN
XIII
XIIIa
PLASMINOGEN
(INSOLUBLE FIBRIN)
CLOT BARRIER
PLASMIN
TISSUE PLASMINOGEN
FIBRIN DEGRADATION PRODUCTS
ENDOTHELIAL CELL
ACTIVATORS
COMPLEMENT SYSTEM
C3a+C5a
ACTIVATED NEUTROPHILS/MONOCYTES
ELASTASE
SMOOTH MUSCLE
CELLULAR PROLIFERATION
VESSEL WALL
VESSEL LUMEN
CATHEPSIN G

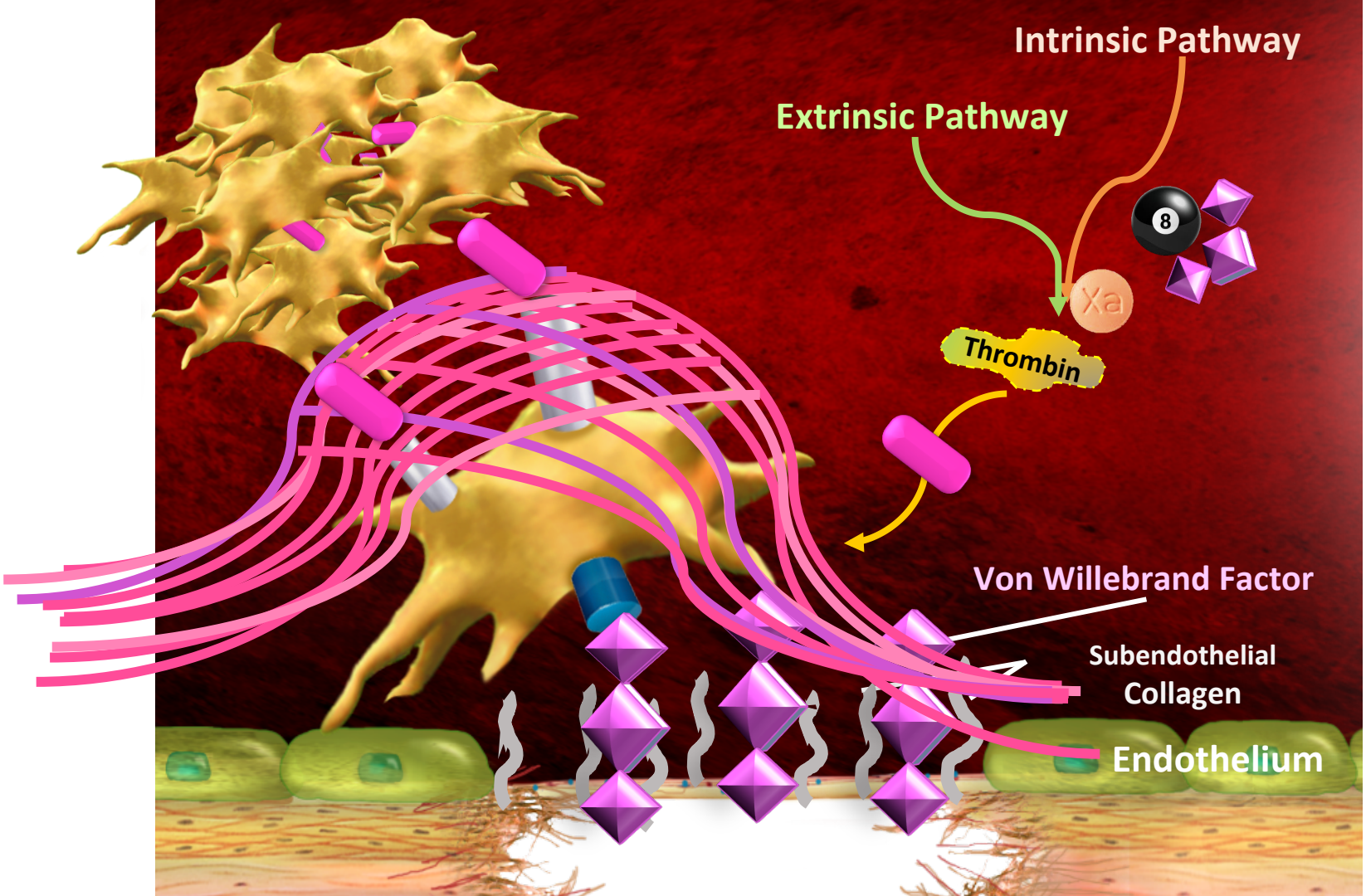
Overview of Hemostasis



Reminder…we do not bleed in a vacuum…




Fibrinogen
GPIIb/IIIa
GP1b
Von Willebrand Factor
Subendothelial
Collagen
Endothelium


Intrinsic Pathway
Extrinsic Pathway
8
Xa
Thrombin
Von Willebrand Factor
Subendothelial
Collagen
Endothelium

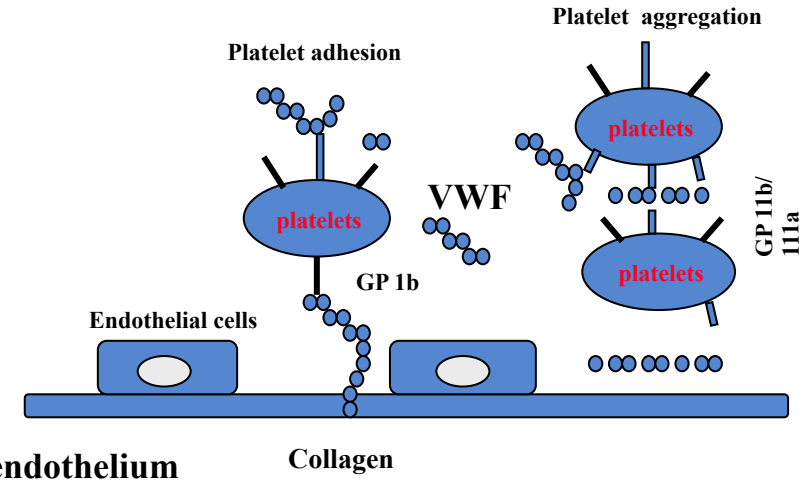

Excessive Fibrinolysis
AKA Heavy Menses
Plasmin
Von Willebrand Factor
Subendothelial
Collagen
Endothelium

