How to Approach a Patient with Bleeding

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International Society on Thrombosis and Haemostasis

ISTH Advanced Training Course

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Disclosures for Nigel Key

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

Research Support/P.I.	**NIH/NHLBI; Doris Duke Foundation; Baxalta/Shire**
Employee	**No relevant conflicts of interest to declare**
Consultant	**CSl Behring; Baxalta/Shire; Genentech/Roche; Novo Nordisk**
Major Stockholder	**No relevant conflicts of interest to declare**
Speakers Bureau	**No relevant conflicts of interest to declare**
Honoraria	**No relevant conflicts of interest to declare**
Scientific Advisory Board	**RTI International**

Presentation includes discussion of the following off-label use of a drug or medical device:
None

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Outline

- Structured history-taking
  - Bleeding Assessment Tools
- Laboratory algorithm
  - Screening tests of hemostasis
  - ‘Specific’ tests of hemostatic components
- ‘Bleeding of undefined cause (BUC)’
  - Prevalence
  - Outcomes
  - Future opportunities

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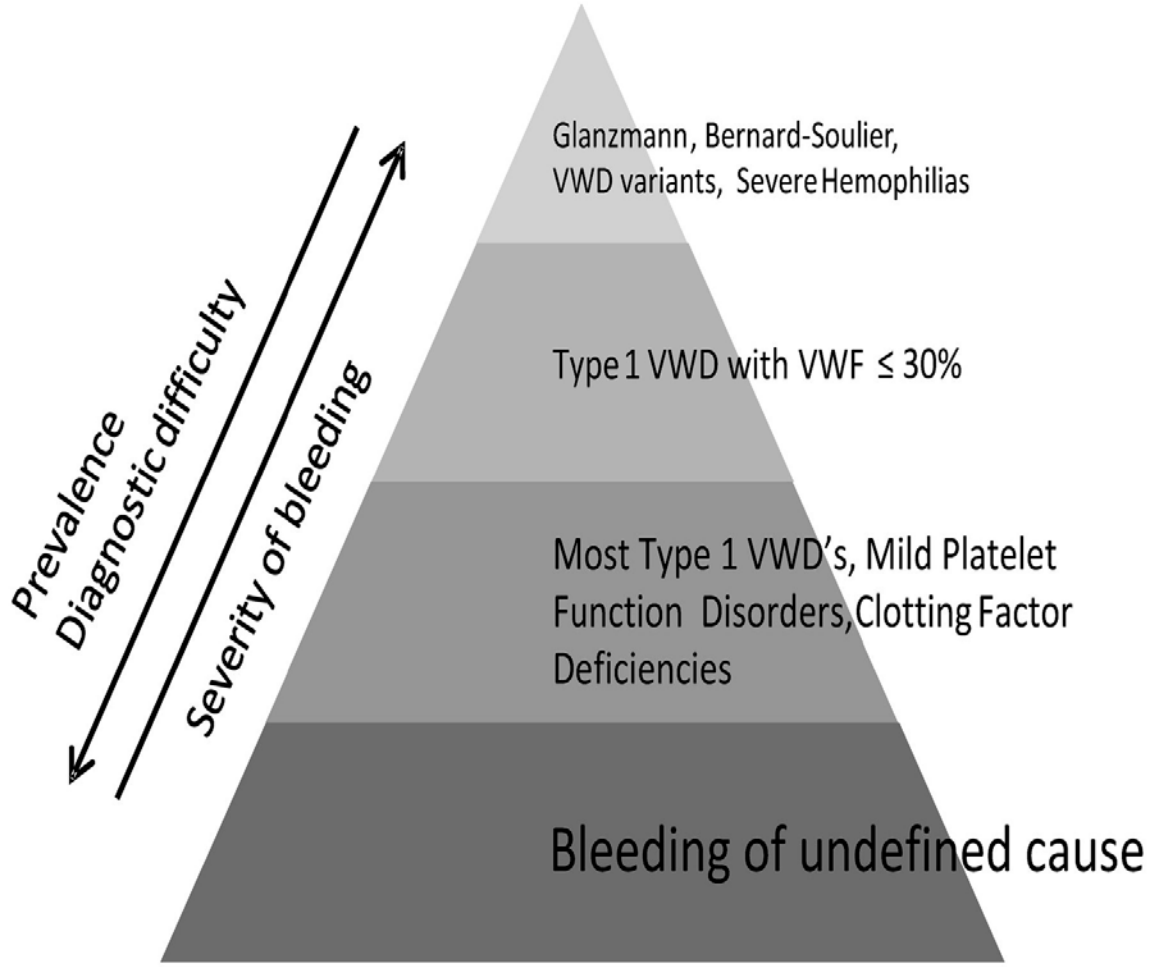
Bleeding Severity, Diagnostic Difficulty and Prevalence of Inherited Bleeding Disorders



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Quiroga T, *Hematology* 2012

Prevalence of Bleeding Symptoms in Normals and in Patients with vWD

Symptoms	Normals $n = 500$ $n = 341$ $n = 215$	All types of VWD $n = 264$
Epistaxis	5–11	63
Menorrhagia	17–44	60
Post-dental extraction bleeding	5–11	52
Hematomas	12	49
Bleeding from minor wounds	0.2–5	36
Gum bleeding	7–37	35
Postsurgical bleeding	1–6	28
Postpartum bleeding	3–23	23
Gastrointestinal bleeding	1	14
Joint bleeding	6	8
Hematuria	1–8	7
Cerebral bleeding	NA	NA

NA, not available.

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Bleeding Assessment Tools (BATs)

- Quantitative screening tools for bleeding disorders
- Standardized way of describing disease characteristics and of assessing disease severity

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Bleeding Assessment Tools (BATs)

- **Clinical utility**
  - To improve diagnostic accuracy; to separate affected and unaffected individuals
  - To describe symptom severity (0 to 3 *vs*. -1 to 4 scales)
  - To predict risk of future bleeding
  - To inform future treatment options
- **Characteristics**
  - Sensitive to both vWD and PFDs
  - High negative predictive value (i.e. effectively excludes those who don't need further testing)
  - Catalogs *frequency* as well as *severity* of symptoms
  - Can be readily incorporated into a busy clinical situation

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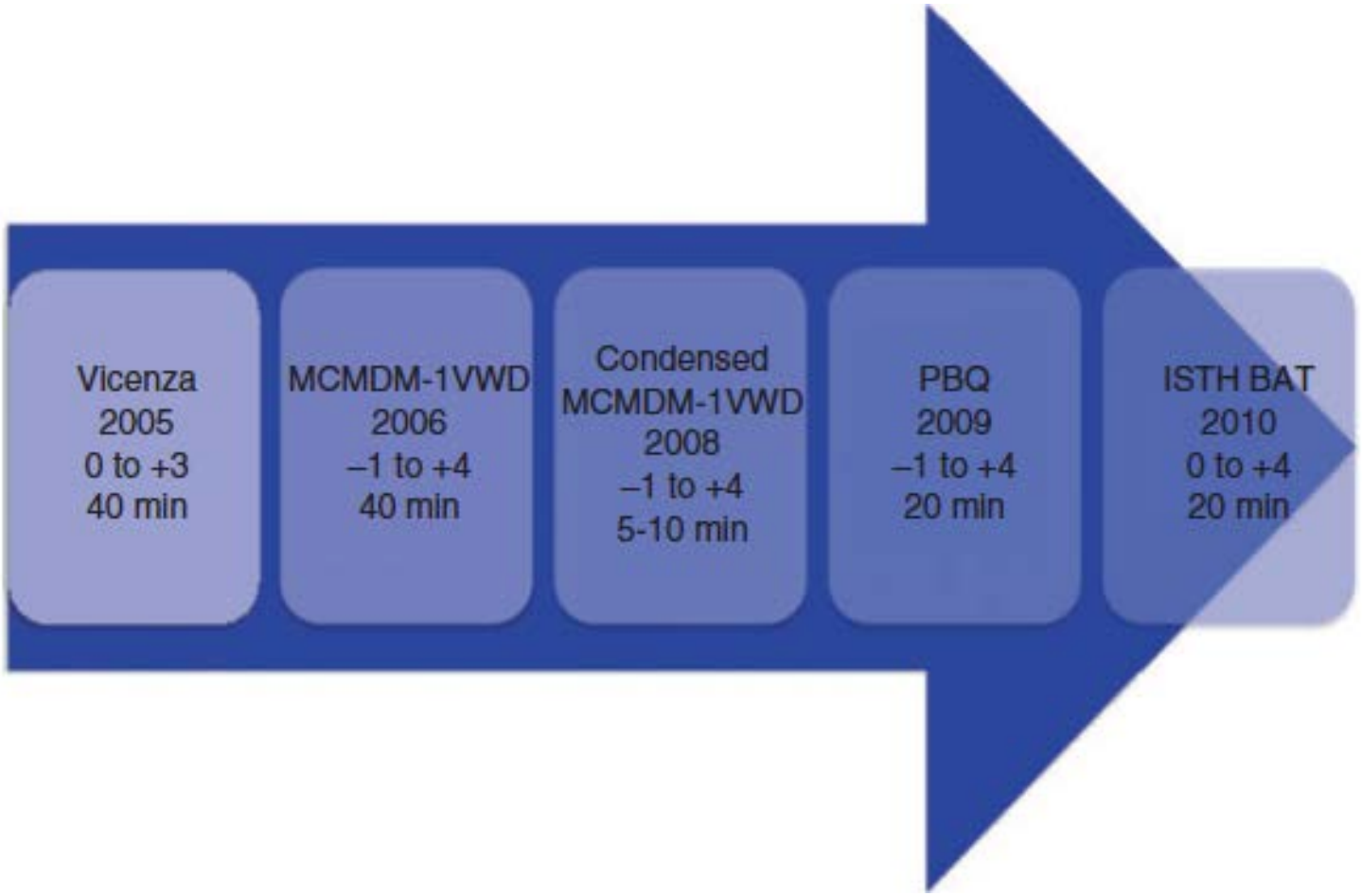
Evolution of BATs



James PD, *J Thromb Haemost* 2012

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ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders

F. RODEGHIERO,* A. TOSETTO,* T. ABSHIRE,† D. M. ARNOLD,‡ B. COLLER,§ P. JAMES,¶ C. NEUNERT** and D. LILLICRAP†† ON BEHALF OF THE ISTH/SSC JOINT VWF AND PERINATAL/PEDIATRIC HEMOSTASIS SUBCOMMITTEES WORKING GROUP[1]

Major Targeted Categories:

- Von Willebrand Disease (vWD)
- (Inherited) Platelet Function Defects ((I)PFD)
- [Mild factor deficiency states]

Cutoffs for normal males, females & children established*

Rodeghiero F. *J Thromb Haemost* 2010
*Elbatarny M. *Haemophilia* 2014

How do BATs Perform in Prospective Clinical Studies?

