TREATMENT & MANAGEMENT OF VON WILLEBRAND DISEASE

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HFA Meeting 2015

What is von Willebrand Factor?

- VWF is a large multimeric protein
- Two main functions in hemostasis (clotting)
  - 1. Flow-dependent tethering of platelets to the subendothelium (adhesion) and bridging to other platelets (aggregation) securing platelet plug formation and primary haemostasis.

Coagulation

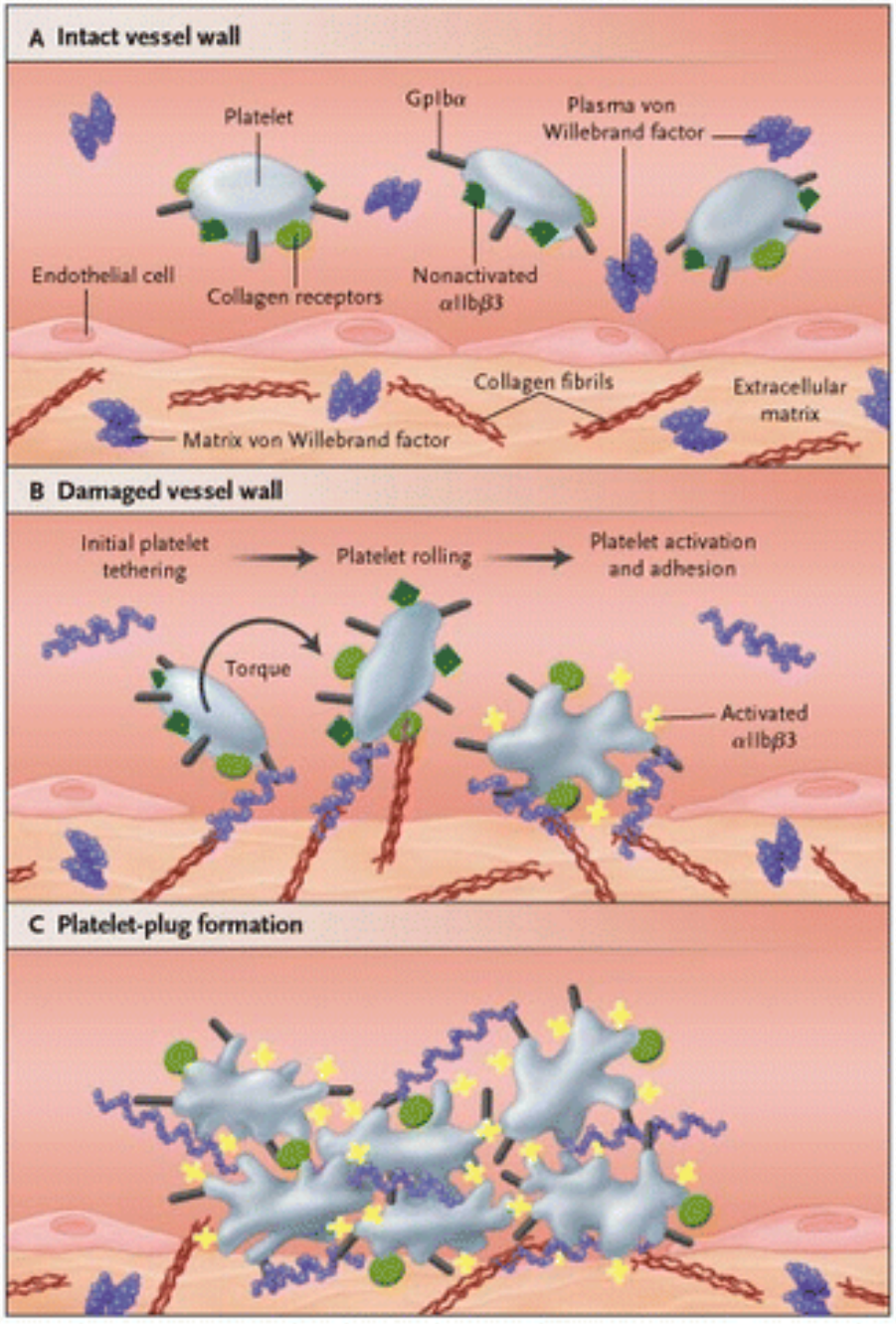


Figure 1. Simplified Model of von Willebrand Factor Functions in Platelet-Plug Formation.

