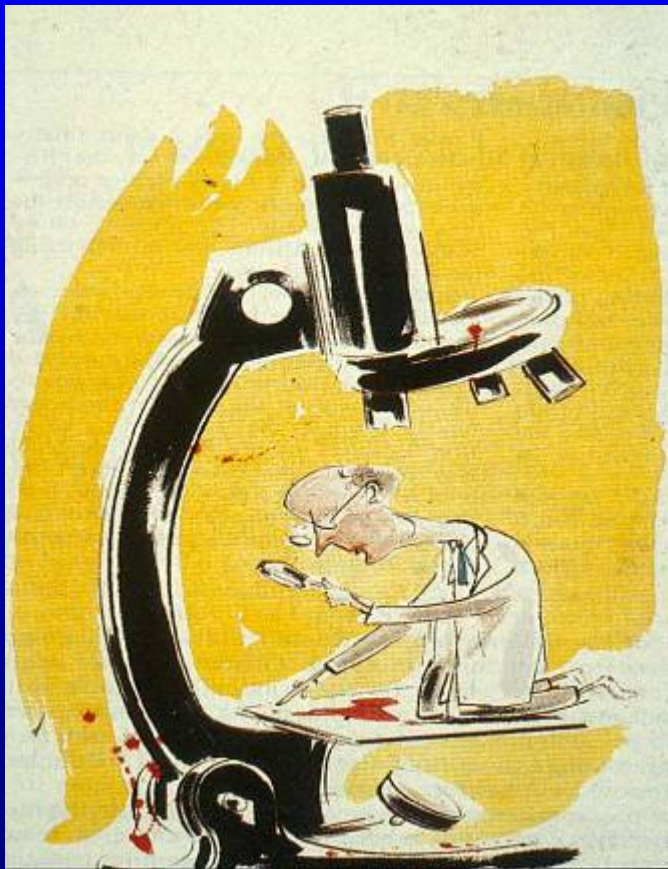


Von Willebrand Disorder 2008



A/Professor Ross Baker

*Haemophilia Centre of
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University of WA

vWD

- Erik von Willebrand
1926
- Aland Islands in Gulf
of Bothnia
- Hereditary Pseudo-
haemophilia
- Mucosal and surgical
bleeding
- Most common
bleeding disorder



Presentation of “vWD”

- Population 1:100
- Menorrhagia 1:10
- “bleeding symptoms” common in normal
- Abnormal lab tests not reproducible
- Surgical haemorrhage preventable

Dilemma

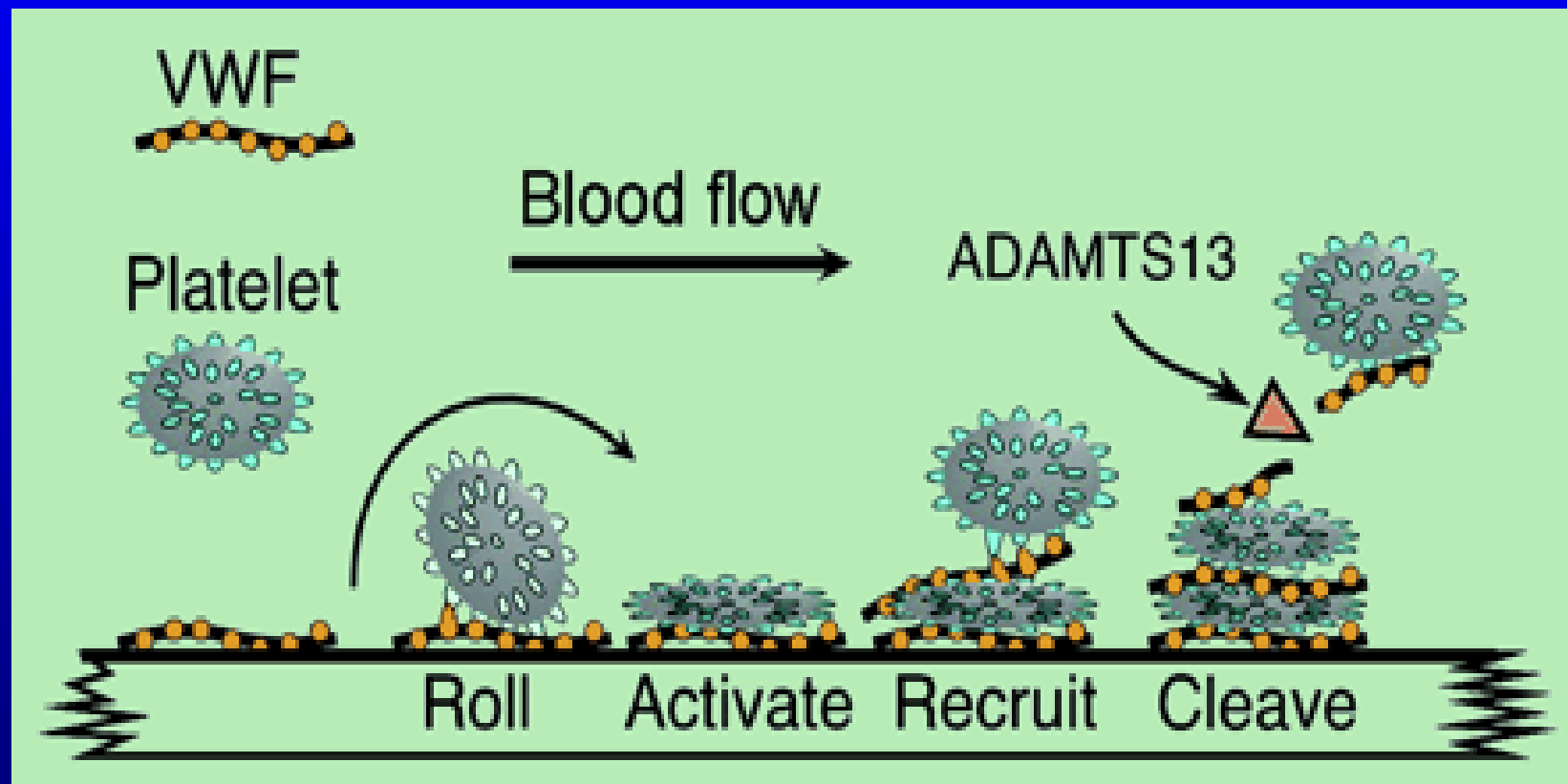


The Way Forward.....