- Sensitive for the diagnosis of VWD (and probably IPFDs)[1]
  - high specificity and positive predictive value (70-80%)
- Normal bleeding score essentially rules out a diagnosis of vWD (and probably IPFDs)[1]
  - high sensitivity and negative predictive value (≈99%)
- Predict the risk of future bleeding in vWD [2]

[1]Tosetto A, *J Thromb Haemost* 2011
[2] Federici AB, *Blood* 2014

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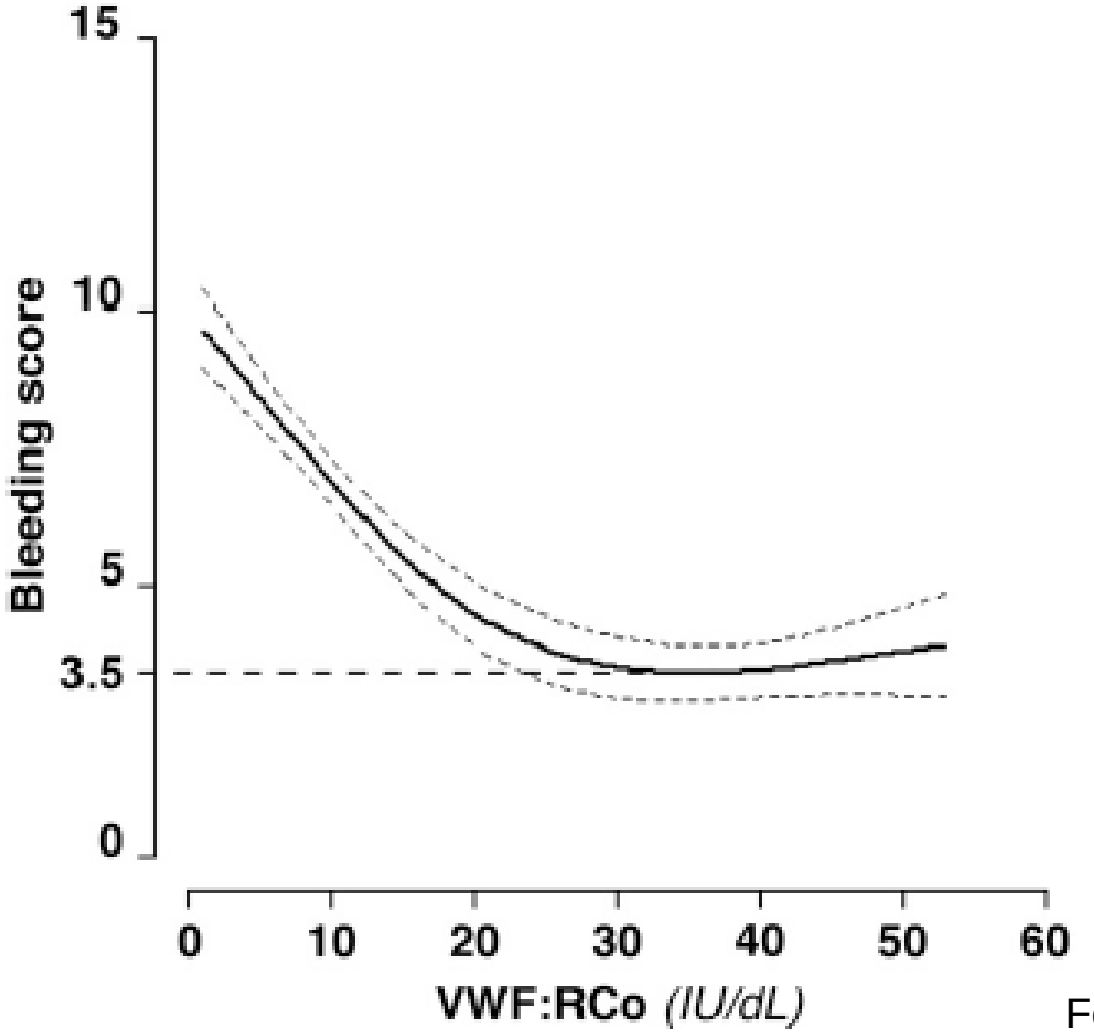
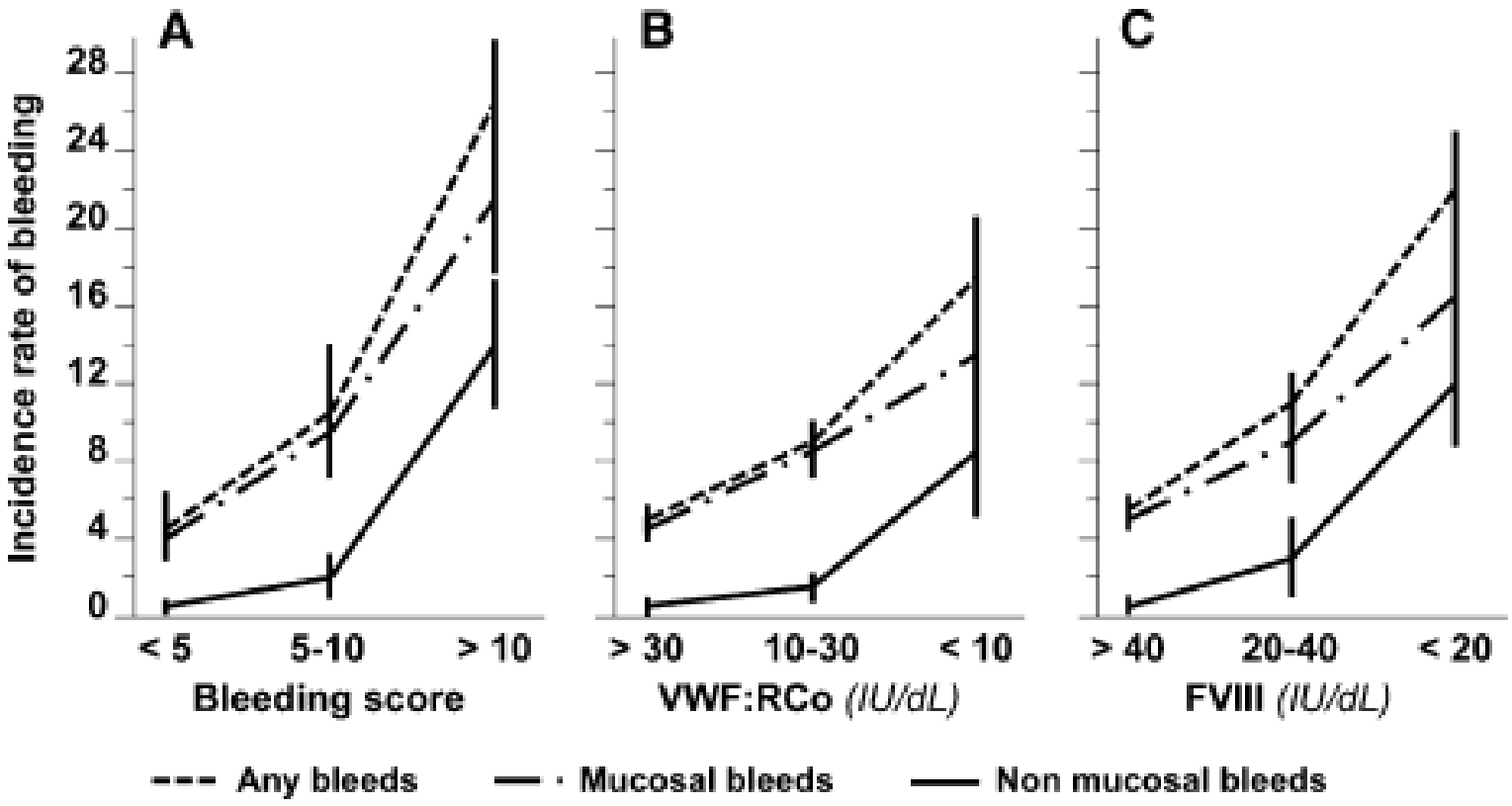
Relationship Between BS and VWF:RCo In 796 Patients with VWD



Federici AB, *Blood* 2014

Bleeding Incidence Rates by Baseline BS, VWF:RCo, and FVIII:c



Federici AB, *Blood* 2014

BS: Best Predictor of Future Bleeding in vWD

Table 1. Risk of bleeding in the 796 VWD patients according to clinical and laboratory predictors