In the intact vessel wall (Panel A), endothelial cells hamper the interactions of circulating platelets and their membrane glycoproteins Ibα (GpIbα), nonactivated IIb–IIIa (αIIbβ3), and collagen receptors GpVI and α2β1 with von Willebrand factor and collagen fibrils localized in the subendothelial extracellular matrix. When the vessel wall is intact and blood flow is normal, plasma von Willebrand factor that is present in a coiled structure and platelets coexist in circulating blood with minimal interactions. In the damaged vessel wall (Panel B), collagen and von Willebrand factor of the subendothelial matrix become exposed to flowing blood and shear forces. Plasma von Willebrand factor efficiently binds to exposed collagen and uncoils its structure, supporting the adhesion of circulating platelets in synergy with collagen. Bound von Willebrand factor interacts, at first, only with the platelet receptor GpIbα and platelet tethering occurs. This interaction has a fast dissociation rate, and platelets tethered to the vessel wall still move in the direction of flow (rolling). In this interaction, collagen receptors GpVI and α2β1 bind to collagen and promote platelet adhesion and activation in synergy with the von Willebrand factor–GpIbα interactions. Once platelets are activated (represented by irregular margins), a conformational change of αIIbβ3 enhances its affinity for the ligand von Willebrand factor (receptors are shown as yellow crosses). This event, together with the rolling of platelets due to the von Willebrand factor–GpIbα interaction, allows αIIbβ3 to bind platelets to the vessel wall (Panel C); αIIbβ3 is also responsible for platelet-to-platelet interactions that eventually lead to platelet-plug formation mediated by von Willebrand factor and, at slow flow conditions, by fibrinogen (not shown).

n engl j med 351;7 www.nejm.org august 12, 2004

What is von Willebrand Factor?

- 2. VWF is a carrier protein for coagulation factor VIII (FVIII), which is thereby protected from degradation in plasma ie VWF protects FVIII in the circulation

VWF-FVIII Complex

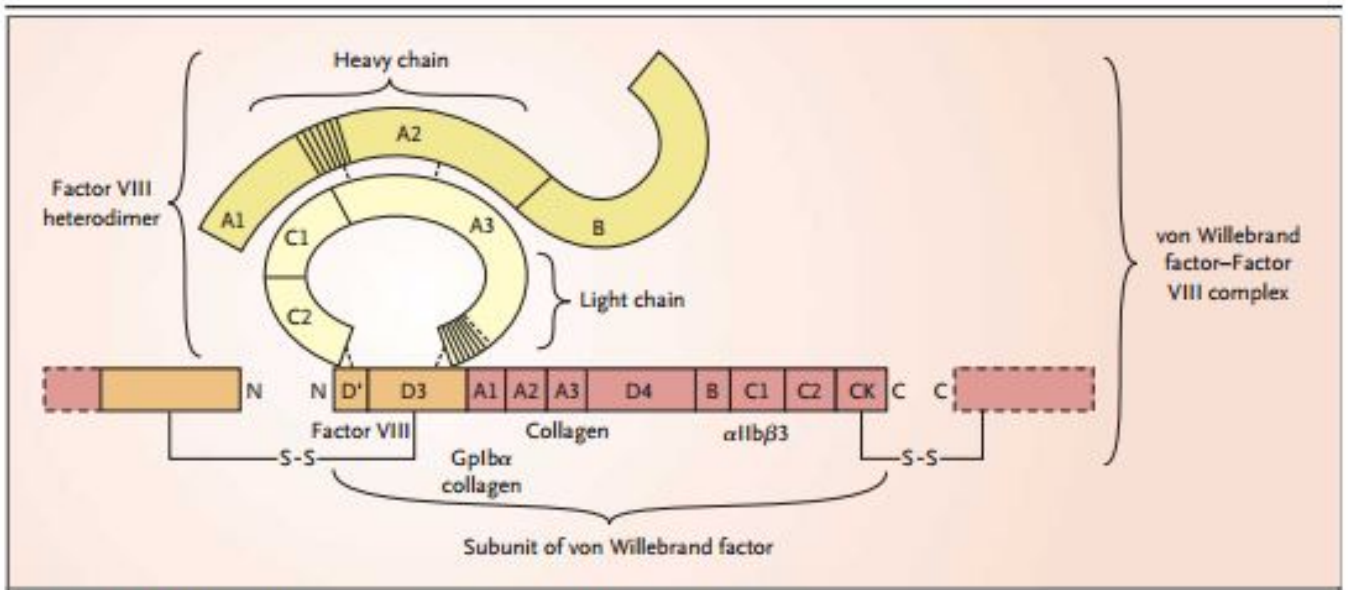


Figure 2. Model of von Willebrand Factor–Factor VIII Complex in Plasma.

