

Role of DDAVP testing in Von Willebrand Disease

A. Professor Stephen Opat

4th Haemostasis Update Weekend

Saturday 29th March 2008

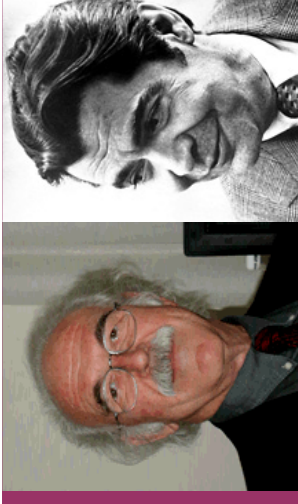
Prevention & Treatment of Bleeding

- *Normalising levels of functional vWF & factor VIII*
 - *stimulating endogenous release from endothelial cells with DDAVP*
 - *infusion of plasma-derived FVIII and VWF concentrate.*
- *Other haemostatic measures*

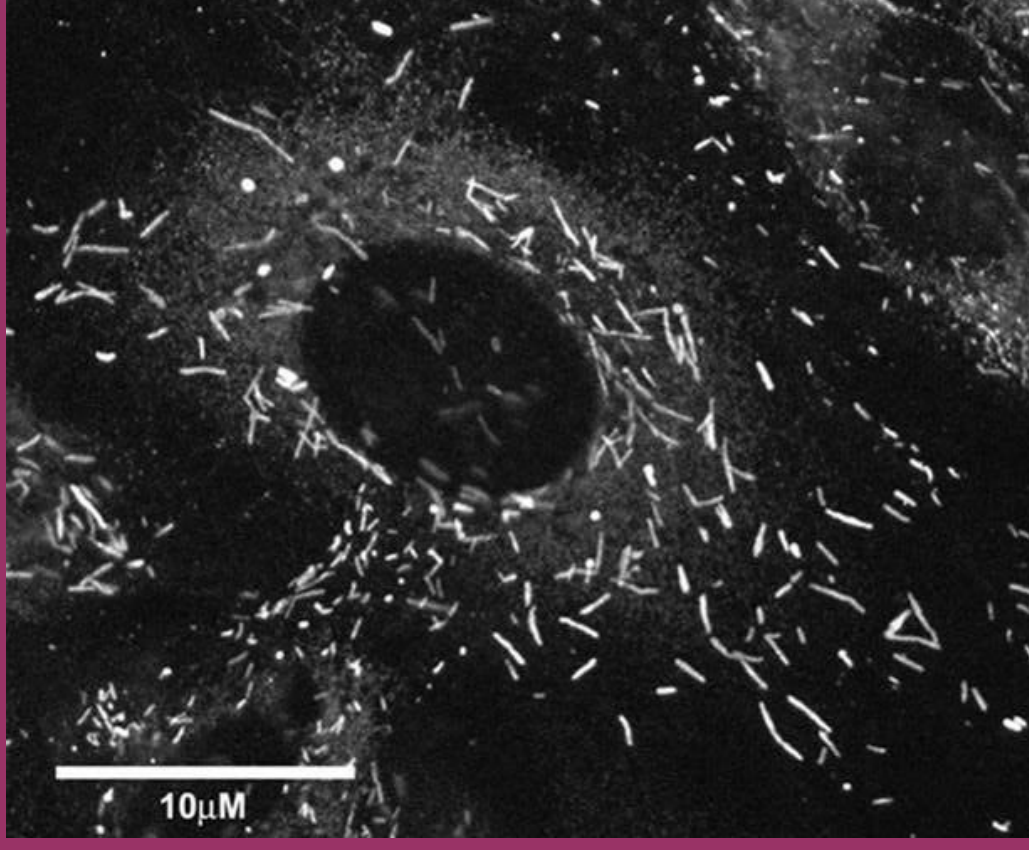
A short history of DDAVP

- 1772 (Hewson) Blood collected under stress clotted rapidly
- 1914 (Cannon) Adrenaline \Rightarrow \uparrow clotting
- 1957 (Marciniak) Adrenaline \Rightarrow \uparrow FVIII
- 1972 (Mannucci) VP and insulin \Rightarrow \uparrow FVIII
- 1974 (Cash) DDAVP \Rightarrow \uparrow FVIII & vWF
- 1977 (Mannucci) First patients treated