Possible Hemostatic Defects in Menorrhagia (HMB)

INADEQUATE INDUCTION: — **and/or** → **OVER-COMPENSATION:**

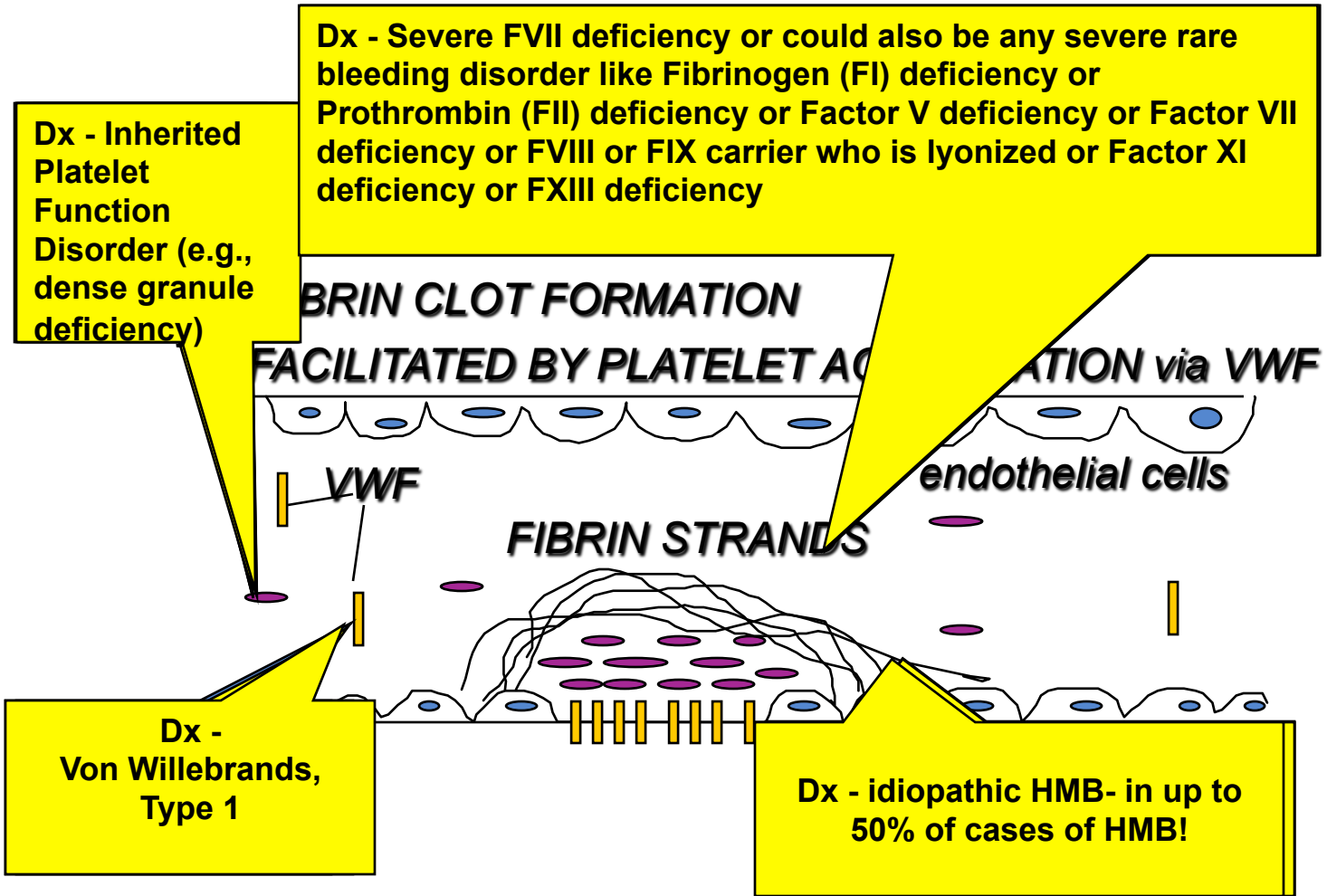
- vWF mediated platelet aggregation
- Fibrin formation
- Vasoconstriction
- Tissue regeneration

- PG induced platelet inhibition
- Fibrinolysis
- Vasodilatation



Increased menstrual blood flow >80 cc = MENORRHAGIA (HMB)

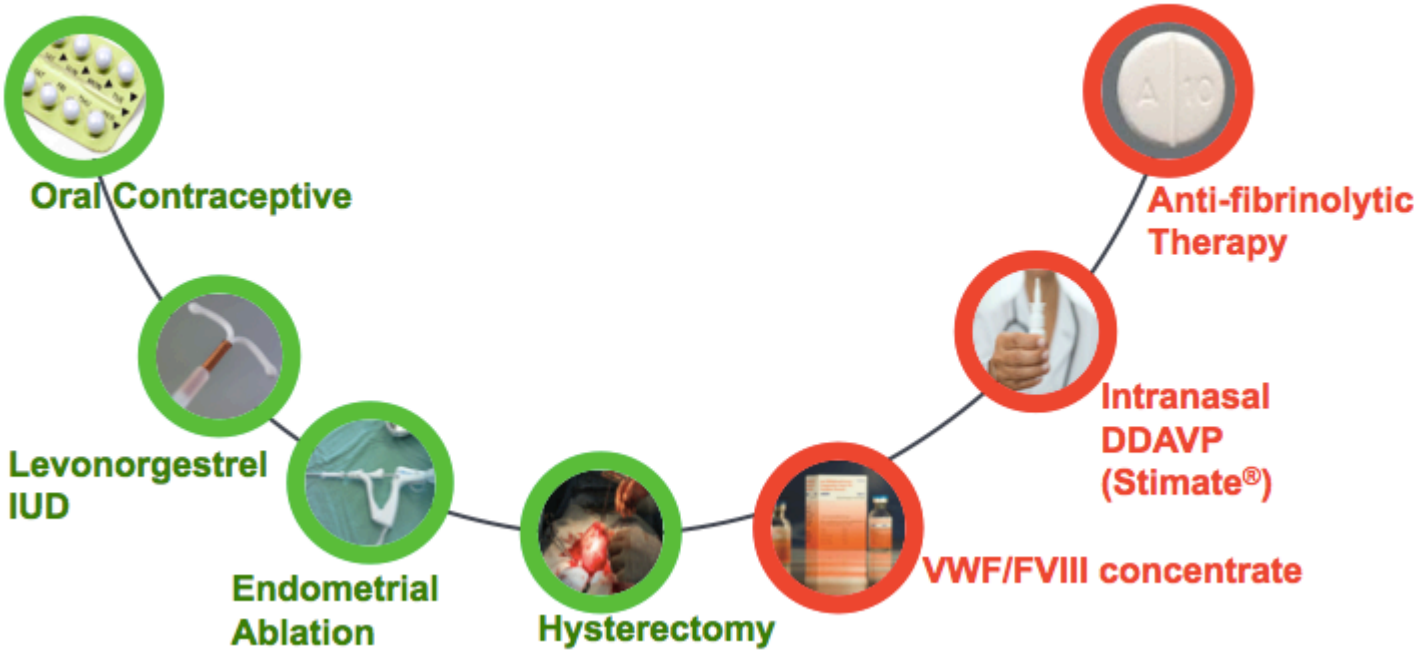
Where/why a 22 y/o may present with heavy menses (HMB)



