LA ZONE GRISE DANS LA MALADIE DE WILLEBRAND

CAMILLE PARIS ET JENNY GOUDEMAND

RÉUNION SEMESTRIELLE – FILIÈRE MHEMO

14/06/2018 INSTITUT IMAGINE - PARIS

Perspective

Von Willebrand disease type 1: a diagnosis in search of a disease

J. Evan Sadler

- Prévalence élevée des signes hémorragiques dans la population générale
- + seuil au 2,5è percentile de la normale
- = 0,4% de la population normale à un phénotype de MW **par hasard**

- Concept de **facteur de risque** hémorragique, avec un continuum entre taux bas et MW

Sadler, Blood 2003;101:2089-2093

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

An investigation of the von Willebrand factor genotype in UK patients diagnosed to have type 1 von Willebrand disease

Anthony Cumming[1], Pamela Grundy[1], Stephen Keeney[1], William Lester[2], Said Enayat[2], Andrea Guilliatt[2], Derrick Bowen[3], John Pasi[4], David Keeling[5], Frank Hill[2], Paula H. B. Bolton-Maggs[1], Charles Hay[1], Peter Collins[3] on behalf of the UK Haemophilia Centre Doctors' Organisation

- **Critères d'inclusion**:
  - Diagnostic de type 1 dans un Haemophilia Center
  - Antériorité VWF:Rco<50UI/dl
  - VWF:Rco/VWF:Ag>0,7
  - MM N
  - Sgnt significatif
  - Ant familial de MW de type 1

- 32 Cas Index
- **Bio :** 10 <30UI/dL 10 entre 30 -50UI/dL 12 >50UI/dL
- **Age** ?
- **Sexe** : 7F 3H 8F 2H 8F 4H
- **Gpe O** 3A +7O 10 O 3A+9O
- **mutés** 80% 70% 42%
- **BS** Sites des hémorragies (pas de BS)

Cumming, Thromb Haemost 2006; 96:630-41

Journal of Thrombosis and Haemostasis, **4**: 766–773

ORIGINAL ARTICLE

A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD)

A. TOSETTO,* F. RODEGHIERO,* G. CASTAMAN,* A. GOODEVE,† A. B. FEDERICI,‡ J. BATLLE,§ D. MEYER,¶ E. FRESSINAUD,¶ C. MAZURIER,** J. GOUDEMAND,†† J. EIKENBOOM,‡‡ R. SCHNEPPENHEIM,§§ U. BUDDE,¶¶ J. INGERSLEV,*** Z. VORLOVA,††† D. HABART,††† L. HOLMBERG,‡‡‡ S. LETHAGEN,‡‡‡ J. PASI,§§§ F. HILL¶¶¶ and I. PEAKE†

CI: Cas index
AFM: Affected Family Member
UFM: Unaffected family Member

- **Critères d'inclusion**
  - Diag type 1 (pas de critères) avec Ant familiaux
  - 144 Cas Index (CI), 273 Affected family members (AFM), 295 Unaffected family members (UFM)
  - Finalement 1/3 sont type 2
  - 93 (65%) type 1 : MM normaux (« groupe 2+3 »)
- **VWF:RCo médian (25è/100 – 75è/100) CI** 34 (11-49)/ **AFM** 35 (12-54)/ **UFM** 87 (65-112)

- **Age CI** 40 (1-80)/ **AFM** 32 (2-91)/ **UFM** 41 (3-90)
- **Sexe Féminin CI** 63%F/ **AFM** 55% /**UFM** 49%

- **Gpe O CI** 67%/ CI non mut 76%/ CI mut 60%/ **AFM** 59%/ **UFM** 48%/ Popu 38%

- **Mutation :** 55% des CI (51/93) attention parmi eux nombreux avec ratio<0,7

- **BS** Tosetto simplifié **CI** 9 (-1 à 23)/ **AFM** 4 (-2 à 27)/ **UFM** 0 (-2 à 14)
- CI mutés = 8/ CI non mutés = 8

Tosetto, J Thromb Haemost 2006; 4:766-73

Journal of Thrombosis and Haemostasis, **4**: 766–773

ORIGINAL ARTICLE

A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD)