DDAVP



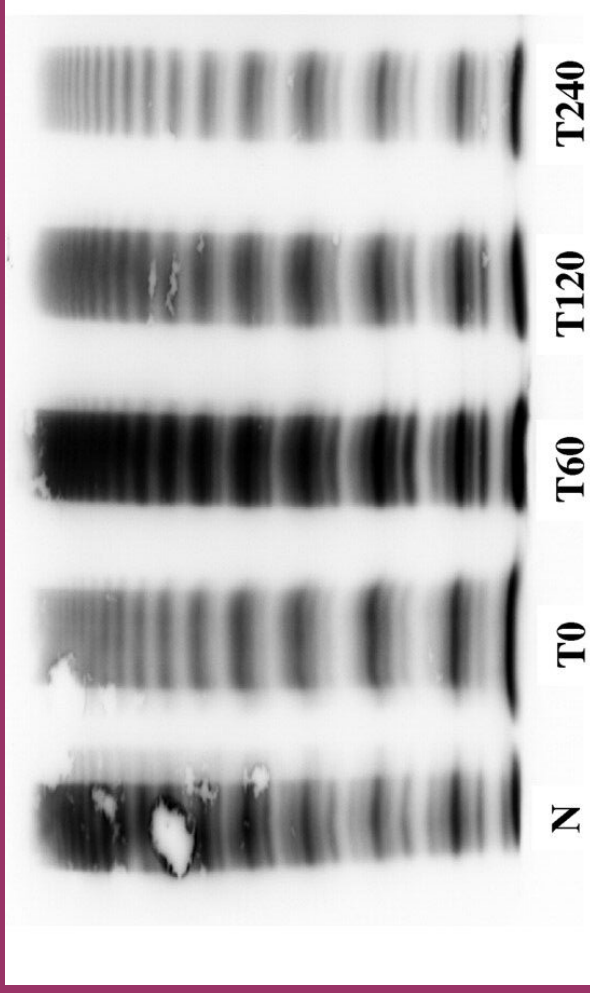
- *DDAVP vasopressin V2 receptor agonist*
- *devoid of V1 agonist effects*
 - *no vasoconstriction*
 - *no hypertension*
 - *no uterine contraction*
 - *colic abdominal pain*
- *c-AMP–mediated signaling.*
 - *Vasodilator*
 - *Anti-diuretic*
- *induces secretion of VWF from endothelial cells*



Kaufmann JE, et al Blood. 2000;106:107-116.

DDAVP

- 2-5 x ↑ vWF
- Less effective in children <2y
- Formulations (Octostim/Minirin)
 - Intravenous 45-60 min
 - Subcutaneous 2 hr
 - Intranasal (1.5mg/ml) ? Availability



Castaman et al Blood, April 1 2008 111(7) 3531-9

DDAVP

- *Advantages*
 - *Limit exposure to plasma products*
 - *Reduce demand for plasma*
- *Disadvantages*
 - *Hyponatremia → Seizures*
 - *Myocardial Infarction, Hypotension*
 - *Flushing, Headache, GI upset*
 - *Tachyphylaxis after 3-5 days*

Side effects

- **Common**
 - headache
 - facial flushing
 - mild tachycardia
- **Rare (!) more common in children**
 - water intoxication
 - cerebral oedema
 - seizures
- **Caution in elderly patients**
 - myocardial infarction
 - stroke
- **DDAVP probably safe in pregnancy**
 - Not oxytocic.



Biological Response v Clinical Efficacy

- *Biological response (vWF:RiCOF)*
 - *↑ 3 x baseline and >30%*
 - *CR >50%, PR <50% & ↑ 3 x baseline*
- *Clinical Efficacy*
 - *Excellent = normal*
 - *Good*
 - *Moderate*
 - *Poor = need additional therapy*

Federici et al. Blood 2004; 103: 2032–8

Castaman et al Blood 2008 111(7) 3531-9

Federici et al Haematologica 2007; 92: 944–51

Guidelines

“Treatment of patients who have VWD with DDAVP should be based on results of a therapeutic trial, ideally one performed in a non-bleeding state and before clinical use.”