Armour

ANTI-MENORRHAGIC FACTOR GLANULES

Best Therapy for Heavy Menstrual Bleeding?



INADEQUATE INDUCTION OF HEMOSTASIS:

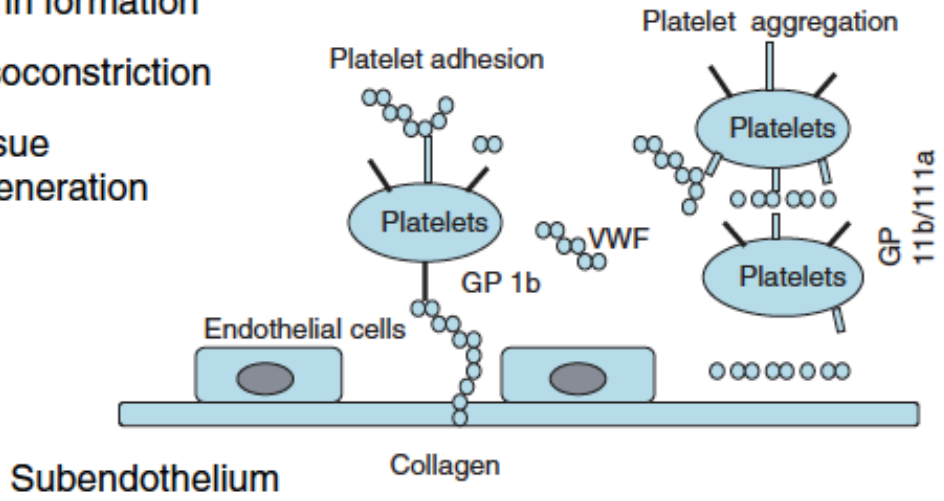
- vWF mediated platelet aggregation
- Fibrin formation
- Vasoconstriction
- Tissue regeneration

and/or

OVER-COMPENSATION:

- Vasodilatation
- PG induced platelet inhibition
- Fibrinolysis

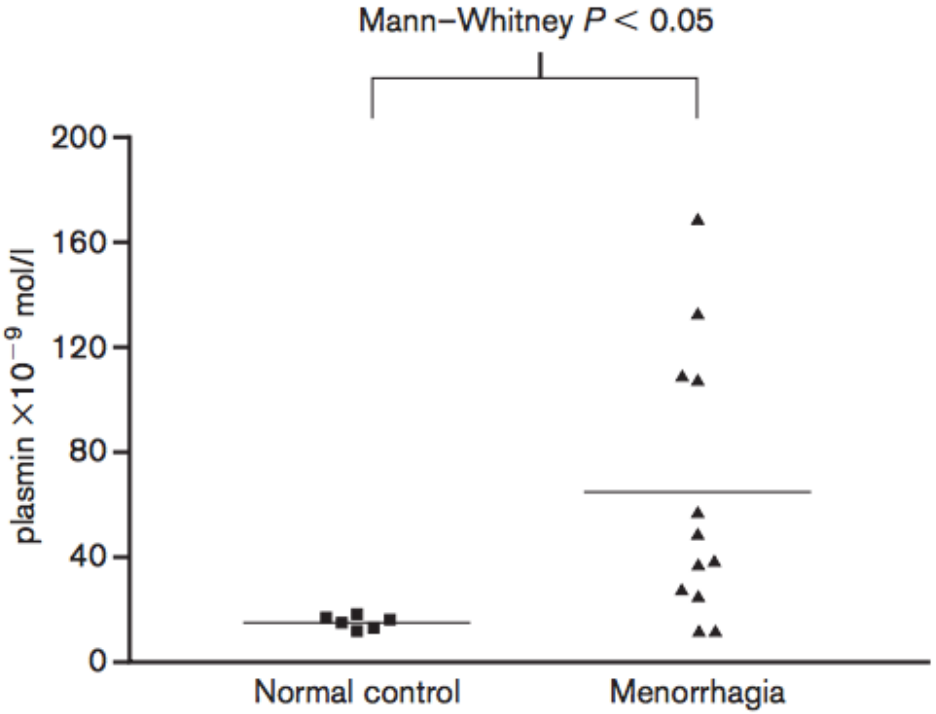
Increased menstrual blood flow > 80 cc



Heavy Menstrual Bleeding as a Disorder of Increased fibrinolysis

- Reports of increased systemic and localized intrauterine fibrinolysis in heavy menstrual bleeding and in postpartum hemorrhage

- Catheterized samples of increased fibrinolytic activity in HMB patients compared to controls



Winkler UH . Ann NY Acad Sci 1992; 667:289-90
Edlund M, Blomback M, He L.. Blood Coagul Fibrinolysis 2003; 14:593-8

Tranexamic Acid in HMB: Systematic Review

- 12 studies involving 690 women-
  - the reduction in MBL ranged from 34% to 56% in those treated with >3 mg tranexamic acid for 5 days

- Superior reduction in MBL over three cycles compared to mefanamic acid (54% versus 10%, $p < 0.001$)

- Overall, TA significantly reduces MBL in women with HMB. However, it does not reduce the duration of menses or regulate the cycle

Bitzer J, et al. Obstet Gynecol Surv. 2015; 70(2):115–30.
Matteson KA, et al. Obstet Gynecol. 2013; 121(3):632–43.