	Crude HRs (95% CI)	Adjusted HRs (95% CI)*
BS		
<5	1†	1†
5-10	2.10 (1.10-3.90)	2.05 (1.07-3.91)
>10	6.80 (3.80-12.30)	7.27 (3.83-13.83)
VWF:RCo, IU/dL		
>30	1†	1†
10-30	1.51 (0.72-3.14)	1.16 (0.54-2.47)
<10	3.27 (1.77-6.06)	1.12 (0.50-2.51)
FVIII:C, IU/dL		
>40	1†	1†
20-40	2.07 (1.16-3.69)	1.52 (0.80-2.90)
<20	4.20 (2.43-7.26)	2.20 (1.05-4.62)

Federici AB, *Blood* 2014

Test Selection/Algorithm

‘**Primary**’

- CBC, blood smear
- LFT, renal function
- PT, aPTT, fibrinogen
- PFA-100
- FVIII, VWF:Ag, VWF:RCo

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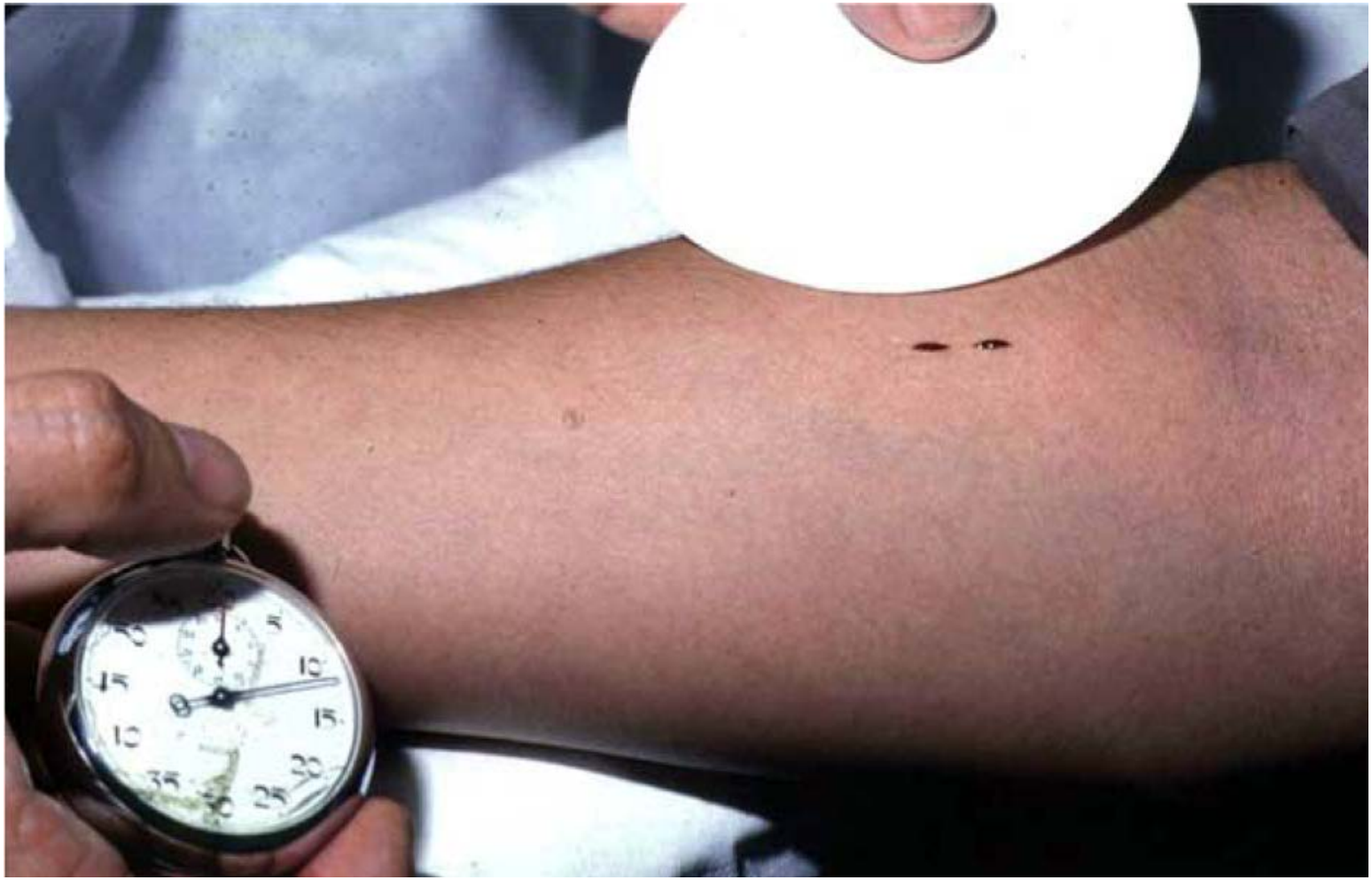
1905 Technology - The Ivy Template Bleeding Time



Harrison*; Blood Reviews* 2005

Limitations of the Bleeding Time

- Invasive
- Time consuming
- Low sensitivity
- Poorly reproducible
- Does not to correlate with surgical blood loss or transfusion needs when used as a pre-operative screening tool
- Does not differentiate between VWD and platelet defects

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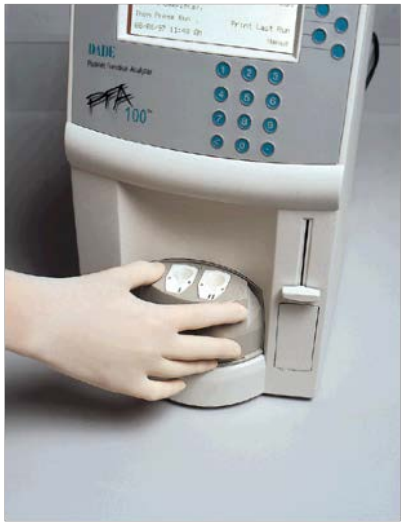
PFA-100™ Test Principle

One

Two



Three

PFA 100®

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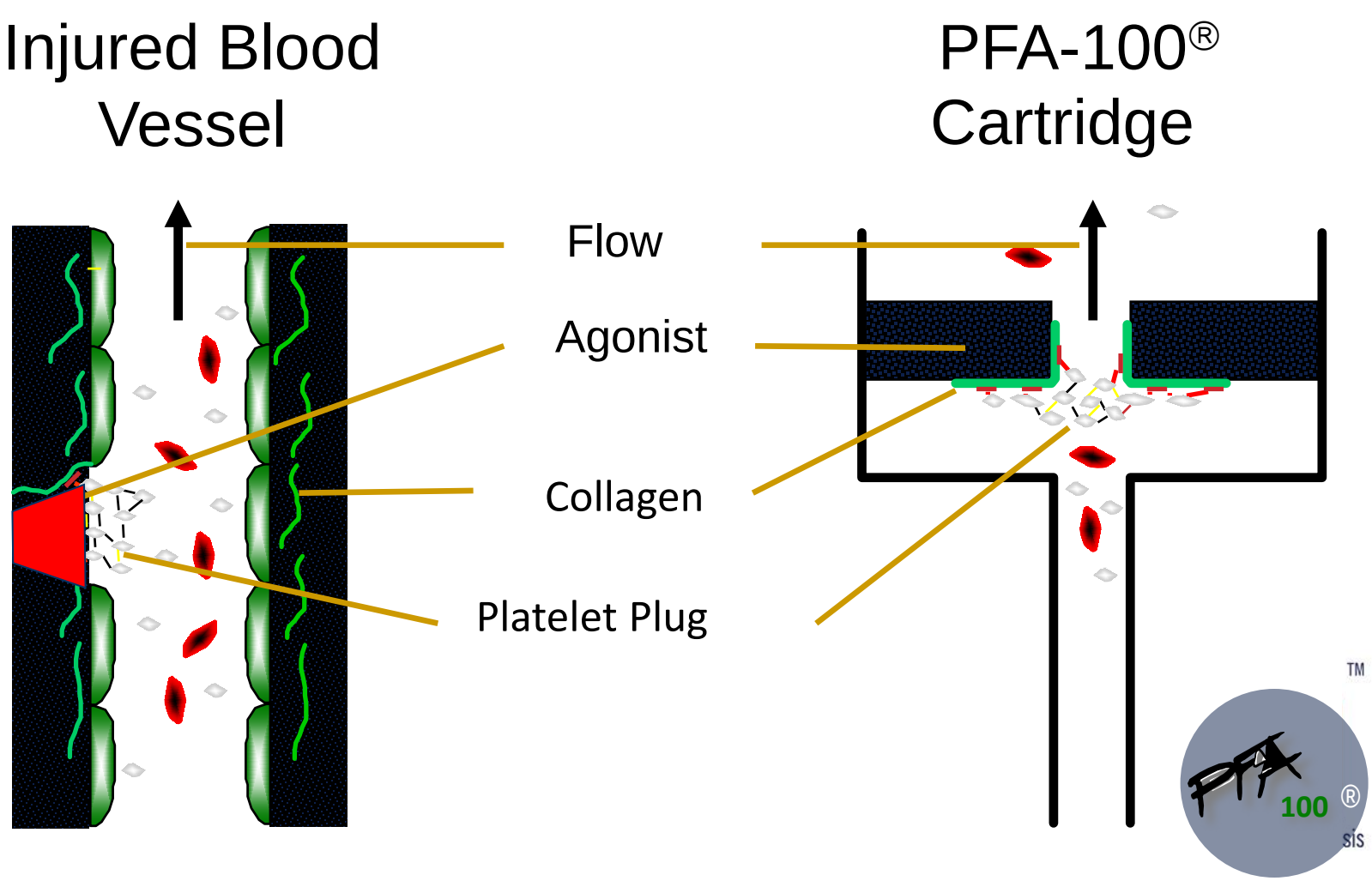
PFA-100™ Simulates *In Vivo* Conditions