1. Science
2. Pragmatism
3. Factor
replacement



vWF is bridge between platelets,
coagulation and vessel wall



Maturation of vWF

Endothelial cells

Synthesis



Multimer assembly



Storage



Function

1. proteolysis
by ADAMTS-13

2. structure

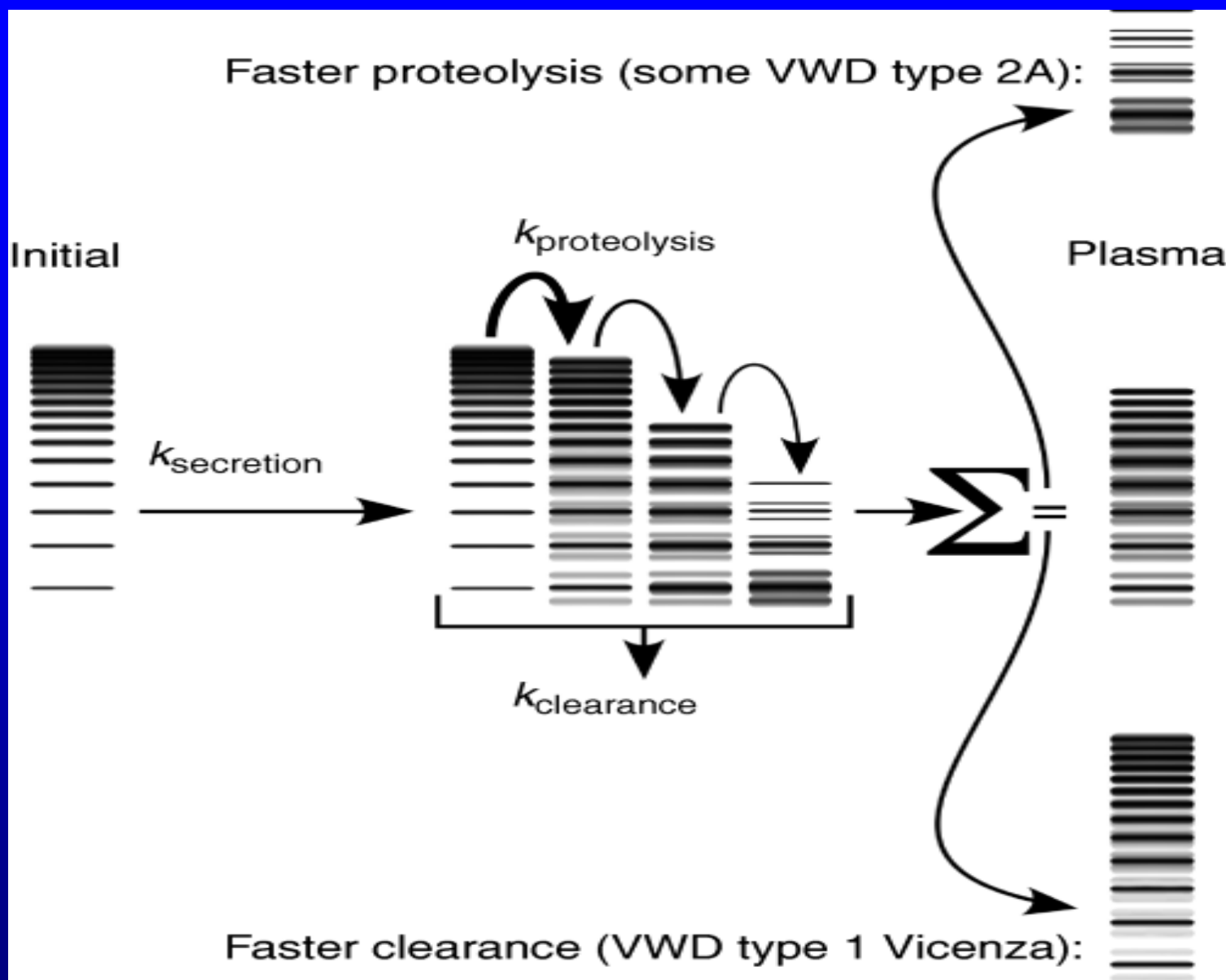
Function and plasma level of VWF

- High molecular weight vWF multimers bind
 - Platelet GP 1b/IX then GPIIb/IIIa
 - Collagen in vessel wall
 - Factor VIII
- Clearance 12-24 hours

Plasma vWF level and activity

- Assembly and secretion
- Function -multimer pattern and structure
- clearance





Sadler *et al* JTH 2006

Diagnosis of VWD

Level

VWF Antigen

Function

FVIII

Ristocetin Cofactor (GP1b/IX)