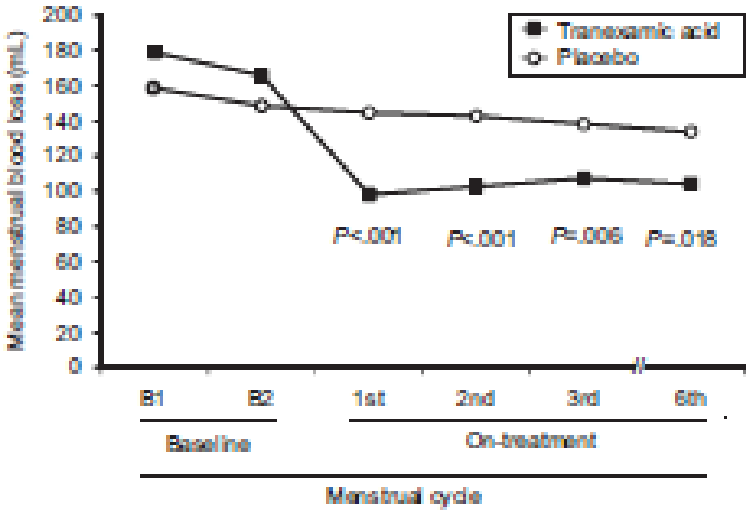
A New and Improved Tranexamic Acid?
Lysteda – brief history

- Unique formulation that provides a higher per-tablet dose and increases drug absorption
- Designed to maintain efficacy of immediate release TA while minimizing gastrointestinal adverse effects
- Xanodyne Pharmaceuticals program (2003)
- FDA approval in November, 2009

FDA Licensure Trial for Lysteda

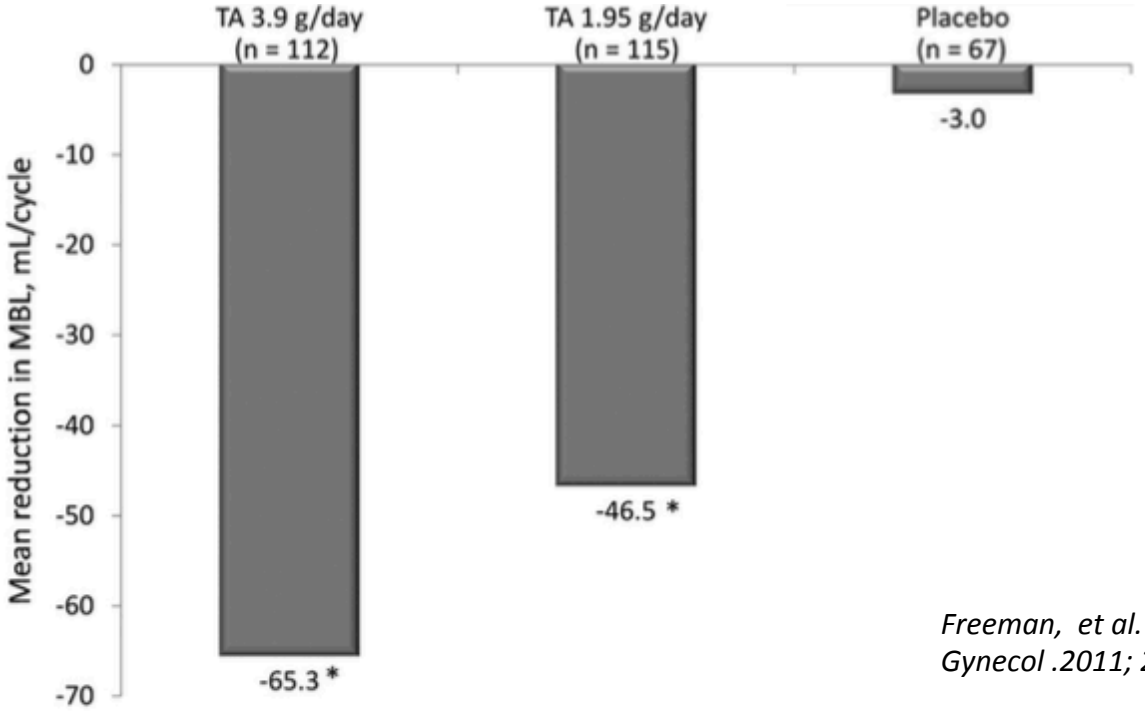
	Reduction of MBL*
TA (n=115)	69.6 mL (40.4%)
Placebo (n=67)	12.6 mL (8.2%)

*(statistically significant difference, P<.001)



Lukes, et al. Obstet Gynecol. 2010; 116:865-75

1.3 g tid dosing superior to 650 mg tid dosing



Freeman, et al. Am J Obstet Gynecol .2011; 205:319.e1-7

*$P < .0001$ vs baseline and placebo.

MBL, menstrual blood loss; *TA*, tranexamic acid (Lysteda; Ferring Pharmaceuticals, Inc, Parsippany, NJ).

Risk Profile of Lysteda

Adverse Event	Tranexamic Acid (n=117)	Placebo (n=72)	P†
Menstrual discomfort/ cramps	72 (61.5)	36 (50.0)	.120
Headache	65 (55.6)	36 (50.0)	.457
Back pain	28 (23.9)	14 (19.4)	.471
Nausea	17 (14.5)	11 (15.3)	.888
Anemia	12 (10.3)	4 (5.6)	.260
Arthralgia	11 (9.4)	5 (6.9)	.556
Viral upper respiratory tract infection	9 (7.7)	7 (9.7)	.626
Multiple allergies	10 (8.5)	5 (6.9)	.692
Abdominal discomfort	8 (6.8)	6 (8.3)	.703
Cough	7 (6.0)	5 (6.9)	.792
Insomnia	6 (5.1)	6 (8.3)	.380
Fatigue	8 (6.8)	3 (4.2)	.446
Muscle cramps	8 (6.8)	3 (4.2)	.446
Dyspepsia	3 (2.6)	8 (11.1)	.015
Migraine	7 (6.0)	4 (5.6)	.903
Sinus headache	9 (7.7)	2 (2.8)	.161

Data are n (%) unless otherwise specified.