PFA-100™ Closure Times: Interpretation

	C-Epi Normal	C-Epi ↑
C-ADP Normal	Excludes: Drug effect Severe thrombocytopenia severe platelet dysfunction Severe VWD	Drug effect (ASA, NSAID) Low Hct Mild thrombocytopenia Mild platelet dysfunction Mild VWD
C-ADP ↑	Rare event	Drug effect Very low Hct Severe thrombocytopenia Severe platelet dysfunction Severe VWD

Sensitivity of C-EPI and C-ADP Closure Times *vs*. Bleeding Time for Abnormalities of Hemostasis

	Sensitivity(%)	
von Willebrand disease	C-EPI	(71)
	C-ADP	(71)
	BT	(29)
Platelet function disorders	C-EPI	(58)
	C-ADP	(8)
	BT	(33)
Defects of clotting factors or fibrinolytic factors	C-EPI	(21)
	C-ADP	(4)
	BT	(4)
Abnormalities of laboratory tests not associated with bleeding risk*	C-EPI	(22)
	C-ADP	(6)
	BT	(17)
Unknown abnormalities	C-EPI	(11)
	C-ADP	(10)
	BT	(6)

Podda GM, *J Thromb Haemost* 2007

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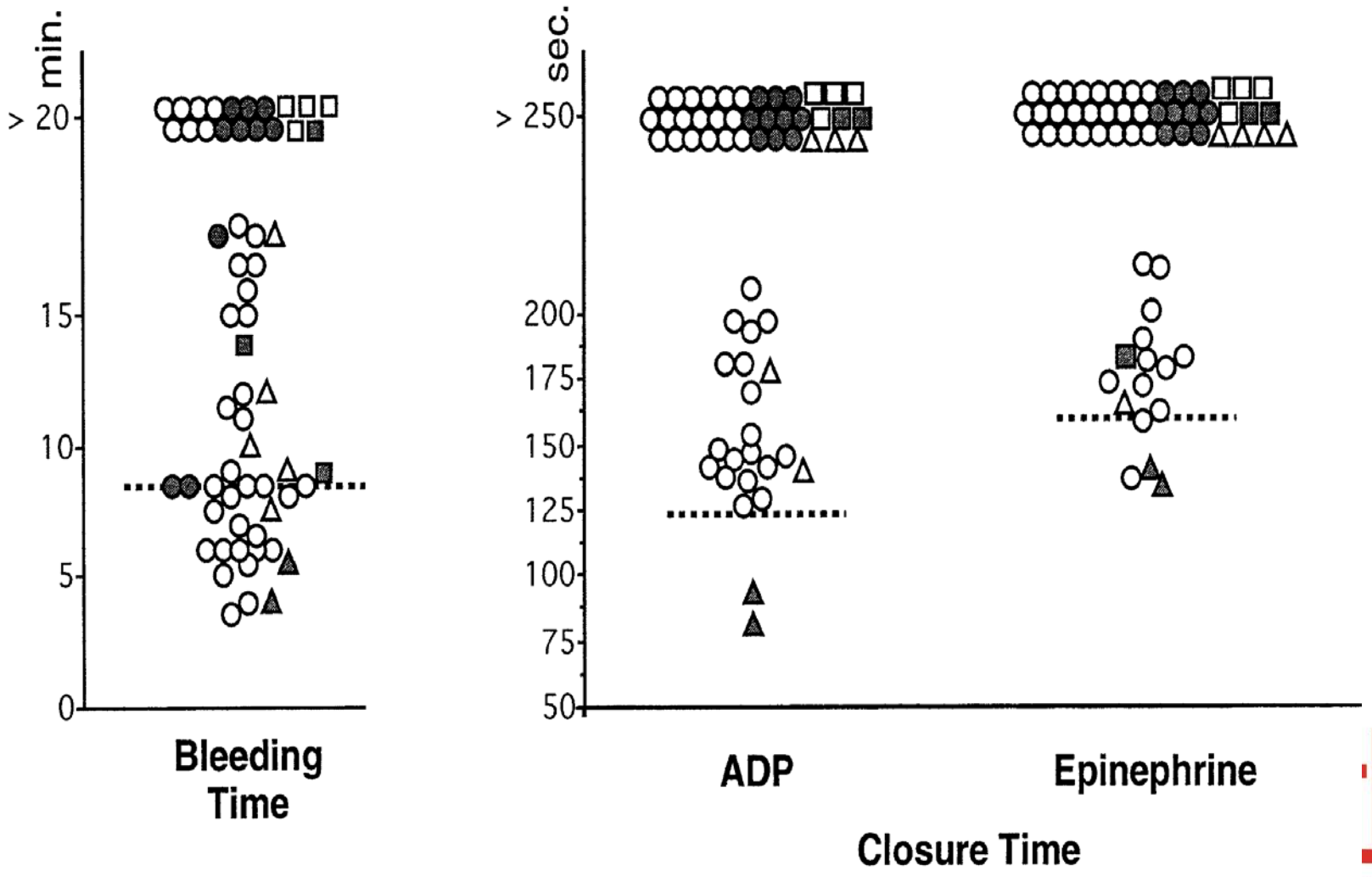
Comparison of BT and PFA-100™ in VWD



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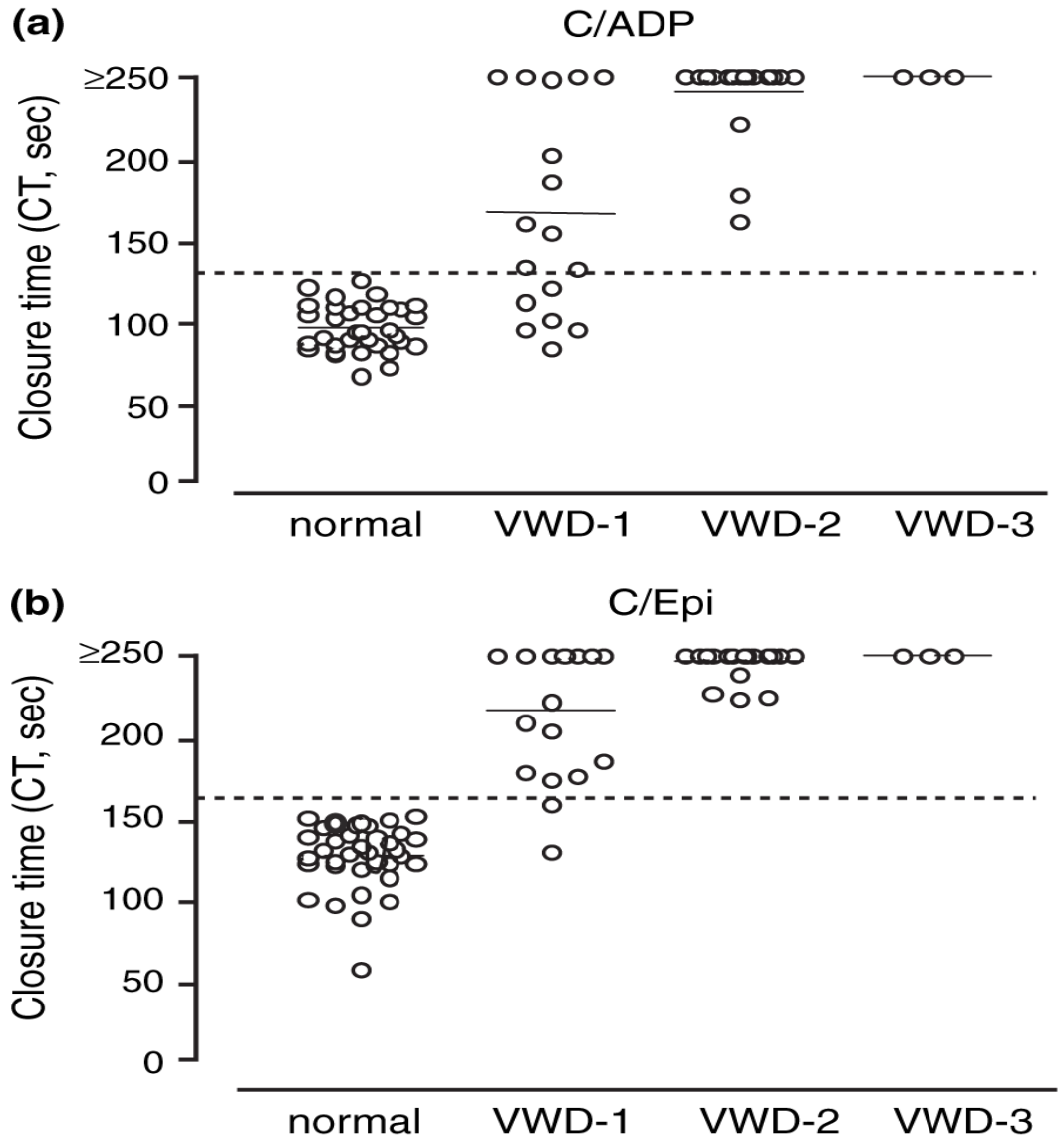
Fressinaud E, *Blood* 1998