DDAVP

- Do all patients with VWD need a trial of DDAVP?



***THE CLINICAL UTILITY OF THE DDAMP
TRIAL IN THE MANAGEMENT OF
PATIENTS WITH VON WILLEBRAND
DISEASE: A RETROSPECTIVE STUDY***

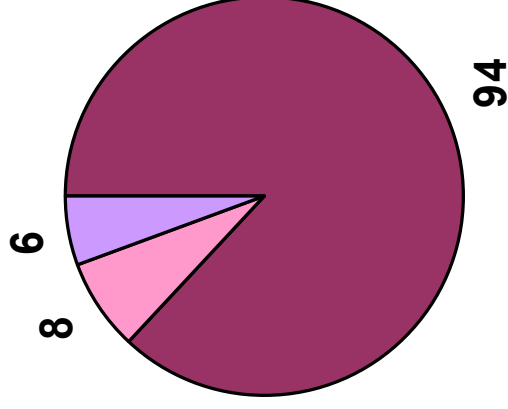
**Stephen S Opat¹, Jake Shortt¹, Malgorzata B Gorniak¹, Heather A
Aumann¹, Margaret F Collecutt¹ and Alison M Street^{1,2}**

Haematology Unit, Alfred Pathology Service¹ and Ronald Sawers
Haemophilia Centre², Alfred Hospital, Melbourne, Victoria, Australia