Von Willebrand factor circulates as a complex with factor VIII, thereby protecting factor VIII from degradation by the naturally occurring anticoagulant-activated protein C and localizing factor VIII at the site of vascular injury. Each mature von Willebrand factor subunit (domains D', D3, A1, A2, A3, D4, B, C1, C2, CK) dimerizes through disulfide bonds (shown as S–S) near the carboxy terminus (C). Each dimer further multimerizes through disulfide bonds near the amino terminus (N). Factor VIII (domains A1, A2, B, A3, C1, C2) is cleaved before secretion and binds to von Willebrand factor as a heterodimer. The acidic region (cross-hatching) of the A3 domain of factor VIII and the carboxy-terminal region on the C2 domain bind (noncovalent bonds are shown as dotted lines) in the amino-terminal region of the von Willebrand factor subunit (domain D'–D3). The A1 and A2 domains of the heavy chain of factor VIII are noncovalently bonded to the A3 domain of the light chain (dotted lines). At the bottom of the figure, areas of the von Willebrand factor subunit involved in the interaction with collagen and platelet glycoproteins Ibα (GpIbα) and αIIbβ3 are shown.

What is von Willebrand Disease?

- VWD is a bleeding disorder caused by
  - deficiency of
  - and/or dysfunctional VWF
- Usually inherited (congenital)
  - rarely acquired
- Mucocutaneous bleeding
  - characteristic due to impaired primary haemostasis:
  - ie disrupted interaction between vessel wall and platelets because the VWF is either ↓ in amount or faulty
  - injury-related or spontaneous

Types of Congenital VWD

TYPE	Defect	Inheritance
1	↓ amount VWF	Autosomal Dominant
2A	↓ platelet binding; ↓ large multimers	Autosomal Dominant
2B	↑ platelet binding	Autosomal Dominant
2M	↓ platelet binding All multimers present	Autosomal Dominant
2N	↓ binding to FVIII	Autosomal Dominant
3	Virtually no VWF	Autosomal recessive

What problems does a person with VWD face?

- Easy bruising; bleeding from wounds
- **Nose bleeds (epistaxes)**
- Mouth bleeding
- Heavy periods (menorrhagia)
- Bleeding after childbirth (post partum haemorrhage)
- **Postoperative bleeding**
  - **Including after tooth extraction**
- Iron deficiency anaemia
- Joint bleeds

Investigations at times of bleeding

- FBC: haemoglobin & platelets
- ± Cross match blood
- Iron studies
- Baseline factor studies
  - Usually not necessary
    - Diagnosis is known
  - Useful if considering monitoring response to treatment by measuring factor levels