A. TOSETTO,* F. RODEGHIERO,* G. CASTAMAN,* A. GOODEVE,† A. B. FEDERICI,‡ J. BATLLE,§ D. MEYER,¶ E. FRESSINAUD,¶ C. MAZURIER,** J. GOUDEMAND,†† J. EIKENBOOM,‡‡ R. SCHNEPPENHEIM,§§ U. BUDDE,¶¶ J. INGERSLEV,*** Z. VORLOVA,††† D. HABART,††† L. HOLMBERG,‡‡‡ S. LETHAGEN,‡‡‡ J. PASI,§§§ F. HILL¶¶¶ and I. PEAKE†

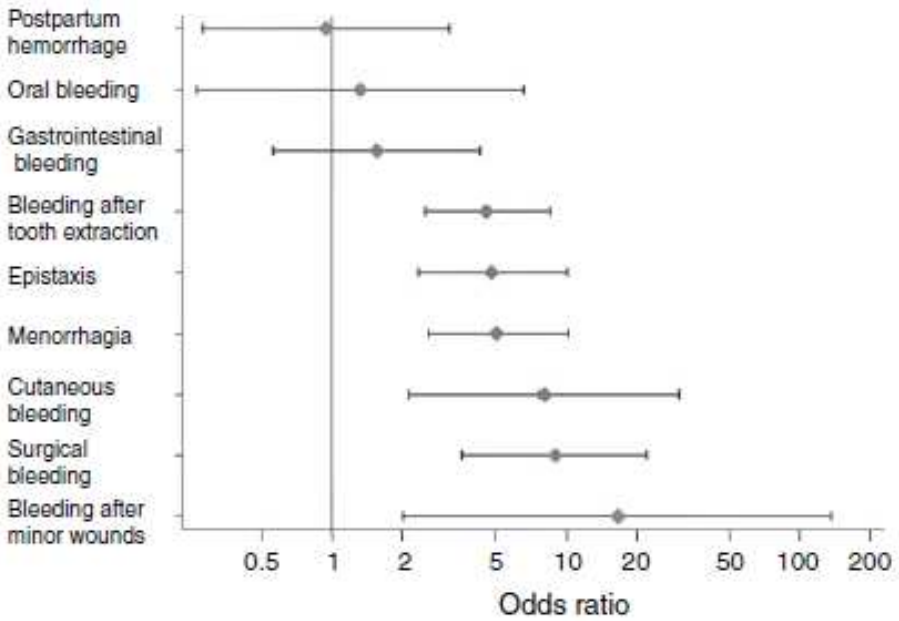


Fig. 2. Association between bleeding symptoms and type 1 von Willebrand disease in the enrolled families in an age-adjusted logistic model. Index cases were excluded from the analysis; a bleeding symptom was considered in the model for a symptom-specific score greater than one. For each bleeding symptom, the graph reports the logistic estimate and its 95% confidence interval.