* Events that occurred in more than 10 participants irrespective of causality.

† P was determined using a χ^2 test.

- No statistically significant adverse events compared to placebo
  - No thrombotic events
- Thrombosis has not been observed in men or women receiving tranexamic acid for-
  - bleeding 2° to cardiac or oral surgery, acute upper GI bleeding, or ocular trauma
- Use of tranexamic acid not associated with an increased risk or incidence of thromboembolic events compared with the background rate of thrombotic events in women of childbearing age

Lukes, et al. Obstet Gynecol. 2010; 116:865-75

Outstanding Issues With Lysteda

- Concurrent estrogen-containing contraception

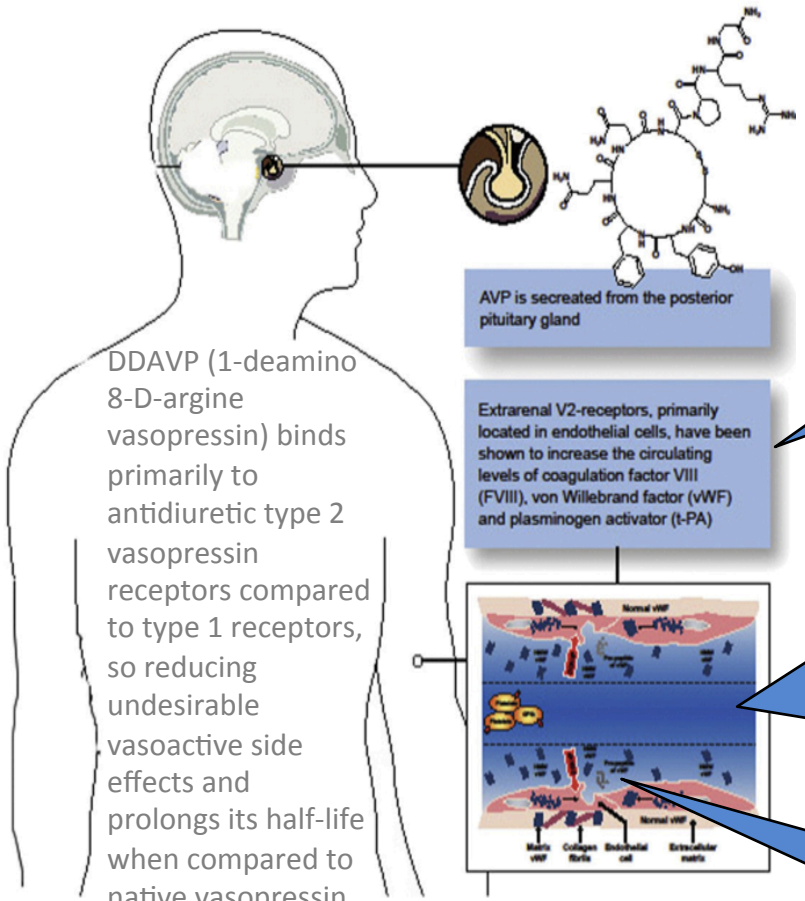
----------CONTRAINDICATIONS----------

- Women who are using combination hormonal contraception (4.1)
- Women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion (4.1)

- Adolescents - as licensure study excluded age < 18 years age
  - However, a pharmacokinetic study in 20 adolescent females aged 12-16 years of age, no dose adjustment was needed
  - Recent pilot study (n=17) showed oral TA appeared as efficacious as OC in the management of adolescent HMB by reducing MBL and improving quality of life

Srivaths VL , et al. J Pediatr Adolesc Gynecol. 2015; 28: 254e257

Physiology of Vasopressin Extracted by DDAVP



DDAVP (1-deamino 8-D-argine vasopressin) binds primarily to antidiuretic type 2 vasopressin receptors compared to type 1 receptors, so reducing undesirable vasoactive side effects and prolongs its half-life when compared to native vasopressin

DDAVP induces Endothelial cell (EC) via cAMP mediated Weibel-Palade Body secretion increasing membrane-bound and circulating VWF as well as FVIII

DDAVP also induces platelet release and membrane presentation of P-selectin which Mediates platelet rolling on ECs under high shear conditions through PSGL-1/P-selectin Interaction

DDAVP increases EC adhesiveness for platelets and platelet adhesion to collagen probably via VWF

P.J. Svensson Blood Reviews 28 (2014) 95–102

Background, DDAVP responsiveness in VWD

- Type 1 - Usually if FVIII, VWF RCo > 10% will have 2-6 fold response with improved platelet function but-
  - When baseline levels 10-20% beware of Type 1C with its initial excellent response albeit short-lived
- Type 2A - Variable
- Type 2B - Usually contraindicated

Castaman G, et al. Blood. 2008; 111(7):3531–9.

Downside of IN DDAVP for VWD-related HMB:

- Quarter of patients experience moderate to severe side effects -
  - Headache
  - Flushing
  - Nausea/Vomiting
  - Fatigue
  - Weight gain
  - Least common but most severe- Hyponatremia>seizure

Dunn A, et al. Haemophilia. 2000; 6:11-14.

CDC Female Data Collection pilot study (n=319): Treatments used for menorrhagia in Inherited Bleeding Disorders

Treatment	
Oral contraceptive	55%
DDAVP	34%
Anti-fibrinolytics	24%
Blood or plasma products	7%
Clotting factor products	6%
Endometrial ablation	4%
MIRENA	3%
Uterine artery embolization	2%
Platelet transfusion	1%

Byams V, et al. Haemophilia. 2011; 17 (Suppl. 1): 6–13

Bleeding Disorder Related Menorrhagia (HMB) Management: TA (Europe, Canada) or DDAVP (U.S.)

Tranexamic acid (TA)

- In non-VWD menorrhagia-randomized study
  - ➢54% reduction in MBL with TA alone
- In VWD menorrhagia
  - ➢Small studies,
    - ➢Mohri: 3g/dose in 3 patients
    - Ong, et al: 4g/d (1 dose) in 4 patients
    - Onundarson: 4g/d (1 dose) in 1 patient
    - Royal Free London: 15/37 (40%) with PBAC <100

Bonnar J, Sheppard BL. BMJ. 1996; 313:579-582;

Mohri H. Thromb& hrombolysis. 2002; 14:255-257;
Ong YL, et al. Haemophilia. 1998; 4:63-65;
Onundarson PT. Haemophilia. 1999; 5:76.