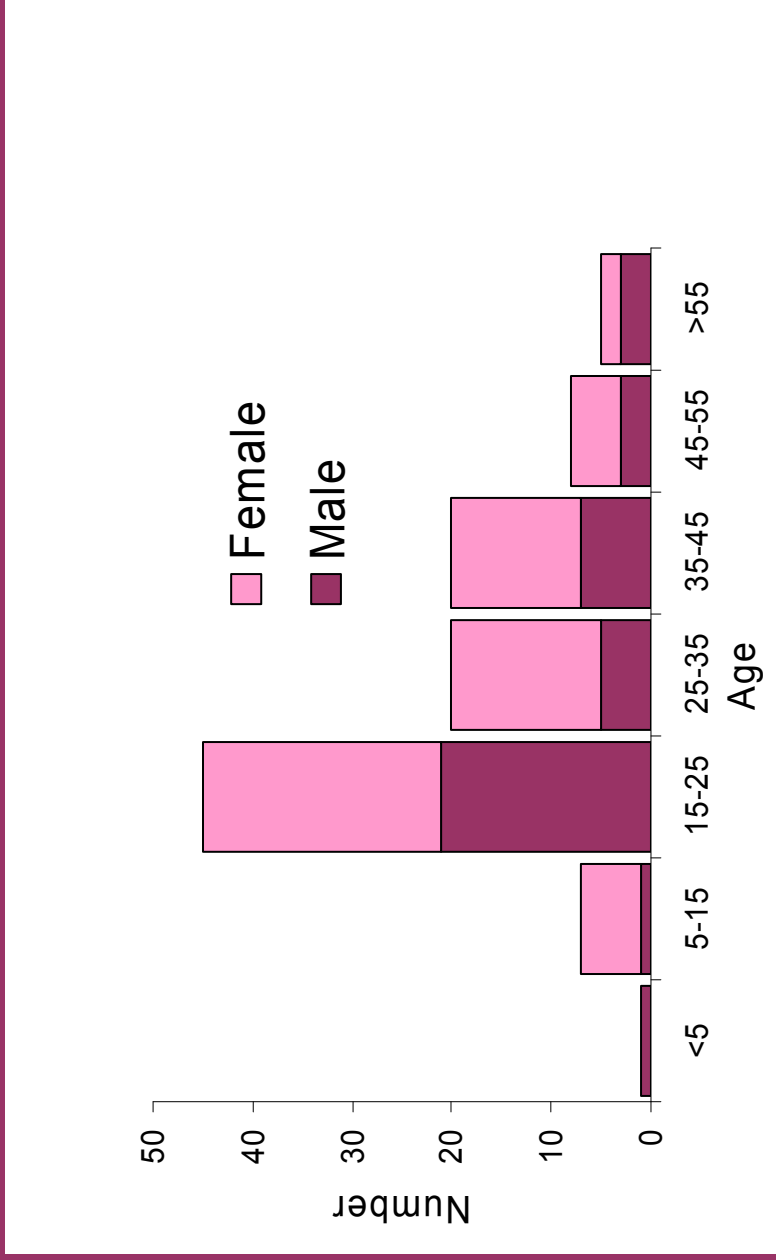
vWD subtypes

1990-2006

- Type 1
- Type 2A
- low vWF:RiCof



Demographics



Protocol

- *DDAVP 0.2-0.4 mcg/kg IV*
- *samples taken*
 - *pre-infusion*
 - *between 1-2 hours post infusion.*