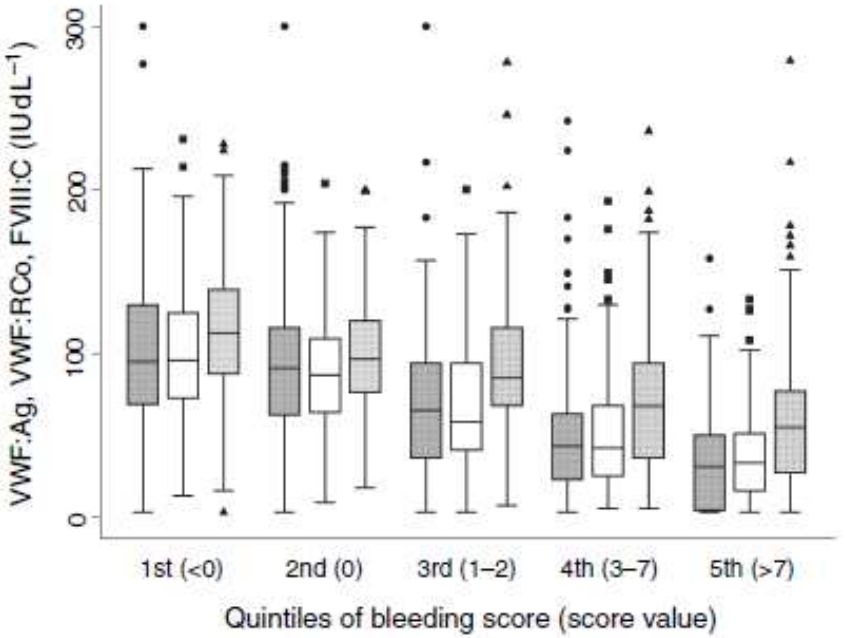


Fig. 3. Association between bleeding score and von Willebrand factor (VWF)/FVIII:C levels. For each quintile of bleeding score, the boxes span from the 25th to the 75th percentile. The center line represents the median value; dark gray boxes: VWF:RCo; light gray boxes, FVIII:C; white boxes, VWF:Ag.

Tosetto, J Thromb Haemost 2006; 4:766-73

Phenotype and genotype of a cohort of families historically diagnosed with type 1 von Willebrand disease in the European study, Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease (MCMDM-1VWD)

Anne Goodeve,[1] Jeroen Eikenboom,[2] Giancarlo Castaman,[3] Francesco Rodeghiero,[3] Augusto B. Federici,[4] Javier Batlle,[5] Dominique Meyer,[6] Claudine Mazurier,[7] Jenny Goudemand,[8] Reinhard Schneppenheim,[9] Ulrich Budde,[10] Jorgen Ingerslev,[11] David Habart,[12] Zdena Vorlova,[12] Lars Holmberg,[13] Stefan Lethagen,[14] John Pasi,[15] Frank Hill,[16] Mohammad Hashemi Soteh,[1] Luciano Baronciani,[4] Christer Hallden,[14] Andrea Guilliatt,[16] Will Lester,[16] and Ian Peake[1]

Table 7. Association between the presence of mutations and VWF level in index cases

VWF level in IC		Mutation	No mutation	OR (95% CI)
VWF:Ag, IU/dL				
More than 45	**50%**	27	27	1*
31 to 45	**69%**	24	11	2.2 (0.90-5.3)
16 to 30	**83%**	30	6	5.0 (1.8-14.0)
0 to 15	**96%**	23	1	23.0 (2.9-182.6)
VWF:RCo, IU/dL				
More than 45		23	25	1*
31 to 45		24	12	2.2 (0.89-5.3)
16 to 30		17	6	3.1 (1.04-9.2)
0 to 15		40	2	21.7 (4.7-100.3)

OR indicates odds ratio; CI, confidence interval.
*Reference category.

57%

88%

Goodeve, Blood. 2007;109:112-121

The mutational spectrum of type 1 von Willebrand disease: results from a Canadian cohort study

Paula D. James,[1,2] Colleen Notley,[2] Carol Hegadorn,[2] Jayne Leggo,[2] Angie Tuttle,[2] Shawn Tinlin,[2] Christine Brown,[2] Chandler Andrews,[2] Andrea Labelle,[2] Yvette Chirinian,[2] Lee O'Brien,[2] Maha Othman,[2] Georges Rivard,[3] Dilys Rapson,[2] Christine Hough,[2] and David Lillicrap,[2] for the Association of Hemophilia Clinic Directors of Canada

- **Critères d'inclusion**: 123 cas index
  - Ratios>0,6
  - MM N
  - 2N et 3 exclus
  - 5 à 50 Ag

- **Bio** VWF:Ag 36 (7-50)/ VWF: RCo 34 (7-50)/ FVIII 54 (9-136)
- **Age** 24 (1-65)
- **Sexe** 86F/ 37H
- **Gpe O** 50% O <30/ 66% O 30-50/ 46% popu

- **Mut 75% de mut <30/ 49% de mut 30-50**

- **BS** non

James, Blood. 2007;109:145-154

THROMBOSIS AND HEMOSTASIS

Clinical and laboratory variability in a cohort of patients diagnosed with type 1 VWD in the United States