PFA-100™ Closure Times in VWD Sub-types



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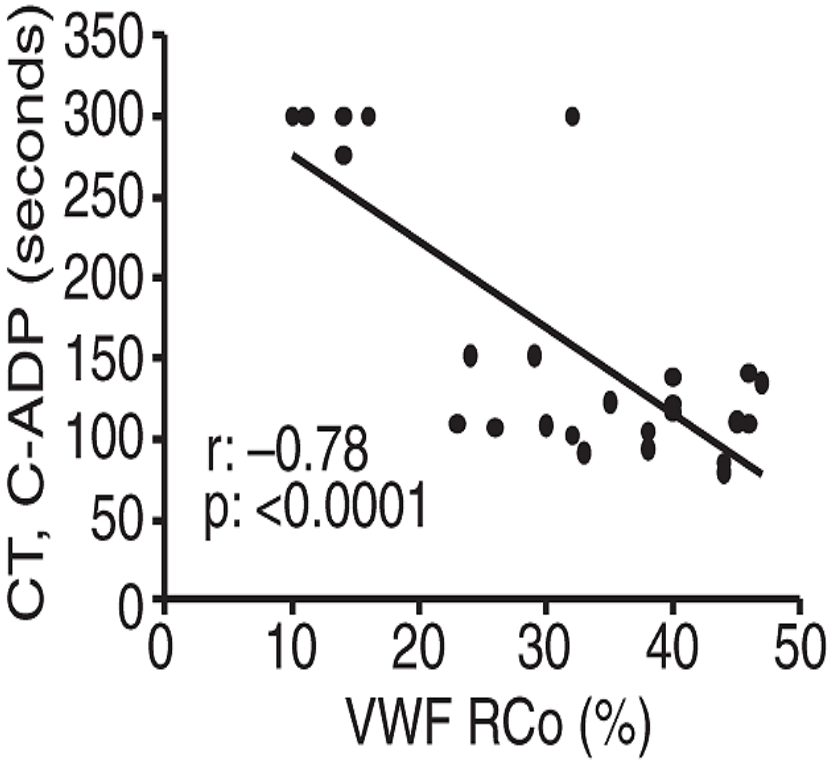
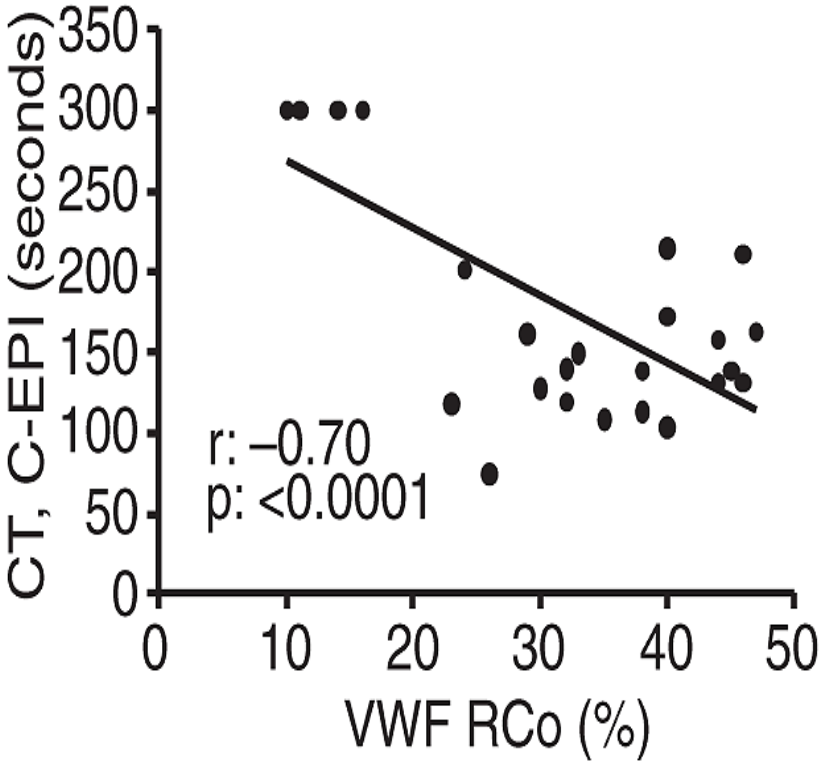
Favaloro E. *J Thromb Haemost* 2004; 2:2280

Correlation Between VWF:RCo With Closure Times in Type I VWD.





High correlation coefficients are mainly explained by the patients with VWF:RCo below 20 IU dL^{-1}.

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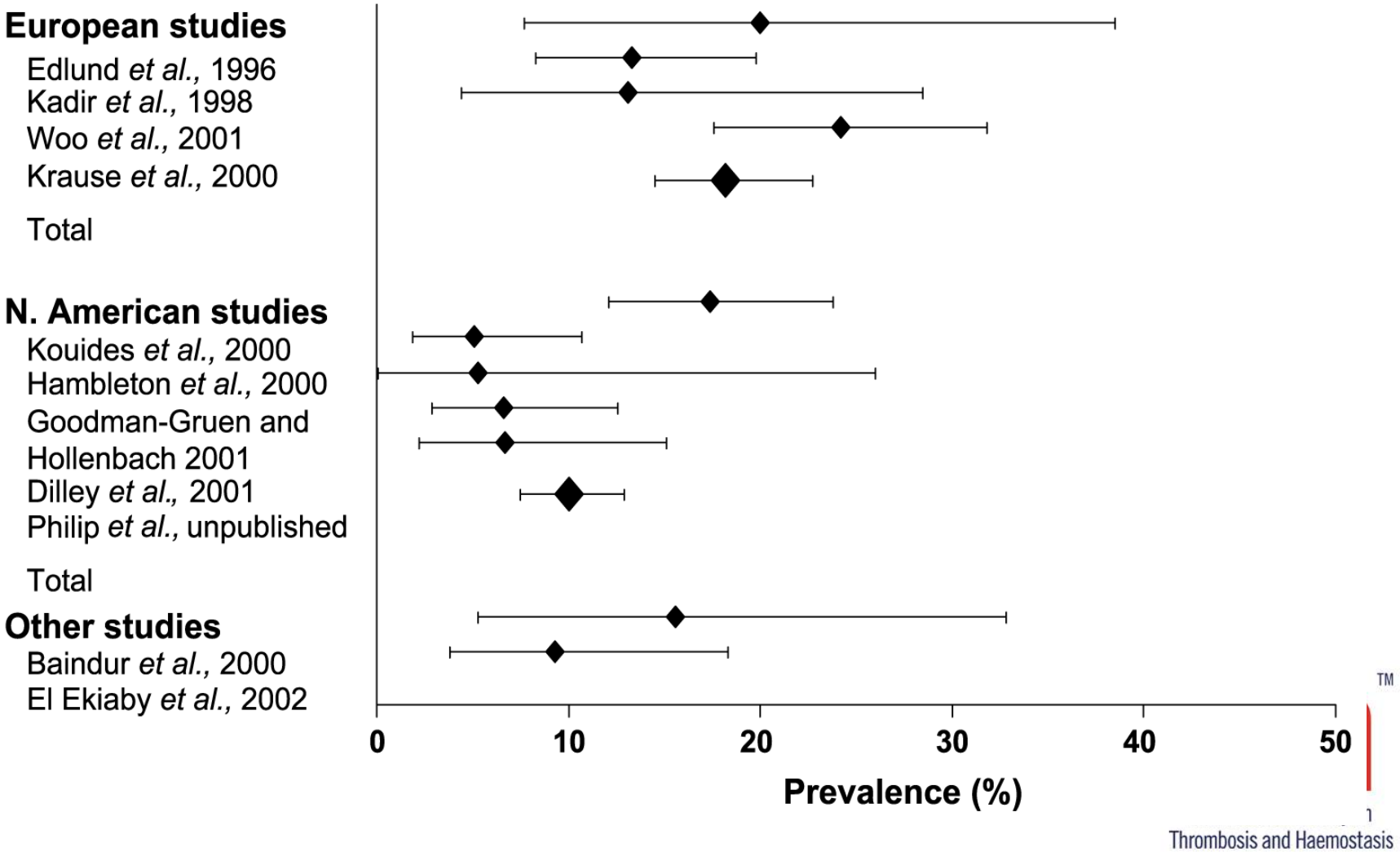
Quiroga T *J Thromb Haemost* 2004; 2:2283-2285

Prevalence of VWD in Women Presenting With Menorrhagia



Thrombosis and Haemostasis

M Shankar *et al; Br J Obstet Gynaecol* 2004

Test Selection/Algorithm

‘**Primary**’

- CBC, blood smear
- LFT, renal function
- PT, aPTT, fibrinogen
- PFA-100
- FVIII, VWF:Ag, VWF:RCo

‘**Secondary**’

- Platelet aggregation
- Platelet secretion/EM
- (Platelet flow cytometry)

‘Tertiary’