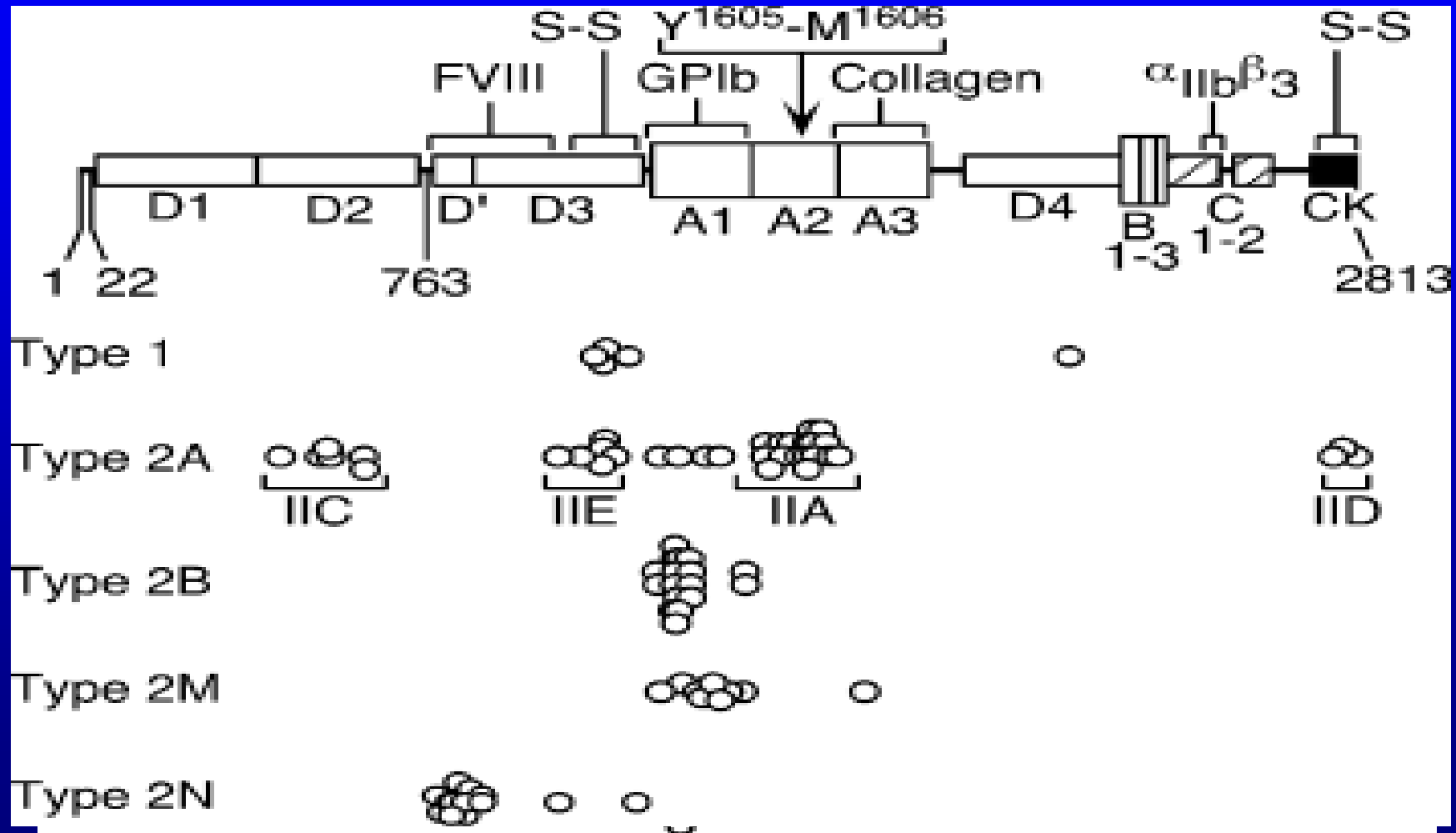
Collagen binding

PFA 100

Types of VWD

- **Type I** 80% amount and function decreased equally
- **Type II** 15% discordant decrease in function (0.5-0.7)
- **Type III** 5% absent VWF