Veronica H. Flood,[1-3] Pamela A. Christopherson,[3] Joan Cox Gill,[1-3] Kenneth D. Friedman,[3,4] Sandra L. Haberichter,[1-3] Daniel B. Bellissimo,[3] Rupa A. Udani,[3] Mahua Dasgupta,[5] Raymond G. Hoffmann,[5] Margaret V. Ragni,[6] Amy D. Shapiro,[7] Jeanne M. Lusher,[8] Steven R. Lentz,[9] Thomas C. Abshire,[1-4,10] Cindy Leissinger,[11] W. Keith Hoots,[12] Marilyn J. Manco-Johnson,[13] Ralph A. Gruppo,[14] Lisa N. Boggio,[15] Kate T. Montgomery,[16] Anne C. Goodeve,[17] Paula D. James,[18] David Lillicrap,[18] Ian R. Peake,[17] and Robert R. Montgomery[1-3]

- **Critères d'inclusion**: 482 cas
  - Diag de MW antérieur avec ratio VWF:Rco/VWF:Ag >0,5-0,7
  - type 1 si à l'entrée dans l'étude VWF:Ag ou VWF:RCo<30UI/dL
  - Taux bas si VWF:Ag 30-49UI/dL et/ou VWF:Rco 30-53UI/dL
  - MW type 1 historique (36%) : pbl de l'avancée en âge

- **Age** 19 (SD 15) avec 64%<18ans / Hist 21 (SD 16)
- **Bio** VWF:Ag 36 (17-46); 4% t1 sont 2M CB
- **Sexe** F 66%
- **Gpe O** 73%
- **Mutés** gpe O 54%/ A 75%, B 93%, AB 80%

- Mais pas de rech déf modéré/fonctions plaq.

Flood, Blood. 2016;127(20):2481-2488

Clinical and laboratory variability in a cohort of patients diagnosed with type 1 VWD in the United States

Veronica H. Flood,[1-3] Pamela A. Christopherson,[3] Joan Cox Gill,[1-3] Kenneth D. Friedman,[3,4] Sandra L. Haberichter,[1-3] Daniel B. Bellissimo,[3] Rupa A. Udani,[3] Mahua Dasgupta,[5] Raymond G. Hoffmann,[5] Margaret V. Ragni,[6] Amy D. Shapiro,[7] Jeanne M. Lusher,[8] Steven R. Lentz,[9] Thomas C. Abshire,[1-4,10] Cindy Leissinger,[11] W. Keith Hoots,[12] Marilyn J. Manco-Johnson,[13] Ralph A. Gruppo,[14] Lisa N. Boggio,[15] Kate T. Montgomery,[16] Anne C. Goodeve,[17] Paula D. James,[18] David Lillicrap,[18] Ian R. Peake,[17] and Robert R. Montgomery[1-3]

BS ISTH BAT: **Corrélé au VWF:Ag si <5UI/dL**

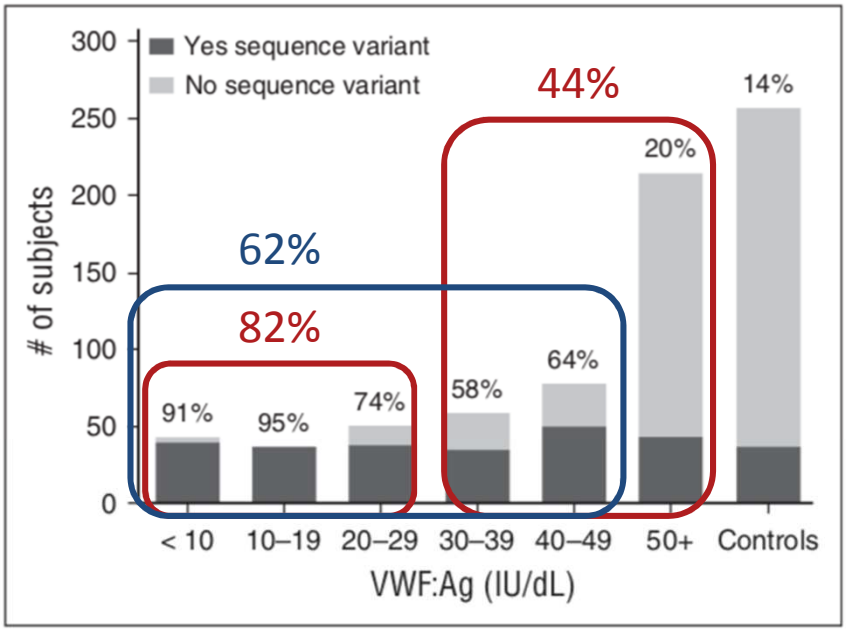


Figure 1. Sequence variations in VWD are most common in subjects with VWF:Ag <30 IU/dL. This graph shows the number of subjects with sequence variations (either point mutations, or insertions or deletions) in the VWF coding sequence (dark gray) as compared with those without sequence variations in the *VWF* coding sequence (light gray) for the entire type 1 VWD cohort by VWF:Ag as compared with the healthy controls. The percent of each group with sequence variations is shown at the top of each column. Sequence variations were most common in those with VWF:Ag <30.