- A2AP
- PAI-1
- FXIII

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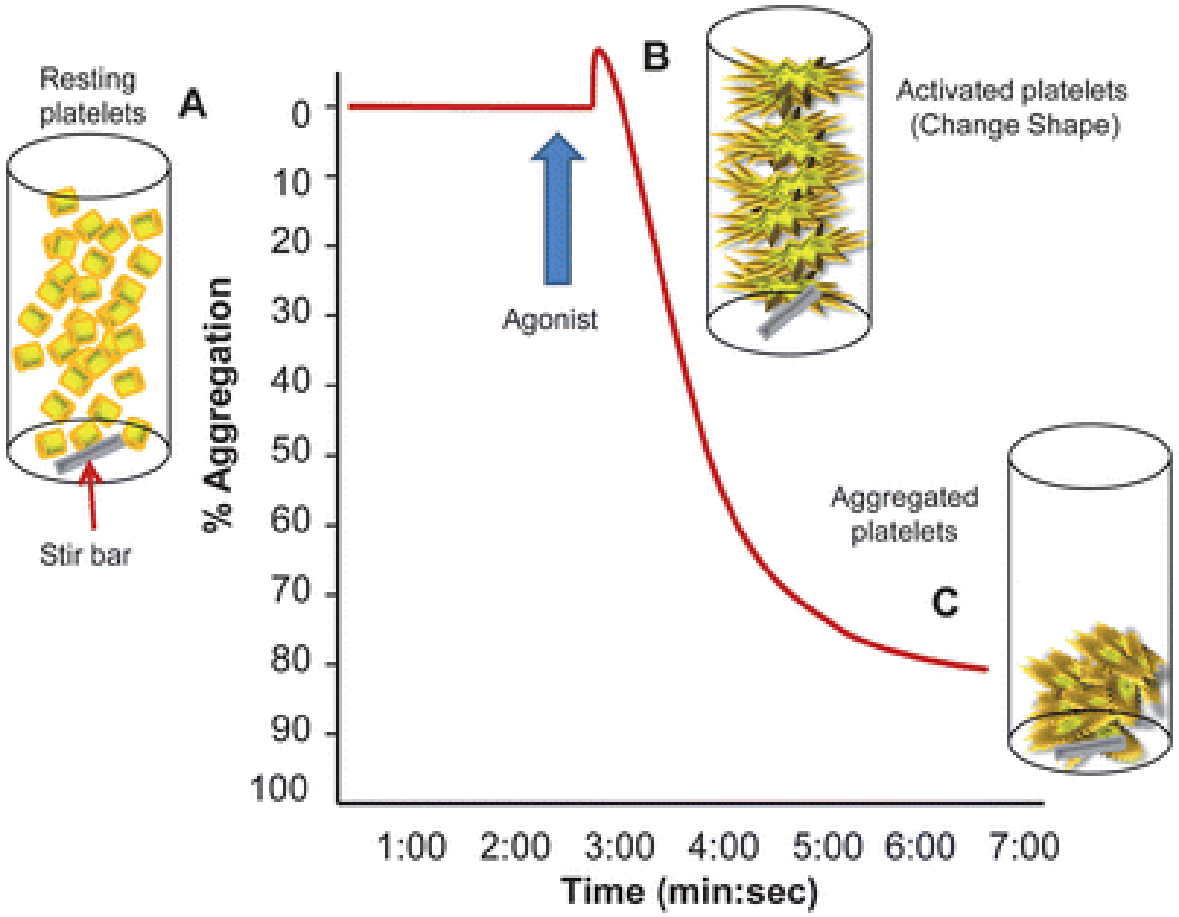
Platelet Aggregometry



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Journal of Thrombosis and Haemostasis, 11: 1183–1189 DOI: 10.1111/jth.12231

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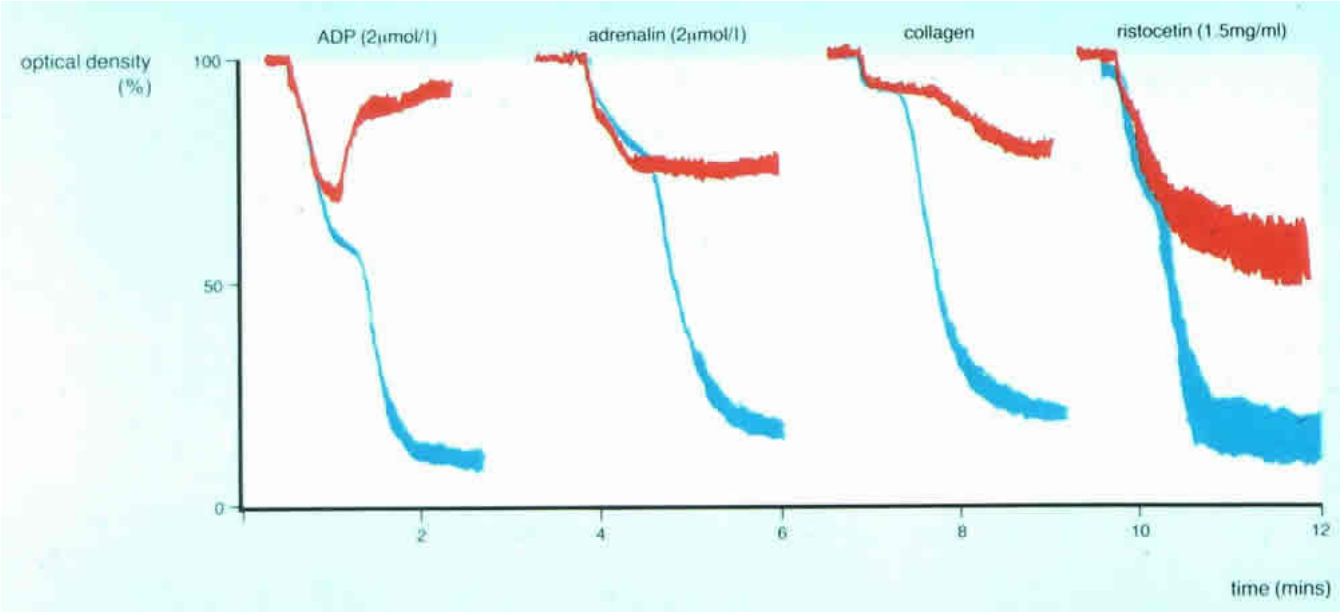
Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the platelet physiology subcommittee of SSC/ISTH

M. CATTANEO,* C. CERLETTI,† P. HARRISON,‡ C. P. M. HAYWARD,§ D. KENNY,¶ D. NUGENT,** P. NURDEN,†† A. K. RAO,‡‡ A. H. SCHMAIER,§§ S. P. WATSON,¶¶ F. LUSSANA,* M. T. PUGLIANO* and A. D. MICHELSON***



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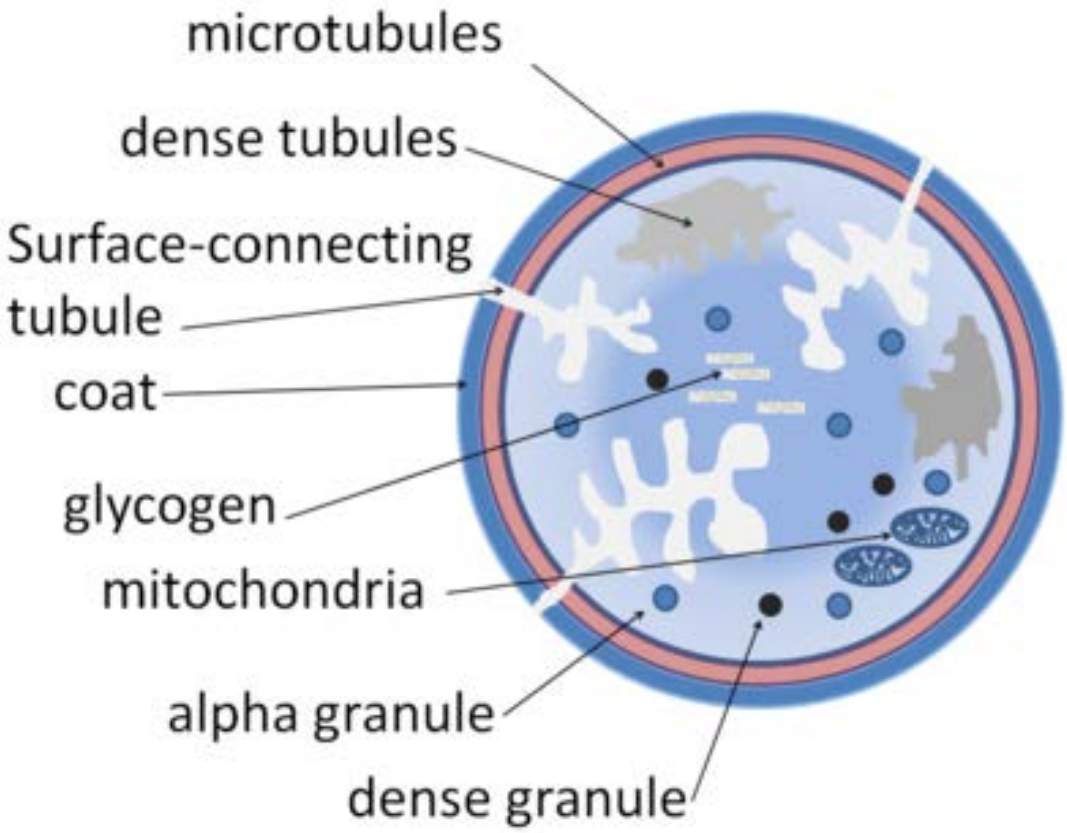
Platelet Structure