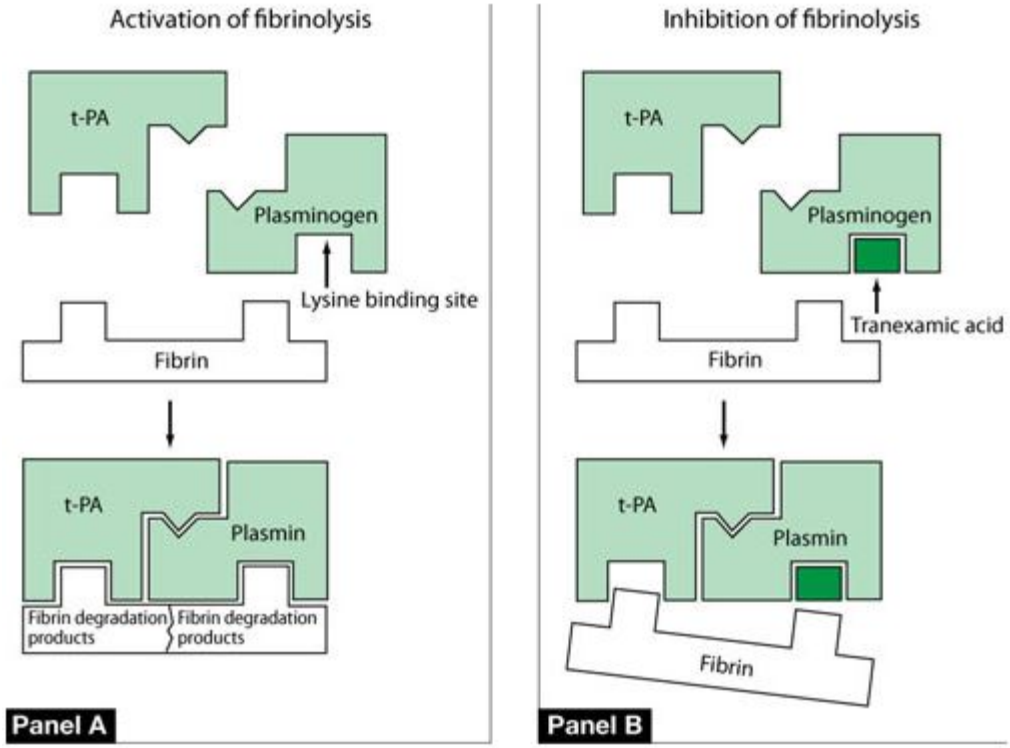
Therapeutic Armamentarium

- "Local" measures
- Tranexamic acid (TXA)
- Desmopressin (DDAVP)
- Von Willebrand factor
  - Plasma derived Factor VIII/VWF concentrate
    - In Australia:
      - "Biostate", funded by NAB
      - "Wilate", licensed by TGA, not funded by NBA
  - Recombinant VWF: in development

TXA

- What is it?
  - an antifibrinolytic agent
- Mechanism of action:
  - interferes with the breakdown (fibrinolysis) of newly formed clots (by binding to plasminogen to inhibit its binding to fibrin)
- Administration:
  - oral, intravenous or topical (e.g. as mouthwash)
  - can be used alone or in combination with DDAVP or VWF concentrate

TXA



Panel A In a healthy, untreated person, plasminogen binds to fibrin at a lysine binding site and is converted to plasmin in the presence of tissue plasminogen activator (t-PA). Plasmin is able to degrade fibrin filaments into fibrin degradation products.

Panel B Tranexamic acid binds to plasminogen and its activated plasmin form, thereby blocking binding sites that would bind lysine residues on fibrin. Consequently, cleavage of fibrin is inhibited.

- http://www.currentpsychiatry.com/home/article/a-new-to-the-us-first-line-agent-for-heavy-menstrual-bleeding/89def9489e8070e03635407caabfb88f.html

TXA

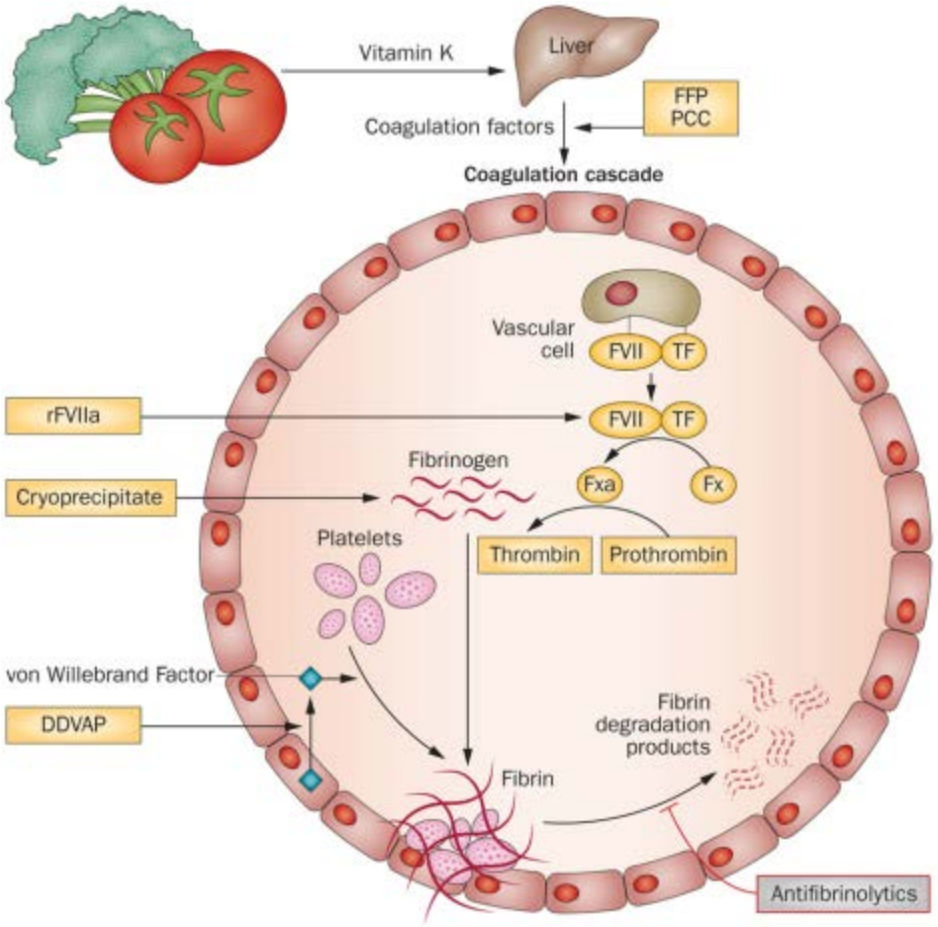
- Dose
  - Orally 25 mg per kg 3- 4 times daily for 5-10 days.
  - IV 10 mg per kg 3-4 times daily for 5-10 days.
- Precautions
  - Do not give if blood in urine (haematuria)
- Side-effects
  - Gastro-intestinal; skin rash
- How to monitor its effectiveness
  - Bleeding does not re/start or stops