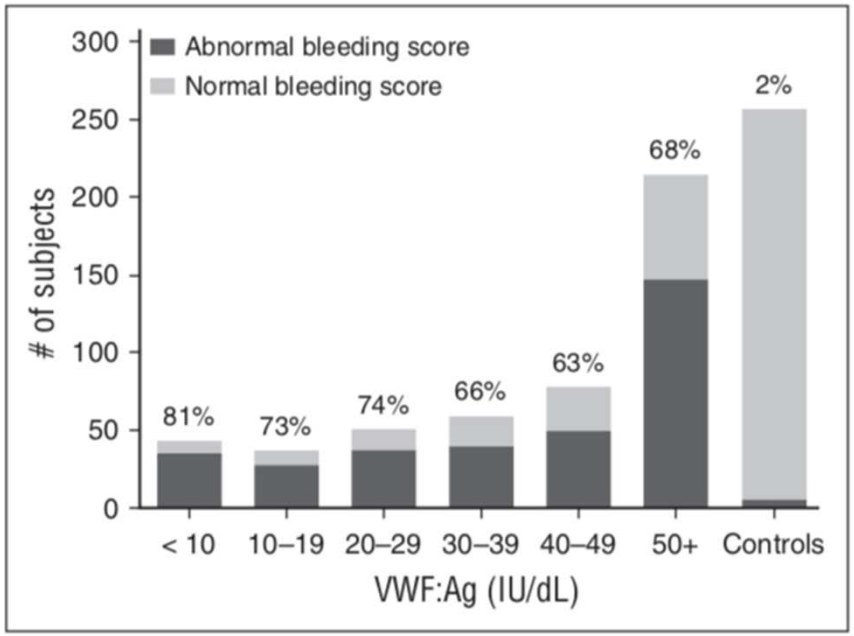


Figure 2. No significant difference in BS for type 1 VWD subjects regardless of VWF:Ag level. This graph shows the number of subjects with abnormal BS (defined as >2 in children <18 years of age, >3 in adult males, and >5 in adult females) in dark gray as compared with those with normal BS (light gray) for the entire type 1 VWD cohort by VWF:Ag. The percent of each group with abnormal BS is shown at the top of each column. BS were similar for type 1 subjects regardless of VWF:Ag.

Flood, Blood. 2016;127(20):2481-2488

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels

Michelle Lavin,[1,2,*] Sonia Aguila,[2,*] Sonja Schneppenheim,[3] Niall Dalton,[2] Kenneth L. Jones,[4] Jamie M. O'Sullivan,[2] Niamh M. O'Connell,[1] Kevin Ryan,[1] Barry White,[1] Mary Byrne,[1] Marie Rafferty,[1] Mairead M. Doyle,[1] Margaret Nolan,[1] Roger J. S. Preston,[5] Ulrich Budde,[3] Paula James,[6] Jorge Di Paola,[4] and James S. O'Donnell[1,2]

- **Critères d'inclusion** : 126 patients >18ans
  - taux bas (30-50)
  - **avec histoire hémo. personnelle significative**

- 69 : VWF:Ag+ RCo + CB 30-50
- 32: VWF:RCo + CB 30-50
- 22: VWF:RCo 30-50
- 3: VWF:CB 30-50 (4 MM aN)

- **Age** 38,8 (18-72)
- **Sexe** 112 F /14 H
- **Gpe O** 89%/ 55% popu générale

- **Mut chez 39,7%**
- **Mécanisme:** défaut de synthèse ou de sécrétion (ratio FVIII.Ag; test DDAVP; ratio VWFpp >3= 6%)