Desmopressin (DDAVP)

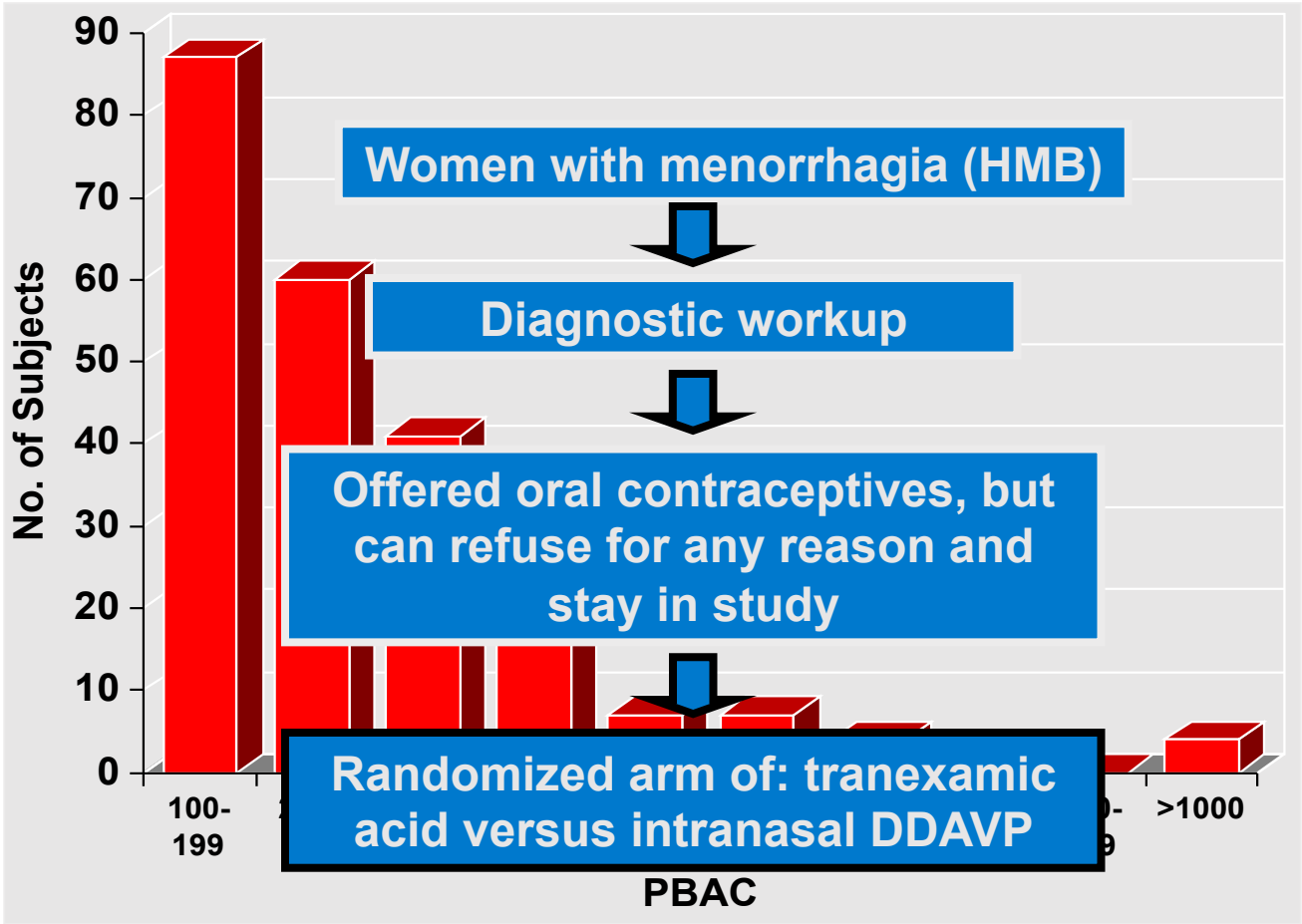
- Positive case series experience based on subjective assessment:
  - ➢80-90% good to excellent
- More recent data:

  Controlled studies using PBAC or spectrophotometry:
  - ➢Royal Free London:
    - Intranasal DDAVP was not better than placebo
  - ➢Karolinska Sweden:
    - Intranasal DDAVP in combination with TA most effective

Rodegherio F, et al. T&H 1996; 76:692-696;
Leissinger C, et al. Haemophilia. 2001; 7:258-266;

Kadir R, et al. Haemophilia. 2002; 8:787-793;
Edlund M, et al. Blood Coag Fibrinolysis. 2002; 13:225-231.