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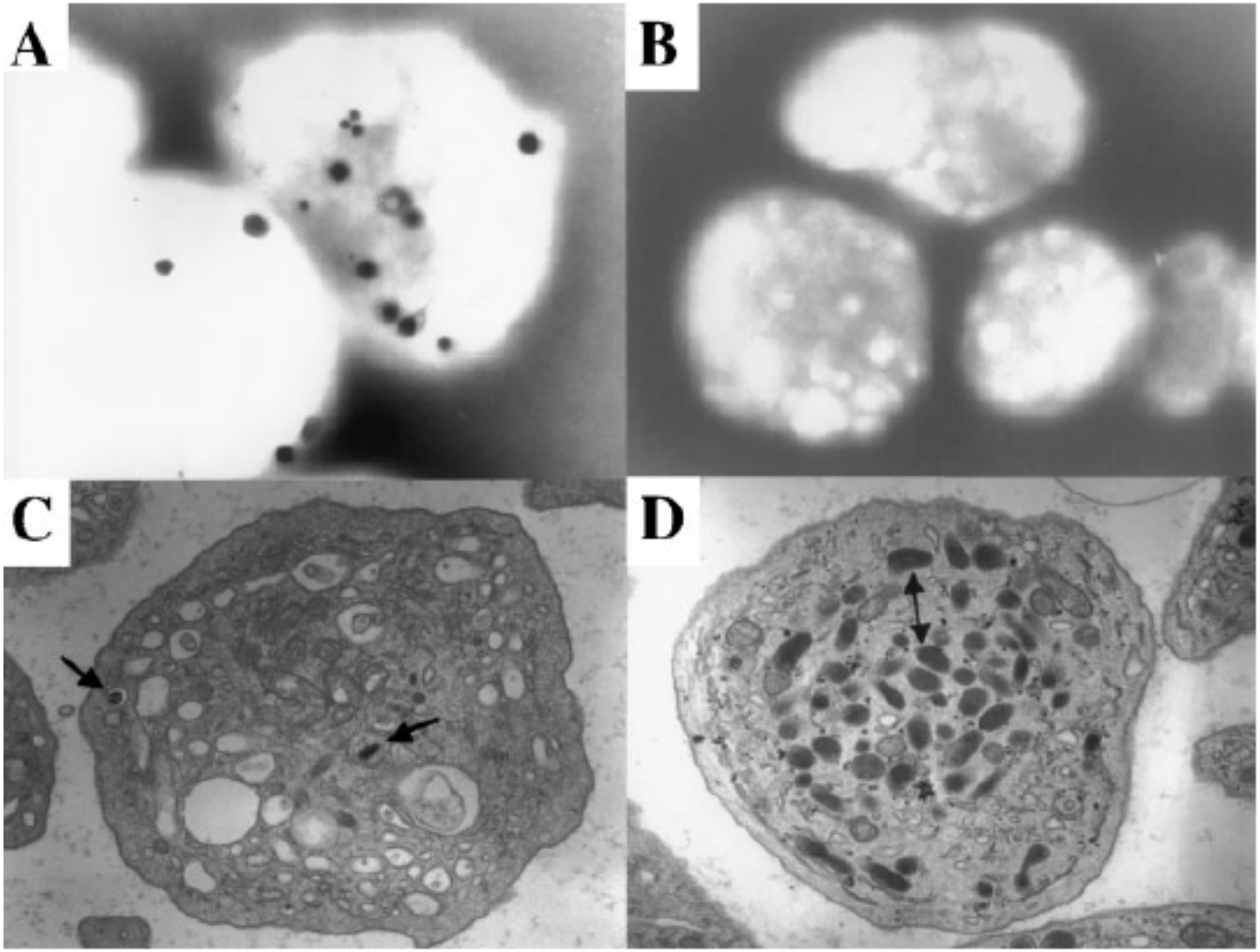
Alpha (C) and Delta (B,D) SPD: Wet Mount and Transmission EM



Gunay-Aygun M, *Semin Thromb Hemost* 2004

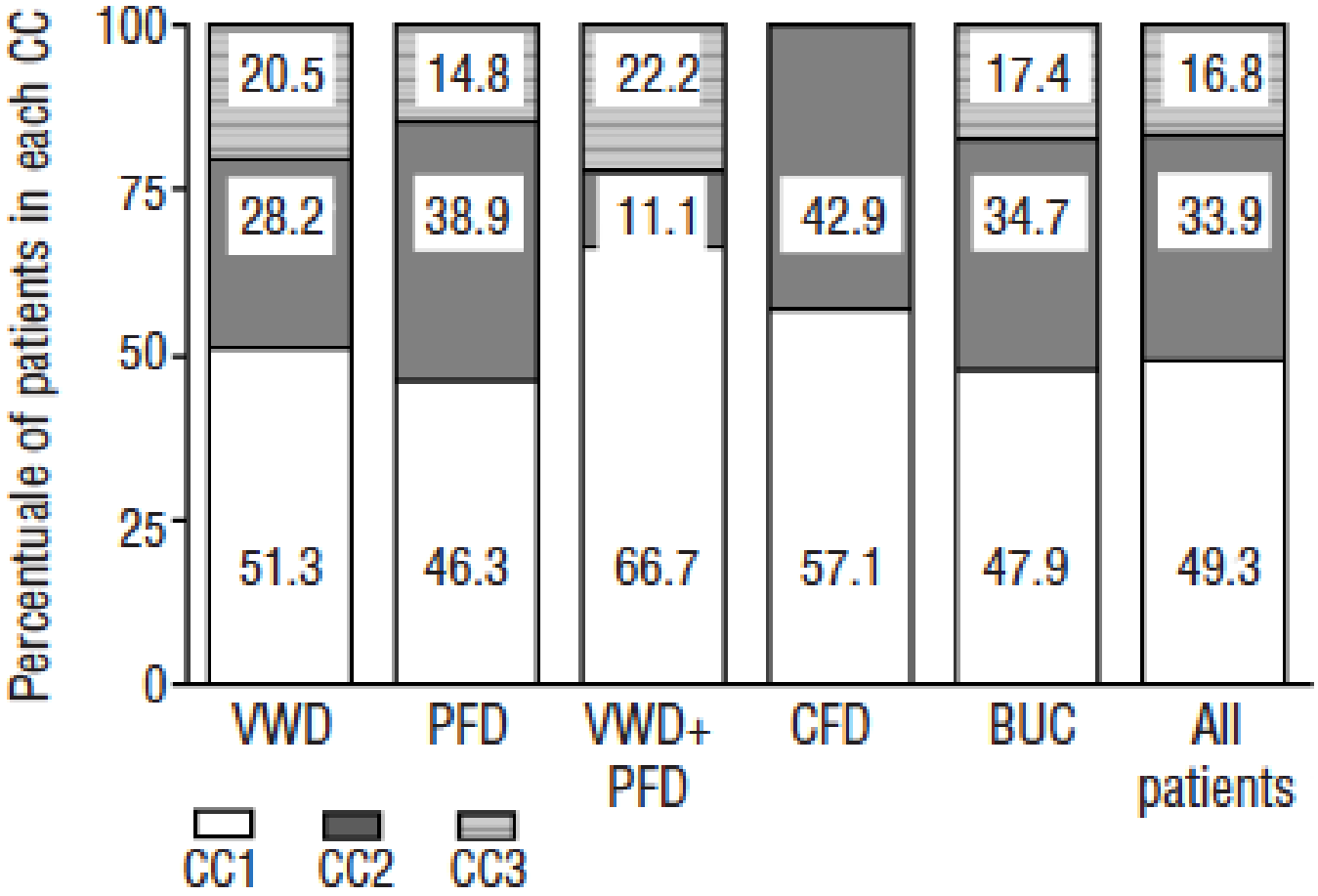
High prevalence of bleeders of unknown cause among patients with inherited mucocutaneous bleeding. A prospective study of 280 patients and 299 controls

Teresa Quiroga, Manuela Goycoolea, Olga Panes, Eduardo Aranda, Carlos Martínez, Sabine Belmont, Blanca Muñoz, Pamela Zúñiga, Jaime Pereira, Diego Mezzano

Diagnosis	Number (%)
vWD	50 (17.9%)
Platelet function defect	65 (23.2%)
Bleeding of unknown cause	167 (59.6%)

Quiroga T, *Haematologica* 2007

Clinical Severity is Similar Among the Various Diagnoses



[CC = Clinical Category]