Lavin, Blood. 2017;130(21):2344-2353

CRMW

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels

Michelle Lavin,[1,2,*] Sonia Aguila,[2,*] Sonja Schneppenheim,[3] Niall Dalton,[2] Kenneth L. Jones,[4] Jamie M. O'Sullivan,[2] Niamh M. O'Connell,[1] Kevin Ryan,[1] Barry White,[1] Mary Byrne,[1] Marie Rafferty,[1] Mairead M. Doyle,[1] Margaret Nolan,[1] Roger J. S. Preston,[5] Ulrich Budde,[3] Paula James,[6] Jorge Di Paola,[4] and James S. O'Donnell[1,2]

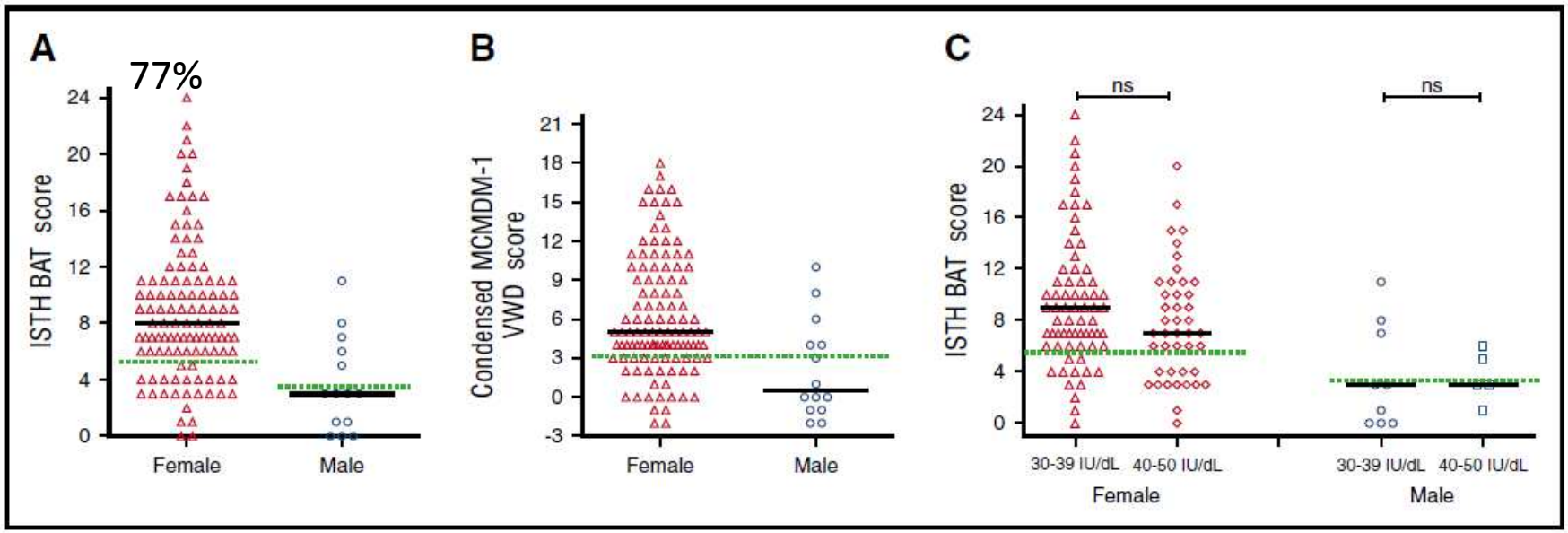


Figure 1. Patients with low VWF have significant bleeding phenotypes. (A) ISTH BAT scores by sex, females, n = 112 (triangles, median = 8), and males, n = 14 (circles, median = 3). (B) Condensed MCMDM-1 VWD bleeding scores by sex. Black lines indicate median scores in females, n = 112 (triangles, median 5), and males, n = 14 (circles, median 0.5). (C) ISTH BAT scores studied in LoVIC subgroups with lowest plasma VWF levels in the range 30 to 39 IU/dL (females, triangles; males, circles) compared with patients with lowest VWF levels in the range 40 to 49 IU/dL (females, diamonds; males, squares). No significant difference was seen for either females (median 9 vs 7, $P = .09$, ns = not significant) or males (median 3 vs 3, $P = .7$). The upper limit of bleeding scores considered normal for each score is indicated by the green dotted line; median is shown by the black line.