Desmopressin (DDAVP)

- What is it?
  - 1-desamino-8-D-arginine vasopressin is a synthetic version of vasopressin used for the treatment of diabetes insipidus (inability to retain water in the body)
- Mechanism of actionDDAVP
  - at high dosage immediately stimulates the release of FVIII, VWF and tissue plasminogen activator (t-PA) into the circulation with an average 2-6-fold increase in levels
- Administration
  - IV
  - Subcutaneous
  - Intranasal

DDAVP Mechanism of Action

DDAVP stimulates release of VWF which enhances primary haemostasis by activating platelets at the site of vessel injury

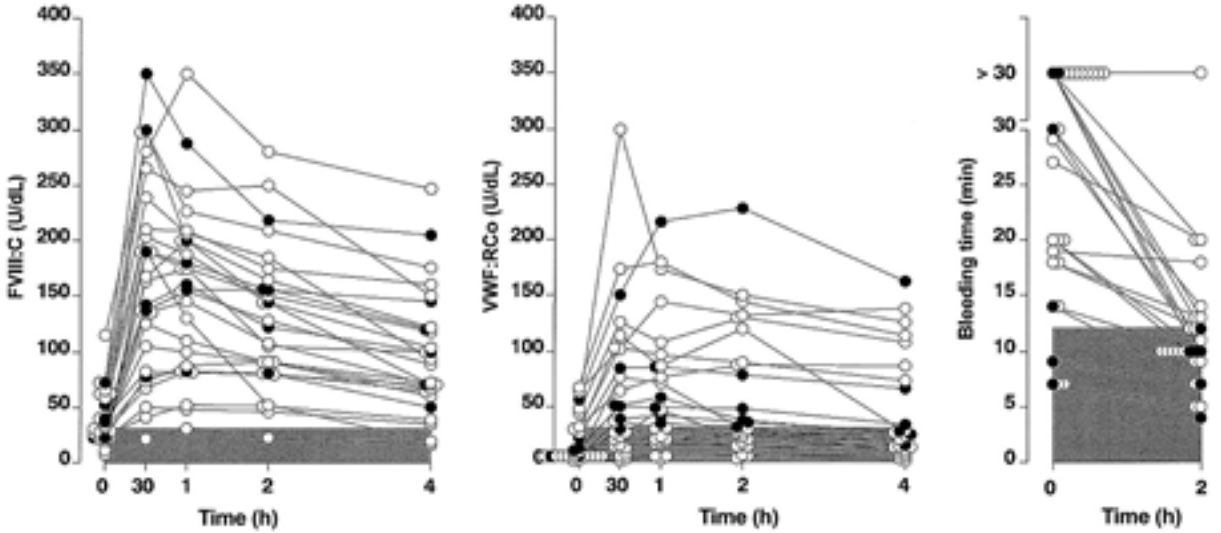


DDAVP TRIAL

- Patients are given a test dose to ensure they respond well enough
- IV infusion of DDAVP (diluted in 50 – 100 ml saline) over 30 minutes
- Measure APTT, FVIII & VWF before and 1 & 4 hours post DDAVP
- Peak FVIII/VWF levels are observed at 60 minute
- Testing of children usually not undertaken until the age of 4 years.