Quiroga T, *Haematologica* 2007

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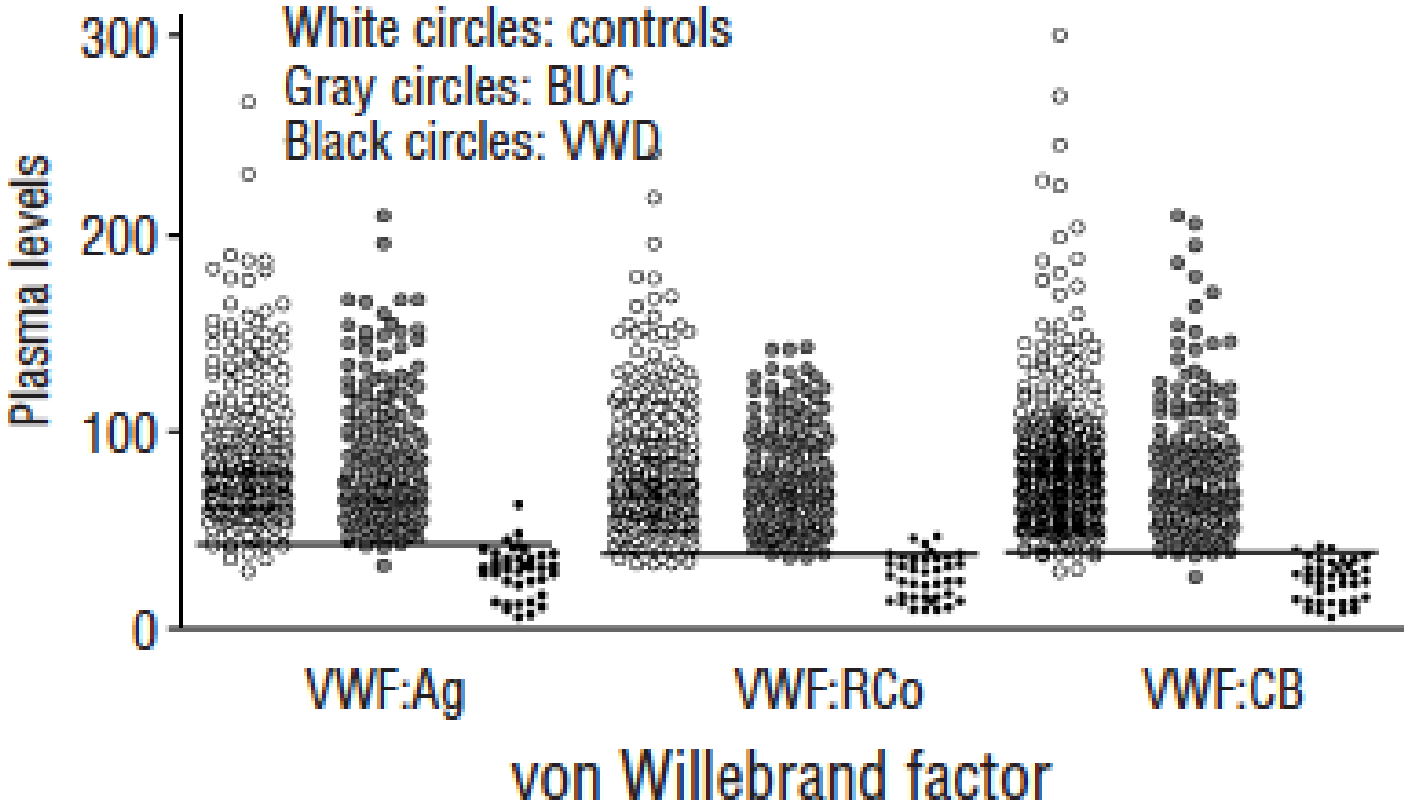
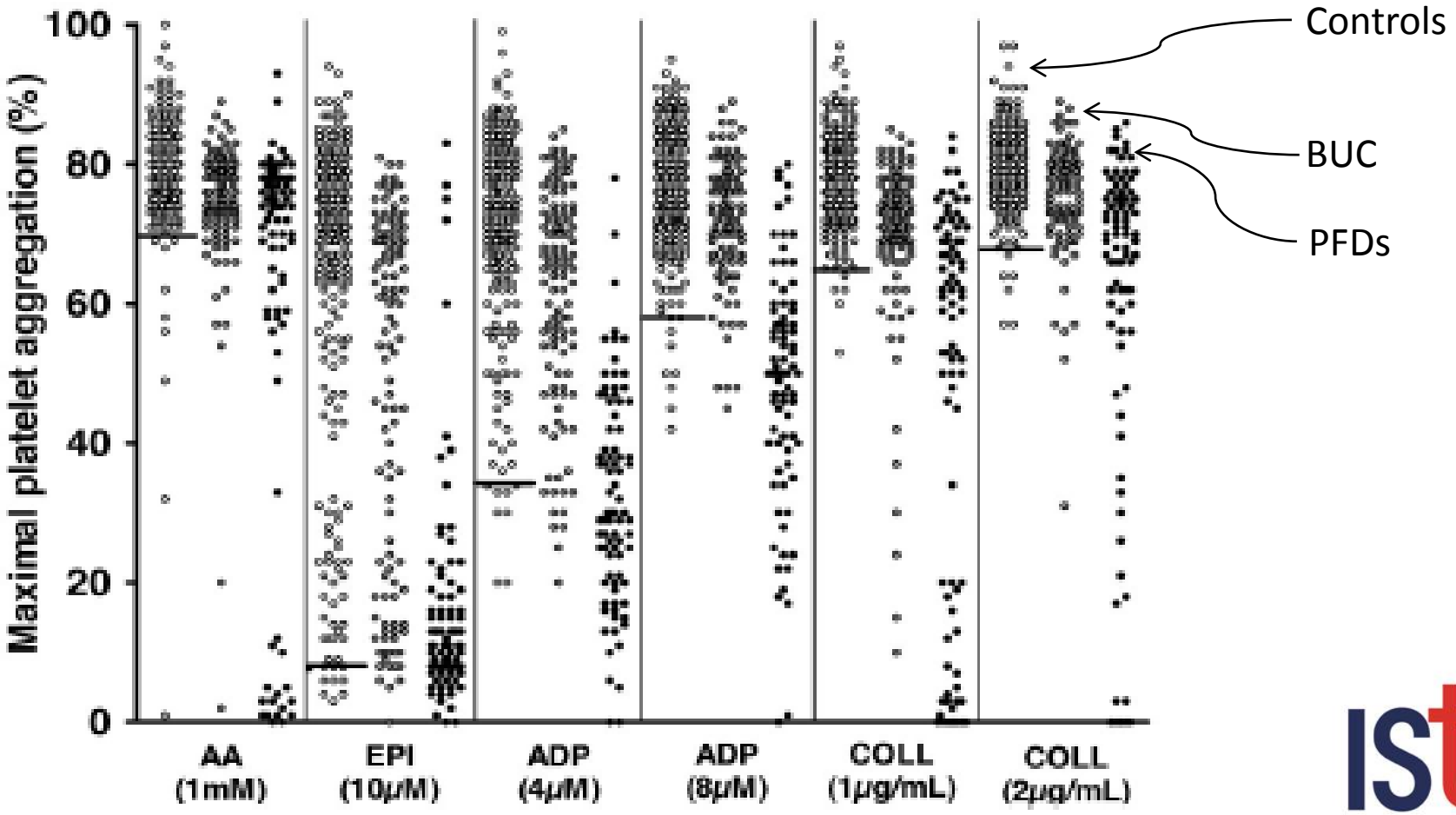
VW Lab Data for 280 Consecutive Patients Evaluated for Bleeding



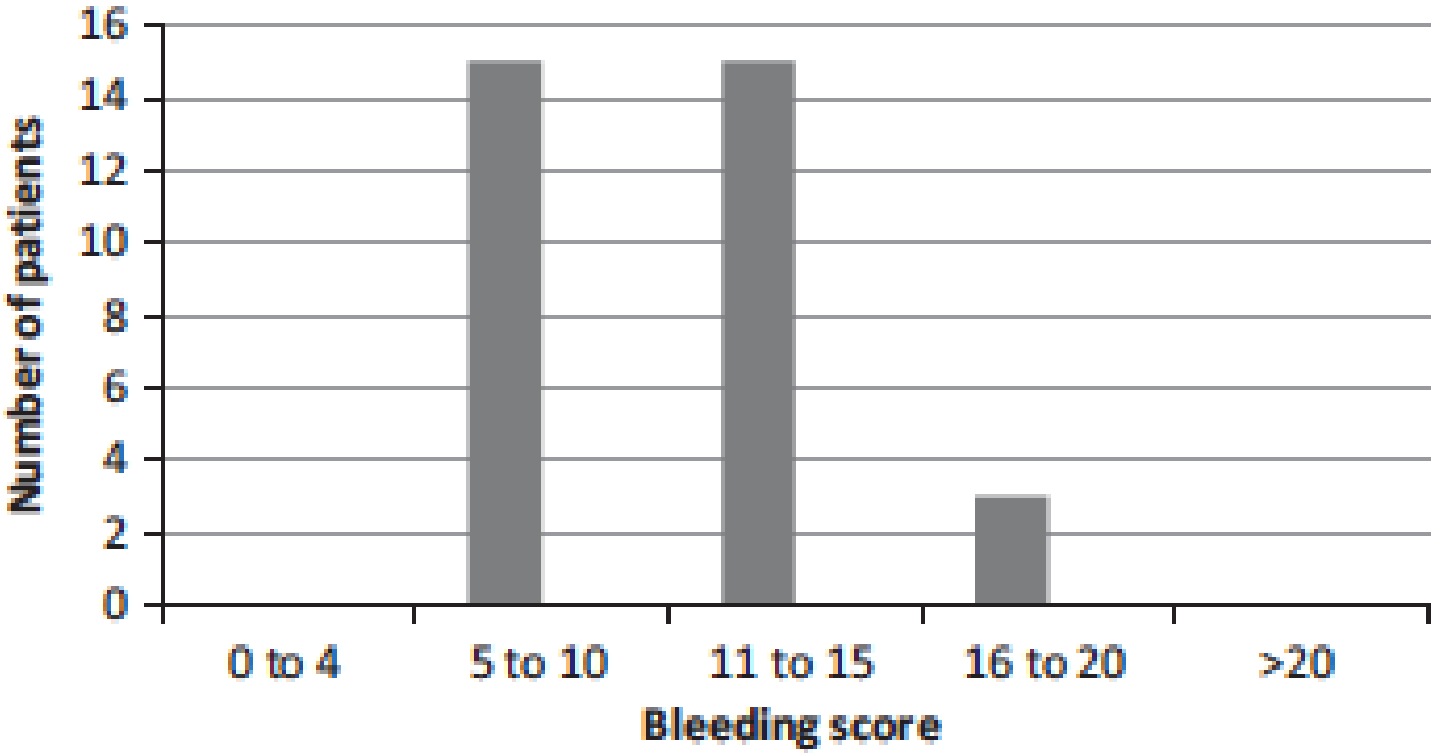
Quiroga T, *Haematologica* 2007

Platelet Aggregation Data for 280 Consecutive Patients Evaluated for Bleeding



Quiroga T, *Haematologica* 2007

Surgery Outcomes in Patients with Bleeding of Undefined Cause (BUC)



33 patients;
78 procedures

Obaji S, *Haemophilia* 2016

Surgery Outcomes in Patients with Bleeding of Undefined Cause (BUC)

- 33 patients underwent 78 procedures
  - 28 received peri-operative tranexamic acid
  - 45 received peri-operative tranexamic acid and DDAVP
  - 2 received DDAVP only

- In 70/78 (90%), hemostatic outcome was excellent
  - Minor bleeding in 4 case on tranexamic acid; controlled by addition of DDAVP
  - Significant bleeding in 1 case on both tranexamic acid and DDAVP; controlled by platelet transfusion

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Obaji S, *Haemophilia* 2016

Conclusions

- Use of a bleeding assessment tool to evaluate patients with suspected bleeding disorders is recommended
- The ISTH-BAT is primarily validated for vWD, for which it is reasonably sensitive
- A normal score on the ISTH-BAT essentially rules out the need for further evaluation.
- Following a ‘complete’ evaluation (history, vWD screen and platelet aggregation), 50-60% of patients with a suggestive history will not have a specific diagnosis (‘bleeding of undefined cause; BUC’)
- More data on clinical outcomes of patients with BUC are needed

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