 - *at 24 hours after 2003.*

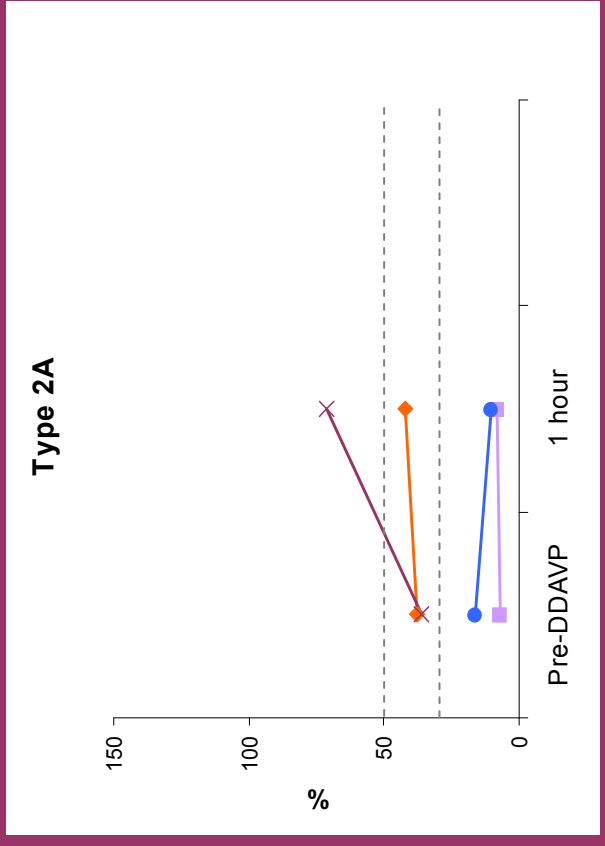
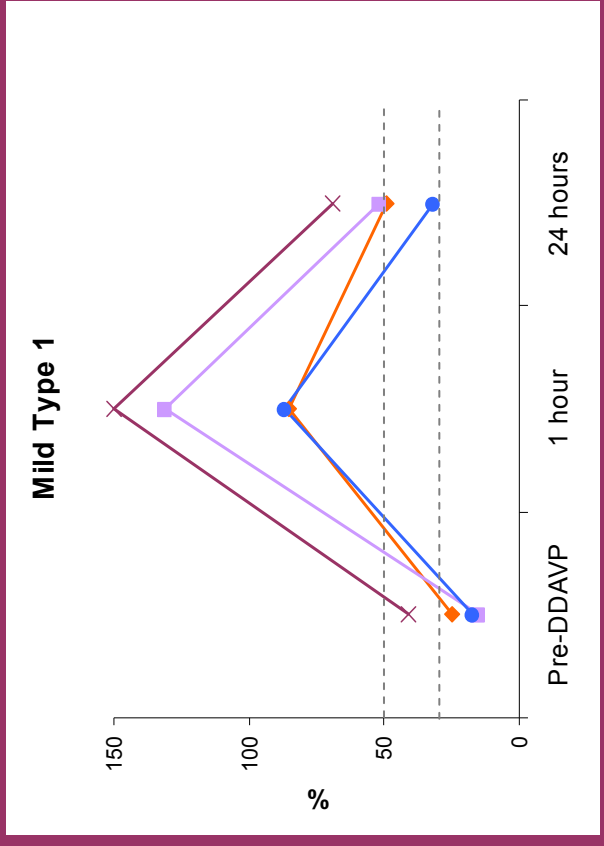
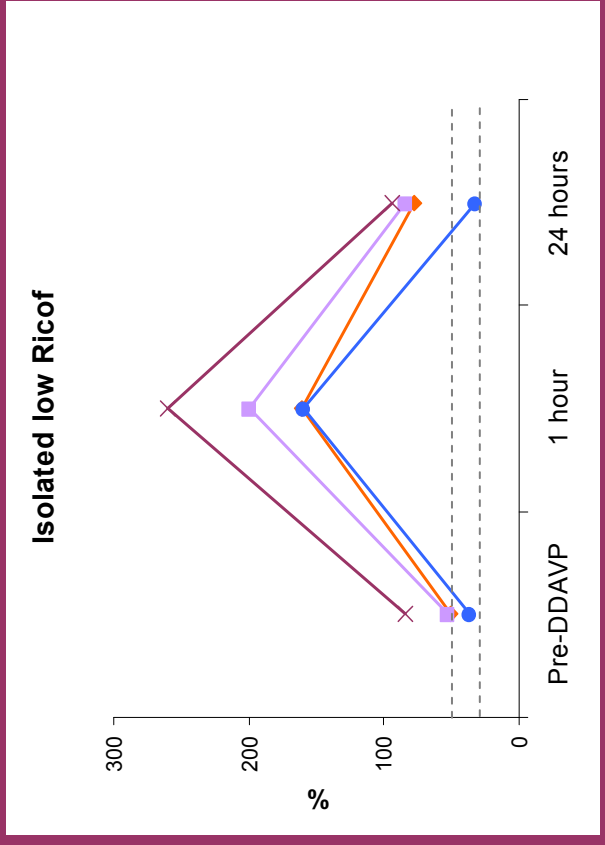
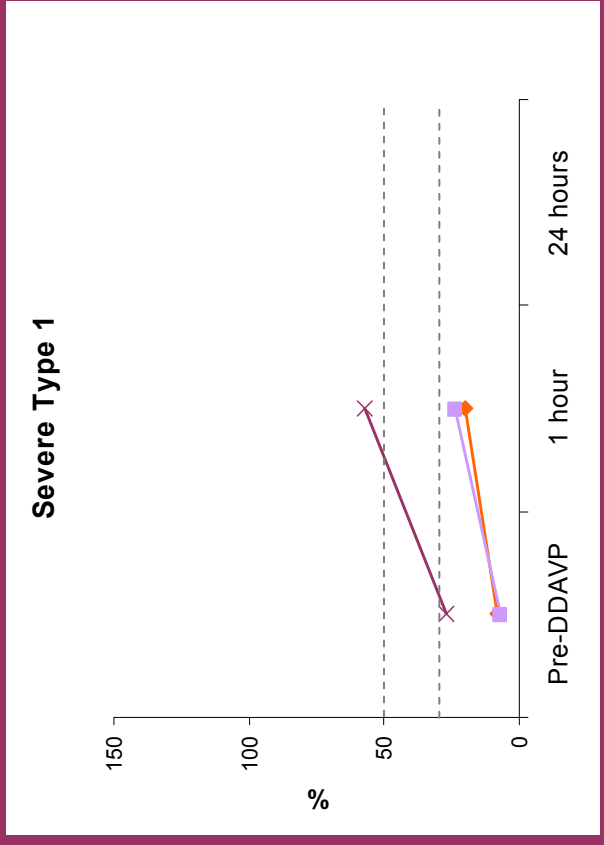