Structural Defects in VWF



Sadler *et al* JTH 2006

Type I vWD



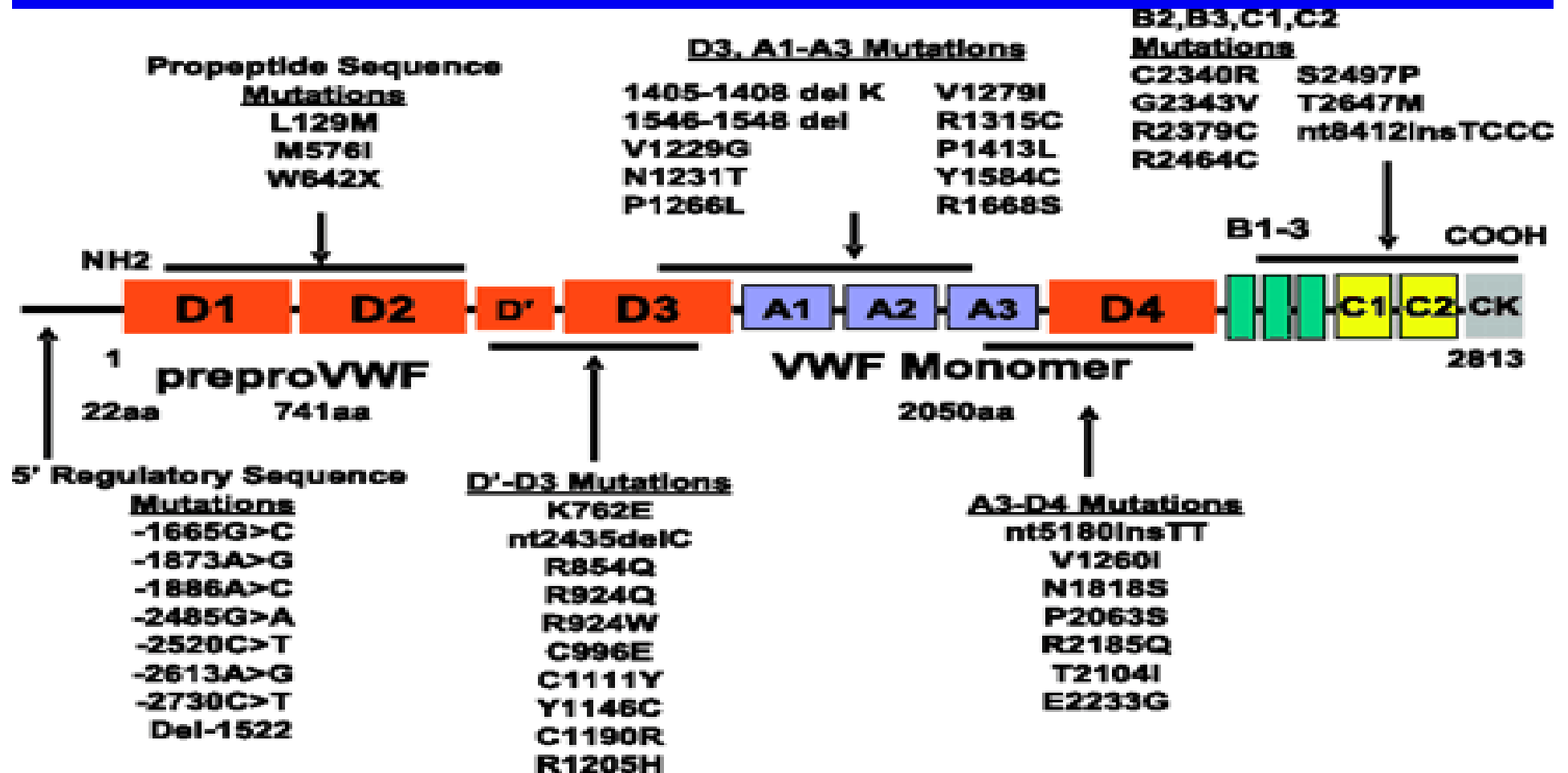
Type 1 VWD

- EU, Canadian and UK
- 388 patients
- Carefully selected personal history plus VWF levels between 5-50%
- Family studied, bleeding score, mutations detected in 50-60%, plasma levels, sensitive multimer analysis