Χεντερ φορ Δισεασε Χοντρολ - ΥΣΑ Ωομεν Ωιτη Βλεεδινγ Δισορδερ Μαναγεμεντ Στυδψ



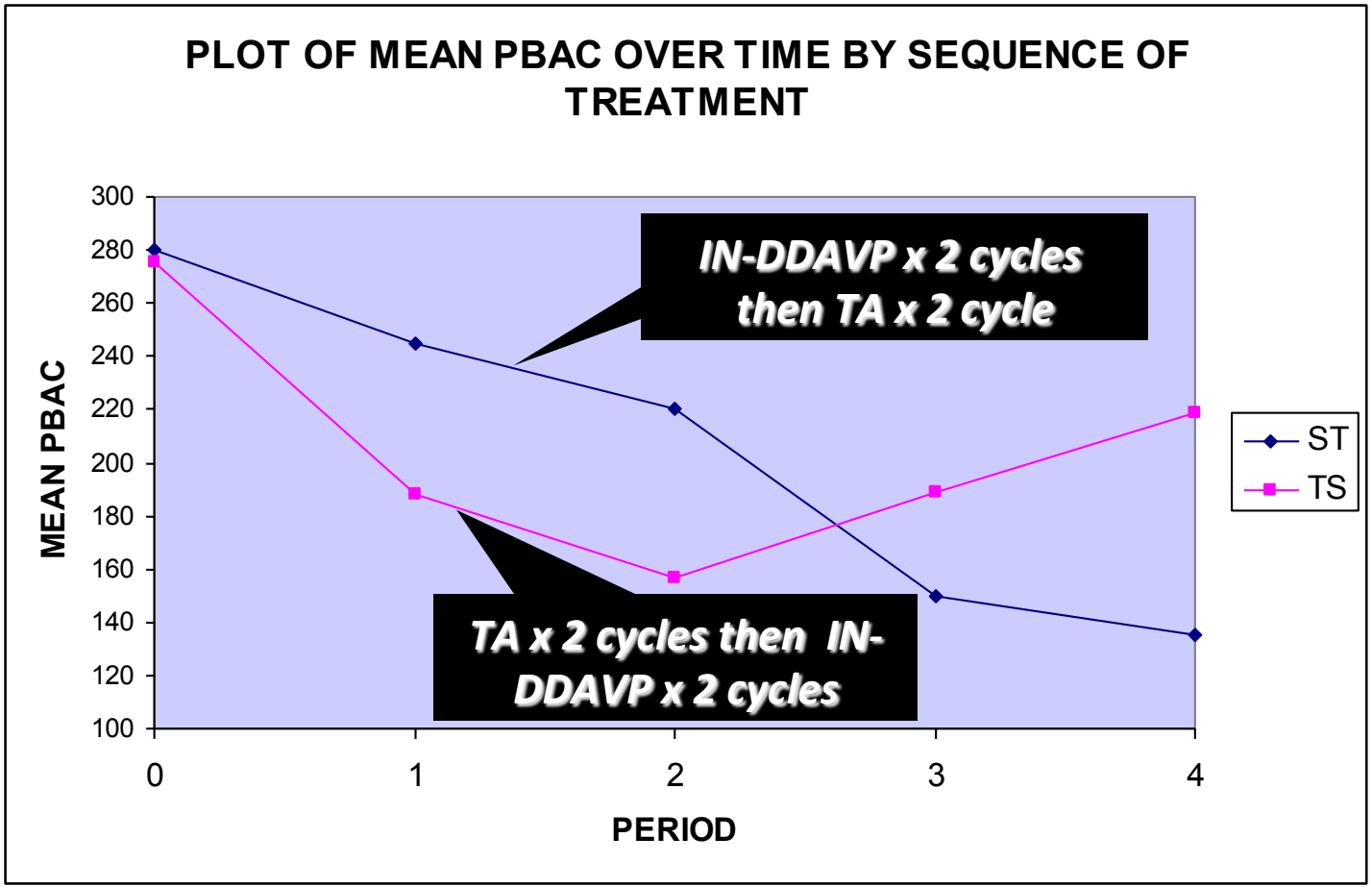
STUDY OUTCOMES

Quality of life

Menstrual flow

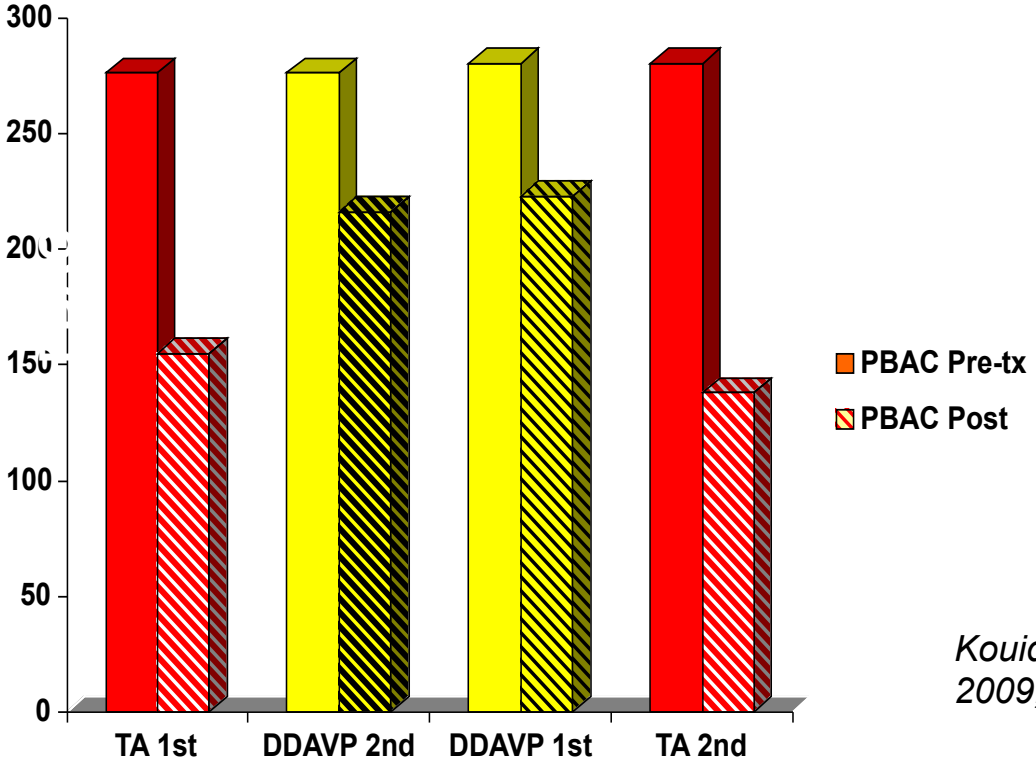
Coagulation parameters

Kouides, et al. British J Haem. 2009; 145 (2):212-220



Kouides, et al. British J Haem. 2009; 145(2):212-220

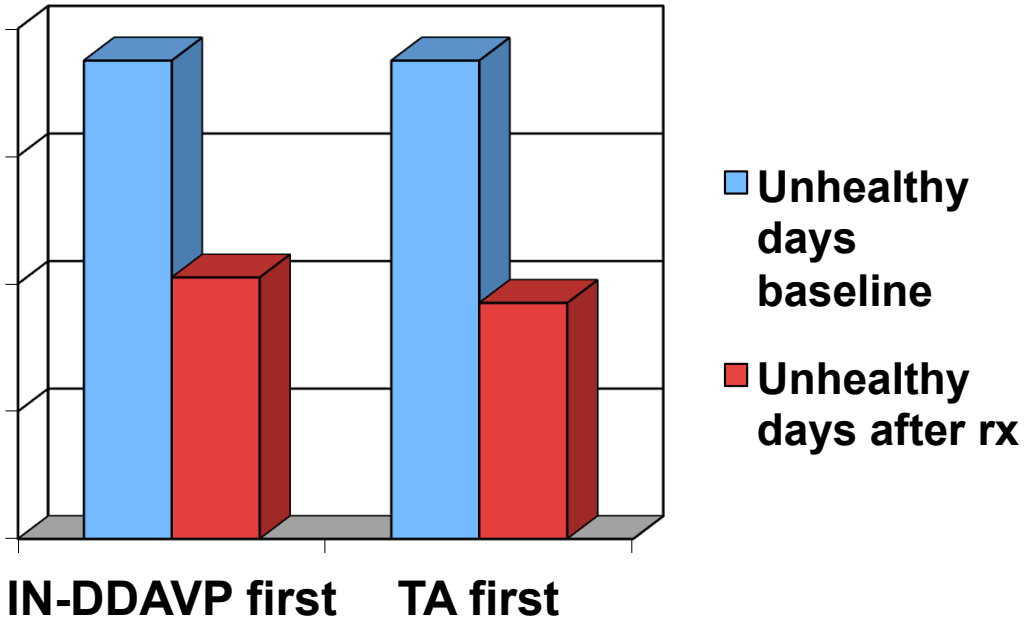
The Center for Disease Control Women With Bleeding Disorder Management Study: Reduction in PBAC - TA vs. DDAVP



Kouides, et al. British J Haem. 2009; 145 (2):212-220

The Center for Disease Control Women With Bleeding Disorder Management Study: Improvement in QOL - TA vs. DDAVP

- The number of unhealthy days by SF-36 QOL instrument:



Kouides, et al. British J Haem. 2009; 145 (2):212-220

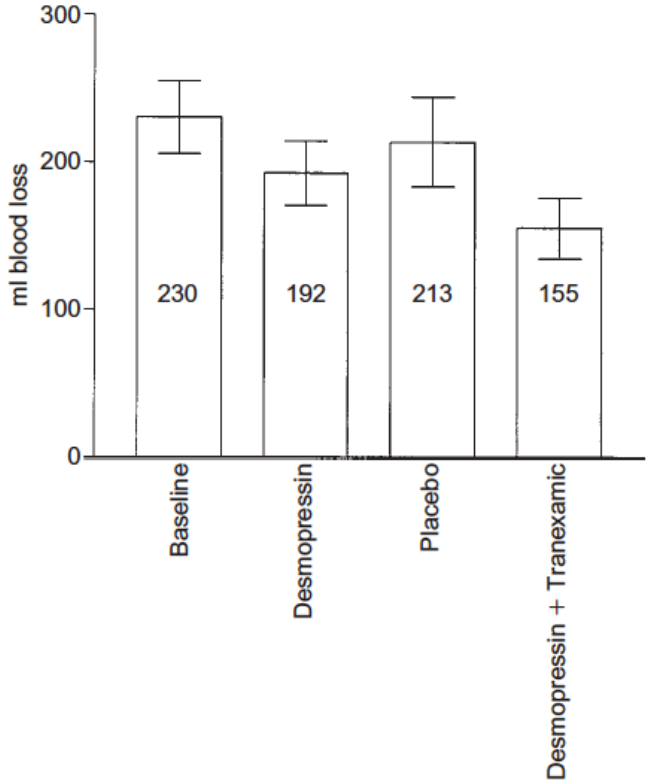
The Center for Disease Control Women With Bleeding Disorder Management Study: Improvement in QOL - TA vs. DDAVP, II

- The Center for Epidemiologic Studies Depression Scale (CES-D)
  - ➢ summary score decreased from baseline, indicating fewer depressive symptoms in both arms
- Ruta menorrhagia questionnaire-
  - ➢Change in mean score from baseline to after IN-DDAVP, p value=0.008
  - ➢Change in mean score from baseline to after TA, p value=0.003

Kouides, et al. British J Haem. 2009; 145 (2):212-220

For DDAVP Failures?

- Combined therapy with TA-



Edlund M, et al. Blood Coagulation and Fibrinolysis. 2002; 13:225-231

VWF concentrates in DDAVP and/or TA refractory cases in VWD-related HMB

VWF for menorrhagia (HMB): A survey and literature review