Fig 3 Examples of DDAVP responses in various vWD subtypes
Key: × FVIII ◆ vWF:Ag ■ vWF:CBA ● vWF:RiCof ▲ vWF:CB
 Dotted lines indicate levels of 30% and 50%.

DDAVP responses

	One hour				24 hours			
	No.	CR	PR	NR	No.	CR	PR	NR
Type 1	94	75 (80)	14 (15)	5 (5)	18	2 (11)	9 (50)	7 (39)
Type 2A	8	0	0	8 (100)	2	0	0	2 (100)
Low RiCOF	6	6 (100)	0	0	6	4 (67)	2 (33)	0

Other studies

- Type 1
 - Complete response 64/77 (83%)
 - Partial response 10/77 (13%)
 - No response 3/77 (4%)

Results

- All type 1 patients with baseline vWF:Ag, vWF:CBA and vWF:RiCof >20% responded at one hour. (55/57 CR, 2/57 PR)
- Only 2/6 type 1 patients with either baseline vWF:Ag or vWF:CBA <10% responded.
- No patient with type 2A responded.
- All patients with mildly reduced vWF:RiCof in isolation achieved CR and had adequate levels (>30%) at 24 hours.
- 18 patients with type 1 disease underwent testing at 24 hours.
 - 11/14 with a CR at one hour had adequate levels (>30%) at 24 h.
 - 0/4 with a PR at one hour had adequate levels at 24 hours.
- Factor VIII levels reached normal levels in all cases.

Conclusion I

- Severity of basal phenotype predicts response:
 - Patients with severe type 1 (baseline vWF:Ag, vWF:RiCoF or vWF:CBA < 10%) and those type 2A, should not undergo DDAVP trial as they are unlikely to achieve an adequate response.
 - Patients with type 1 vWD and baseline vWF:Ag, vWF:RiCoF and vWF:CBA >20% or others with isolated low vWF:RiCoF and bleeding phenotype, need not undergo a DDAVP trial to establish efficacy. However, these patients may still require a DDAVP trial for assessment of safety and tolerability.

Conclusion II

- It is not essential to measure factor VIII levels in patients who are undergoing a DDAVP trial for vWD.
- All patients with vWD parameters in the normal range one hour following DDAVP should be considered for further testing at 24 hours to identify the occasional suboptimal responder.
- Implementation of this testing strategy would reduce the requirement for DDAVP trials by approximately 20%, based upon our series.

Response in other subtypes

- Type 2B
 - May worsen thrombocytopenia
 - Was contraindicated; now useful in selected cases
- Type 2M
 - (3/21) 14% response
- Type 2N
 - (3/4) 75% response
 - Increased FVIII obtained but short $t_{1/2}$
- Type 3
 - Non responders except heterozygous or homozygous C2362F
- AVWS
 - 44% clinical response

Table 4. List and description of several published studies on biological response and/or clinical efficacy of desmopressin (DDAVP) in von Willebrand disease (VWD).

First author (reference)	Year	No. of cases enrolled	VWD types (case no.)	Route of drug administration	Biological response by test infusion	Clinical efficacy in bleeds/surgeries	Major side-effects (no. of episodes)
Mannucci PM [7]	1977	2	1 (2)	i.v.	Tested during surgery	Minor and major surgeries	None
Ruggeri ZM [30]	1982	15	1 (5); 2A (5) 2B (5)	i.v.	Tested prospectively without bleeds/surgery	Not tested	None
De La Fuente B [31]	1985	21	1 (13); 2A (7)	i.v.	Tested during treatment	Minor and major surgeries	Seizure, syncope (2)
Rodeghiero F [14]	1996	43	Mild 1 and 2	s.c.	Tested in 36 cases	Prospectively tested in bleeds/surgeries by excellent/good/poor	None
Nitu-Walley I [32]	2001	27	Mild 1 and 2	i.v.	Tested during treatment	Minor and major surgeries	None
Revel-Vilk S [33]	2003	75	1 (70); 2A (n = 5)	i.v. and i.n	Tested before therapy	Bleedings and surgery	None
Federici AB [17]	2004	66	1 (26); 2 A (15); 2M (21); 2N (4)	i.v.	Tested prospectively without bleeds/surgery	Not tested	None
Castaman <i>et al.</i> [18]	2007	77	1 only	i.v. or s.c.	Tested prospectively without bleeds/surgery	Not tested	None

i.v., intravenous; i.n., intranasal; s.c., subcutaneous.

Co-investigators

- ***Jake Shortt***
- ***Malgorzata B Gorniak***
- ***Heather A Aumann***
- ***Margaret F Collecutt***
- ***Alison M Street***

Conclusion

- *DDAVP*
 - *Safe & effective*
 - *Prevented many cases of Hepatitis/HIV*
 - *Severity of basal phenotype predicts response*
 - *Most useful when activity is 10-20%*
 - *Trial for tolerability is still warranted*



Things aren't always predictable!