Lavin, Blood. 2017;130(21):2344-2353

Regular Article

blood

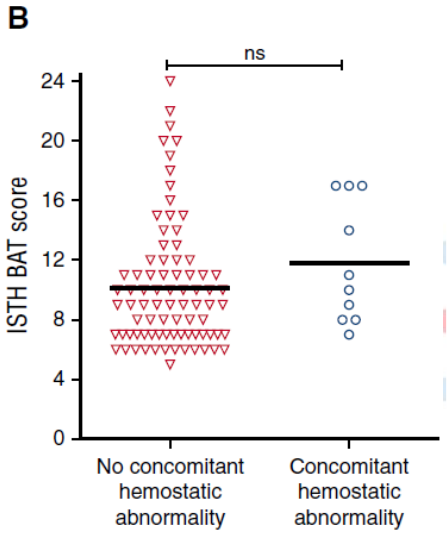
THROMBOSIS AND HEMOSTASIS

Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels

Michelle Lavin,[1,2,*] Sonia Aguila,[2,*] Sonja Schneppenheim,[3] Niall Dalton,[2] Kenneth L. Jones,[4] Jamie M. O'Sullivan,[2] Niamh M. O'Connell,[1] Kevin Ryan,[1] Barry White,[1] Mary Byrne,[1] Marie Rafferty,[1] Mairead M. Doyle,[1] Margaret Nolan,[1] Roger J. S. Preston,[5] Ulrich Budde,[3] Paula James,[6] Jorge Di Paola,[4] and James S. O'Donnell[1,2]

29/64 (45%) ont normalisé leurs taux

Tendance à l'augmentation des BS avec l'âge (ns)