Peake JTH 2007, Goodeve *et al* Blood 2007,

James *et al* Blood 2007, Cumming *et al* TH 2006

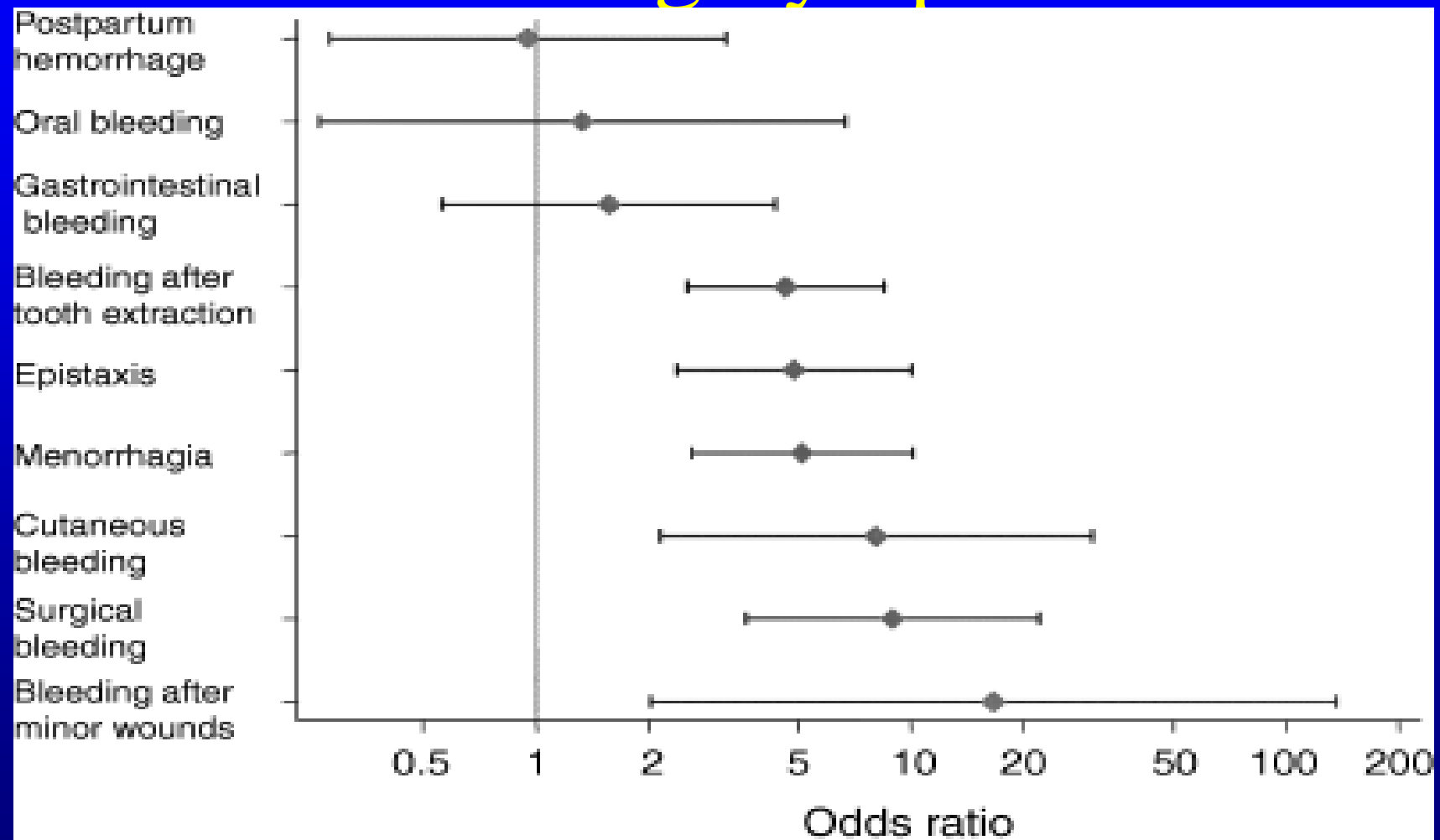
Mutations detected in all regions

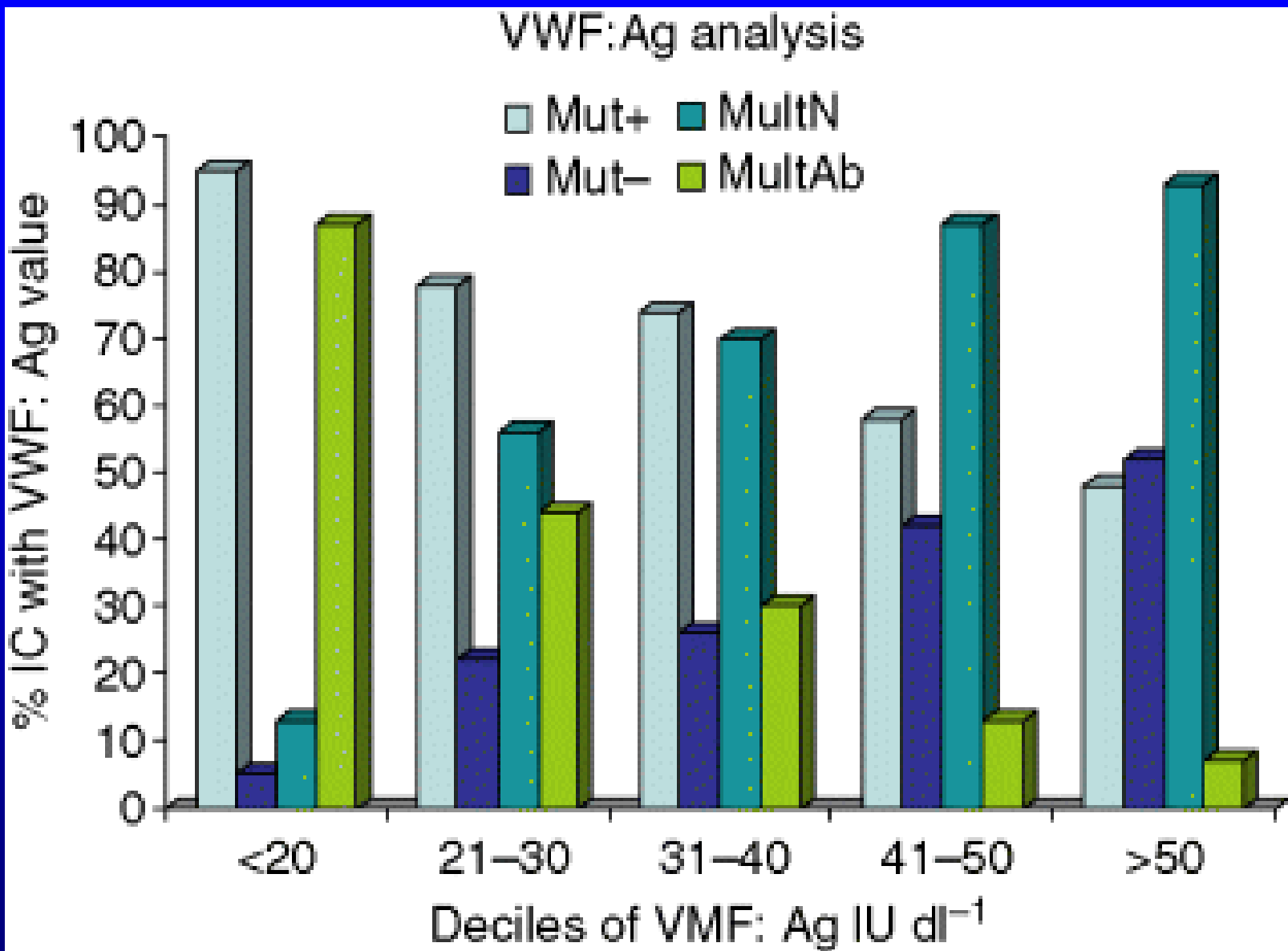


Important Conclusions

- Repeat testing of VWF can be within the “normal” range
- Multiple mutations in the vWF gene can occur (15%)
- Level <30% correspond to gene abnormality, bleeding phenotype and family inheritance
- Levels >30% multiple factor exist eg
Blood Group O
- VWD mutations can predict DDAVP response