DDAVP Trial

Biologic responses to DDAVP in 26 patients with type 1 VWD. Changes of FVIII:C (U/dL) and VWF:RCo (U/dL) are shown for each patient before and 30 minutes, 2 hours, and 4 hours after DDAVP administration.



Augusto B. Federici et al. Blood 2004;103:2032-2038

blood

DDAVP

- Dose
  - 0.3 microgram/kg i.v. or s.c.
    - Sc slower onset of action
  - 300 microgram i.n. (spray)
    - (150 microgram if BW<30 kg)
- How to monitor its effectiveness
  - Measure levels to determine if, and for how long for, the desired response is achieved
  - Is this acceptable for the type of procedure/surgery to be undertaken?

DDAVP

- Limitations/Precautions
  - Use in children < 2 years not recommended
  - Use in elderly, those with cardiovascular disease, history of MI or stroke, epilepsy, not recommended
  - Do not use for life threatening severe bleeding eg due to major trauma: give concentrate
  - Do not use in Type 2B
    - ↓ platelets
  - Of no use in Type 3

DDAVP

- Side-effects
  - Flushing
  - Headache, nausea
  - ↓ blood pressure → ↑heart rate
  - Hyponatraemia → seizure (water intoxication)
    - Risk increases with repeated doses
      - In general 3 doses is the recommended total number
    - Monitor serum Sodium
    - Fluid restriction may be necessary

“Biostate”

- Plasma derived concentrate
- Contains VWF + FVIII
- Ratio = 2:1
- Dosing usually based on FVIII requirement
- Treatment of choice for
  - bleeding due to major trauma
  - Major surgical procedures
  - Most Type 2s
  - Type 3

Nose bleeds (epistaxes)

- Local pressure on soft part of the nose
- Packing
- Vaseline to keep membranes moist
- TXA
- DDAVP
- Concentrate
- Cautery of blood vessels by ENT surgeon

Operations in people with VWD

- This is a highly specialised field
- Involvement of a haematologist is mandatory
- Ideally performed in a centre where there is ready availability of
  - Blood bank and concentrate
  - 24 hour haematology laboratory support
  - 24 hour medical cover
- A treatment plan needs to be in place

Operations

- When to use what treatment to best prevent bleeding?
- Depends on:
  - Type of operation
  - Type of VWD and baseline levels
  - Age of the patient
  - Previous history with operations
  - DDAVP trial outcome

2004 Recommendations

Table 2. Average Recommended Dosages of Factor VIII (Coagulant Activity) and von Willebrand Factor (Ristocetin Cofactor Activity) for Patients with Phenotypes of von Willebrand's Disease Associated with Severely Reduced Factor Levels (10 Percent or Less of Normal Levels).

Type of Hemorrhage	Dose (IU/kg)*	Frequency of Infusions	Target
Major surgery	50	Daily	Trough factor VIII level >50% of normal level until healing is complete (usually, 5–10 days)
Minor surgery	40	Daily or every other day	Trough factor VIII level >30% of normal level until healing is complete (usually, 2–4 days)
Dental extraction	30	Single dose	Factor VIII level >50% of normal level for 12 hr
Spontaneous bleeding episode	25	Daily	Factor VIII level >30% of normal level until bleeding stops (usually, 2–4 days)
Delivery and puerperium	40	Daily before delivery and in the postpartum period	Factor VIII level >50% of normal level for 3–4 days

* In children, all doses should be increased by 20 percent to account for the greater plasma volume. (For instance, instead of receiving a dose of 40 to 50 IU per kilogram, a child would receive 48 to 60 IU per kilogram.)

n engl j med 351;7 www.nejm.org august 12, 2004

Type 3 VWD

- At risk of
  - Mucocutaneous bleeds
    - Especially nose bleeds
  - Menorrhagia
  - Mid cycle bleeding
  - Pregnancy related bleeding
  - Haemarthroses
  - Gastrointestinal bleeding
- VWF concentrate for bleeding and operations

A special plea from your doctor

- Please keep in contact with your HTC, every 1-2 years
  - Make an appointment for a follow-up visit
- Not only when you have a need for an operation or are in the middle of an emergency!
  - But if you are having an operation you MUST talk to your haematologist as soon as you know