- 83 surveys distributed to hemophilia treatment center MDs
  - 20 (24.1%) provided sufficient data for analysis

- Of 1321 women with VWD seen during 2011–2014, 816 (61.8%) had menorrhagia (HMB)
  - Combined oral contraceptives, TA and desmopressin were the most common first-line therapies
  - VWF replacement was a third-line therapy reported in 13 women (1.6%)
- Together with data from 88 women from 6 published studies, VWF replacement therapy safely reduced menorrhagia in 101 women at a dose of 33–100 IU/kg on days 1–6 of menstrual cycle

Ragni, et al. Haemophilia. 2016; 22(3):397-402.

FDA Approved VWF products

	Plasma-derived VWF containing FVIII concentrates				Recombinant
Product	Humate	Alphanate	Wilate	Wilfactin	Vonvendi
Manufacturer	CSL Behring, USA	Grifols, USA	Octapharma, USA	LFB	Baxalta/Shire
Purification method	Multiple precipitation	Precipitation/ heparin ligand CT	Precipitation/ion exchange and size exclusion CT	Ion exchange + affinit chromato-graphy	Chinese hamster ovary cell line
Viral Inactivation	Pasteurization	S/D, dry heat	S/D, dry heat	S/D, dry heat/35 nm filtration	Not required
VWF:RCo/VWF:Ag	0.91	0.43	0.9-1.0	0.95	1.16
VWF:RCo/ FVIII:C ratio	2.88	0.82	1.0	50	No FVIII
ULM	Absent	Absent	Absent	Absent	Present
FDA approved	Yes	Yes	Yes	No	Yes

S/D, solvent detergent; CT, chromatography; FVIII, factor VIII; FVIII:C, factor VIII coagulation activity; VWF:Ag, VWF antigen; VWF: RCo, VWF ristocetin cofactor; ULM, ultra-large multimers.

Singal M and Kouides P: Drugs of Today. 2016; 52 (12):653-666

Thank you!

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