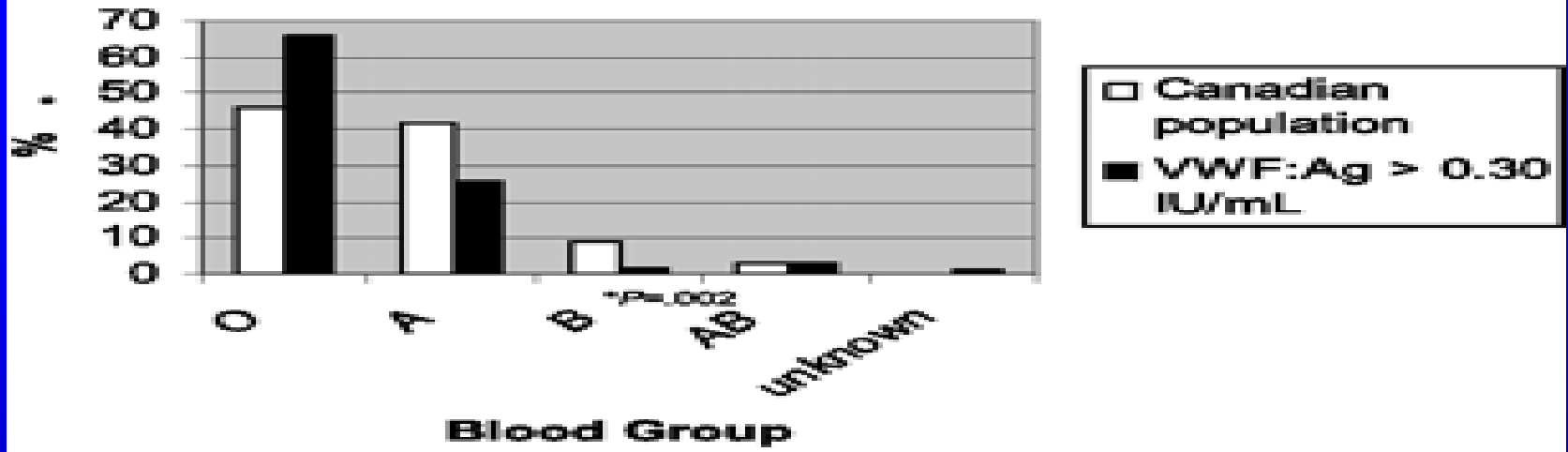
Bleeding Symptoms



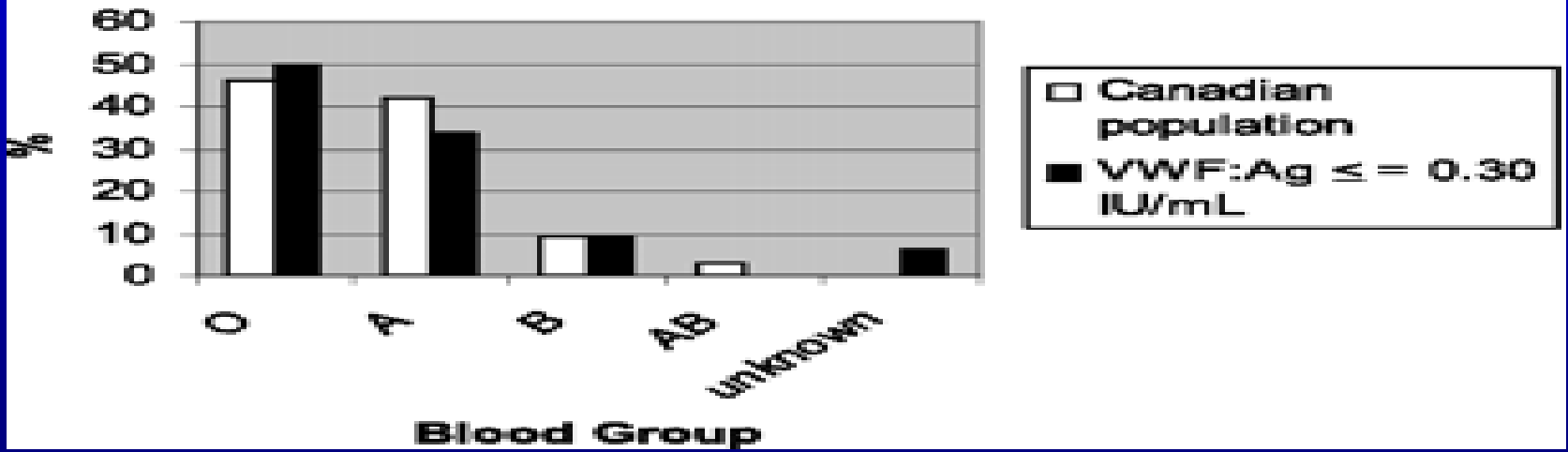


Peake JTH 2007

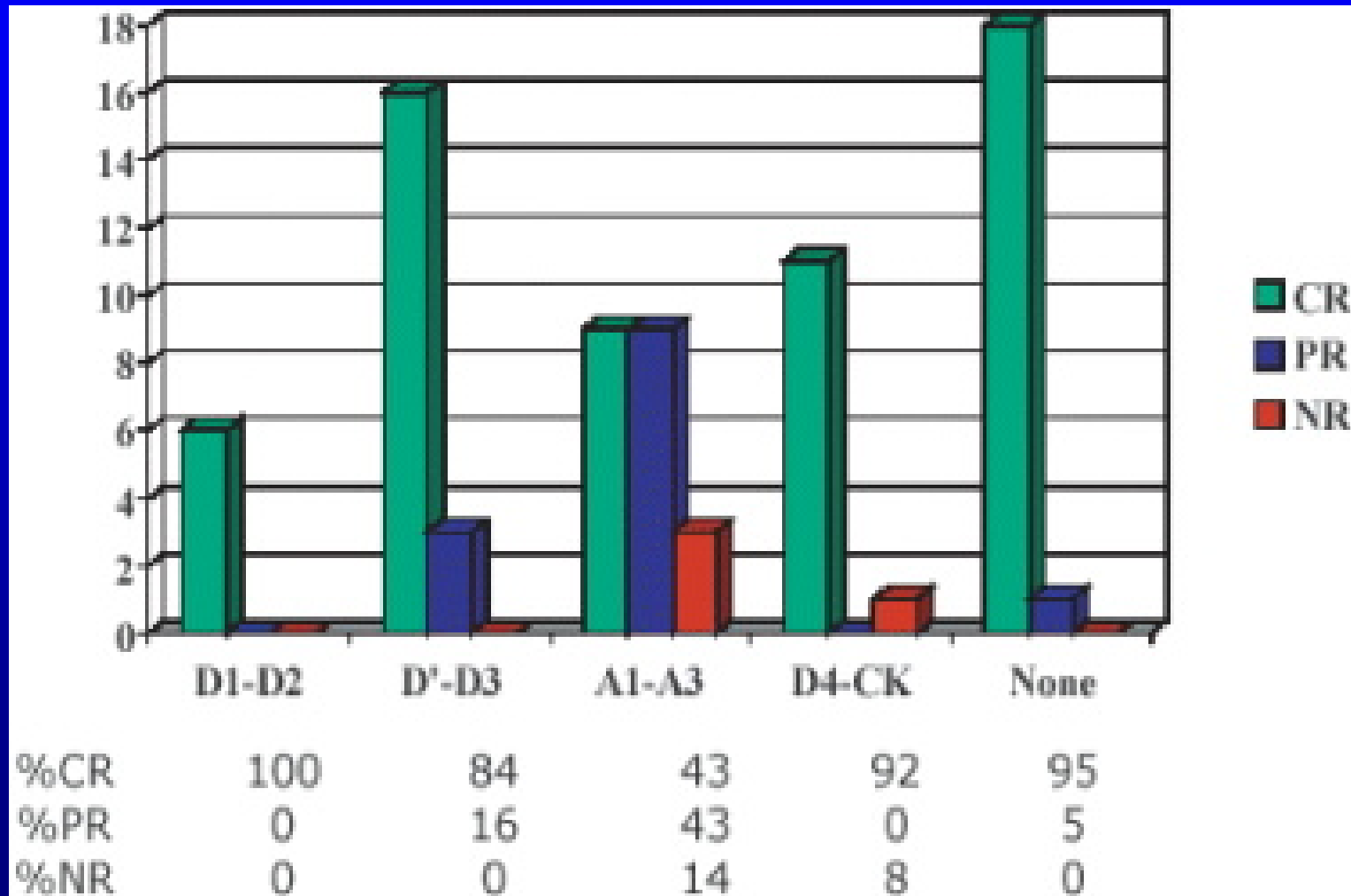
A ABO Blood Group Frequency



B ABO Blood Group Frequency

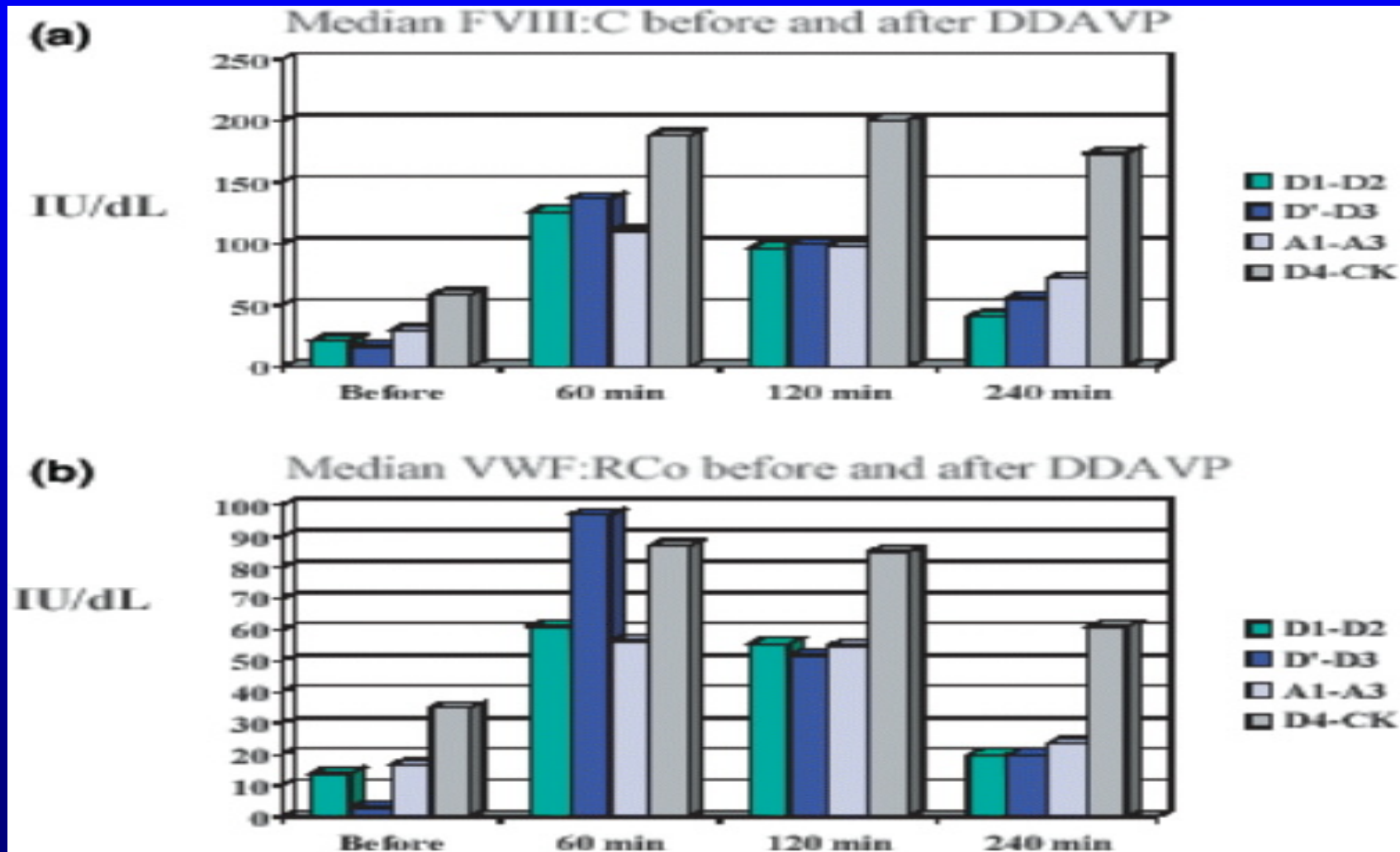


DDAVP non response



Federici *et al* 2006 Haemophilia

Variation in DDAVP response



Reclassification of von Willebrand “Disease”

1. Level <30%
2. Gene abnormality in >90%
3. Family study indicated
4. Predicts bleeding phenotype (bleeding score)
5. DDAVP trial needed (0,1,6 hours)
6. Type II versus Type 1 vWD debate
7. May require plasma concentrate
8. PFA- 100 mostly diagnostic

Low von Willebrand factor (LvWF) with bleeding tendency

1. Level >30-50%
2. Gene abnormality less common
3. Family study may not be helpful
4. Less reliable indicator of bleeding phenotype (other unknown factors, platelet, blood group O)
5. Mostly responds to DDAVP (?dose)
6. PFA- 100 not diagnostic

vWF Concentrate

Variation

- vWF antigen
- vWF function
- FVIII:VWF ratio
- Purification
- Virus inactivation



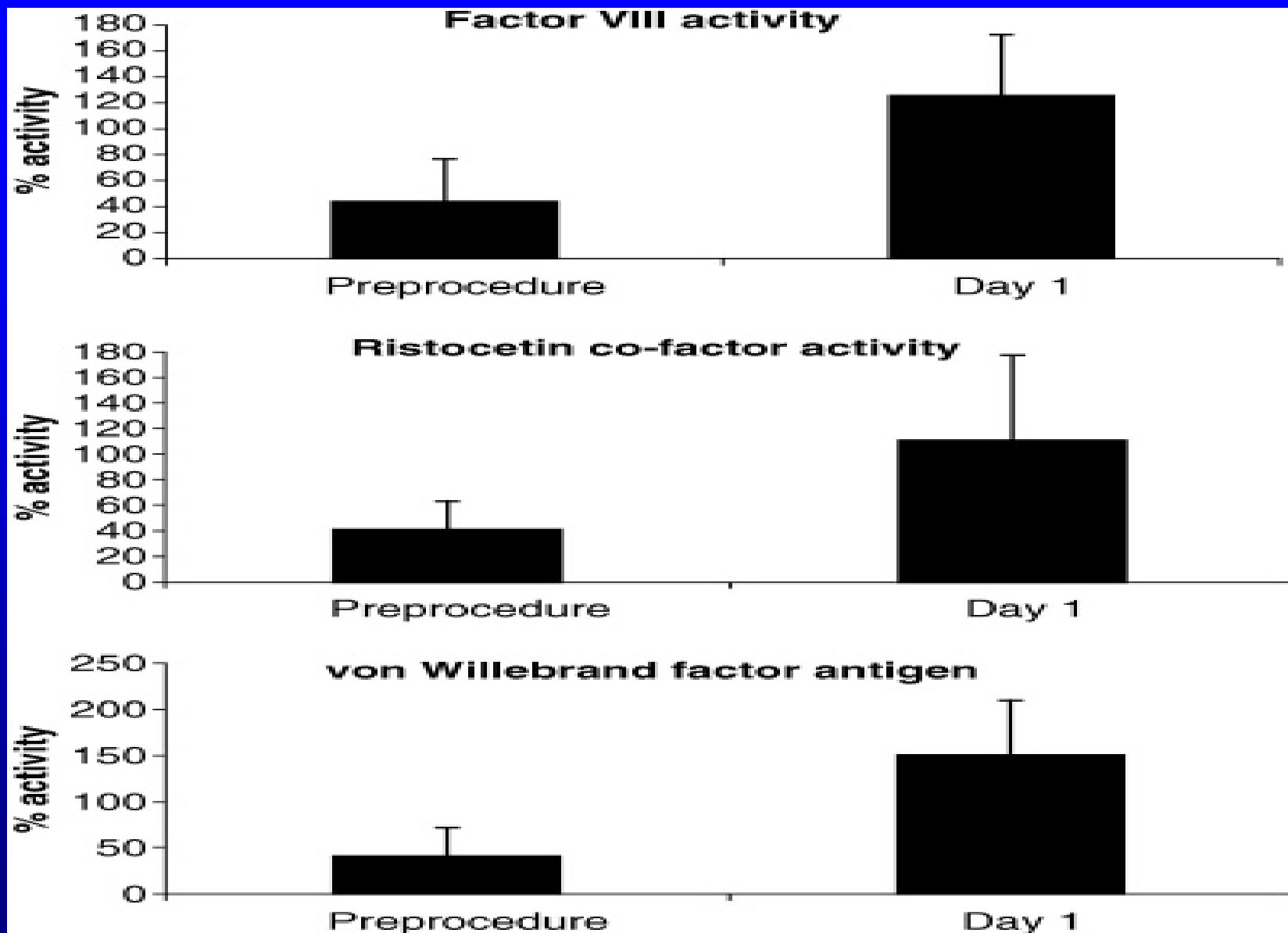
Table 2. Plasma-derived concentrates containing von Willebrand factor.

Concentrate	Purification procedures	Virucidal Rx	VWF:RCo/ Ag [±]	VWF:RCo/ FVIII [±]	Limited to [†]	Manufacturer
<i>Concentrates with published activity in VWD subjects</i>						
Wilfactin	Ion exchange, affinity CTs	SD, nf, dry heat	0.7	60	FR	LFB (France)
Haemate-P [‡]	Polyelectrolyte precipitations	Pasteurization	0.9	2.5	na	ZLB Behring (Germany)
Wilate	Affinity CT, size exclusion	SD, dry heat	1.0	0.8	GE	Octapharma (Germany)
Alphanate	Heparin ligand CT	SD, dry heat	0.9	1.2	na	Grifols (USA)
Fanhdi	Precipitation, heparin ligand CT	SD, dry heat	0.8	1.6	EU	Grifols (SP)
<i>Concentrates with limited activity or no published studies in VWD subjects</i>						
Emoclot	Ion exchange CT	SD, dry heat	0.6	1.2	IT	Kedrion (Italy)
Innobrand	Ion exchange CT	SD	0.8	2.5	FR	LFB (France)
Koate DVI	Precipitations, size exclusion	SD, dry heat	0.5	1.2	na	Talecris (USA)
8Y	Heparin/glycine precipitation	Dry heat	0.3	0.8	UK	BioProducts (UK)
Immunate	Ion exchange CT	SD, vapour heat	0.15	0.16	na	Baxter (Germany)

CT, chromatography; SD, solvent detergent (*t*-N-butyl-PO₄ with polysorbate, Tween, or otoxynol, Triton); nf, nanofiltration; na, not

Australian Biostate Surgical Study

- 3 sites - Alfred, RPA, RPH
- Retrospective n=43 patients, 58 operations
- Type 1-n=26, Type IIa-n=8, Type IIB-n=4
Type III-n=4
- Major surgery 22, Minor surgery 23, dental 13
- Mean daily dose 29 IU/kg for 5 days



Shortt *et al* 2007 Haemophilia

Target and Dosing Uncertainty

	Type I	Type II	Type III
FVIII	✓ 😊	?	?
vWf Ag	✓ 😊	?	?
RiCoF/CBA	✓ 😊	likely	likely
PFA100	✓ 😊	no	no

Conclusion

- vWD diagnosis
- LvWF and bleeding a multifactorial issue
- A better lab marker for vWF haemostatic function required
- vWF concentrates useful for haemostasis