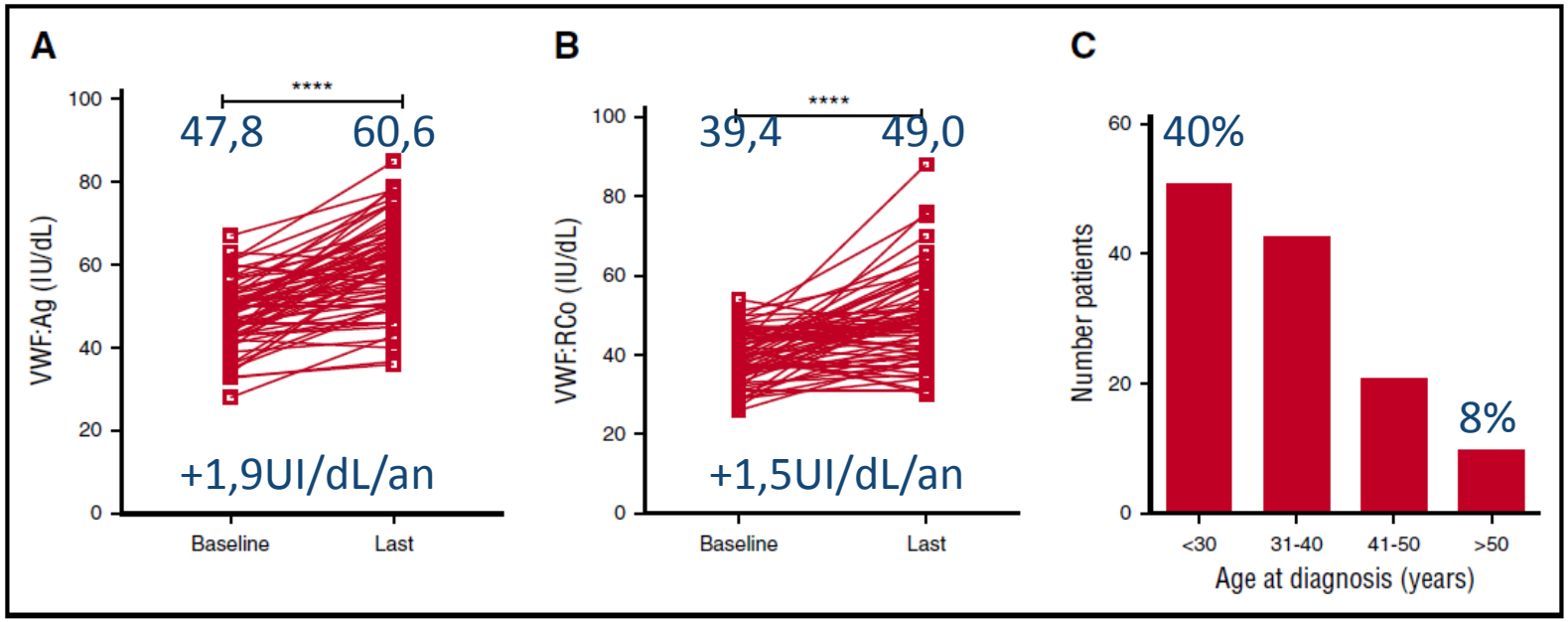


Figure 3. Plasma VWF levels normalize with age in some patients with low VWF. (A) In a subgroup of 64 LoVIC patients followed in the NCC for >5 years, plasma VWF:Ag levels were significantly higher at last follow-up compared with baseline levels (mean VWF:Ag at baseline = 47.8 IU/dL vs 60.6 IU/dL at last follow-up; ****$P < .0001$). (B) Similarly, plasma VWF:RCo levels were also significantly higher at last follow-up compared with baseline levels (mean VWF:RCo at baseline = 39.4 IU/dL vs 49.0 IU/dL at last follow-up; ****$P < .0001$). (C) Age at original registration of patients with a diagnosis with low VWF levels (n = 126).

Lavin, Blood. 2017;130(21):2344-2353

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels

Michelle Lavin,[1,2,*] Sonia Aguila,[2,*] Sonja Schneppenheim,[3] Niall Dalton,[2] Kenneth L. Jones,[4] Jamie M. O'Sullivan,[2] Niamh M. O'Connell,[1] Kevin Ryan,[1] Barry White,[1] Mary Byrne,[1] Marie Rafferty,[1] Mairead M. Doyle,[1] Margaret Nolan,[1] Roger J. S. Preston,[5] Ulrich Budde,[3] Paula James,[6] Jorge Di Paola,[4] and James S. O'Donnell[1,2]

Ccl: diag taux bas = 30-50 et phéno hémo ISTH BAT (≥4 H et 6F)

476 patients vs 115000 Irlandais <50UI:Dl par définition= facteurs additionnels de sgnt

DDAVP efficace dans cette population,
tests inutiles, efficacité à confirmer lors de la 1ère utilisation

Lavin, Blood. 2017;130(21):2344-2353

CRMW

Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease

Eva M. de Wee[1]; Yvonne V. Sanders[1]; Eveline P. Mauser-Bunschoten[2]; Johanna G. van der Bom[3,4]; Manon E. L. Degenaar-Dujardin[5]; Jeroen Eikenboom[6,7]; Arja de Goede-Bolder[8]; Britta A. P. Laros-van Gorkom[9]; Karina Meijer[10]; Karly Hamulyák[11]; Marten R. Nijziel[12]; Karin Fijnvandraat[13]; Frank W. G. Leebeek[1]; for the WiN study group

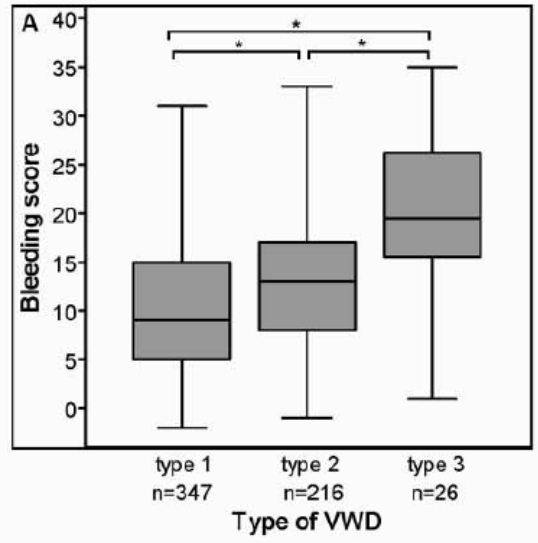
- **Critères d'inclusion**: 664 patients de plus de 16 ans avec MW
  - Signes hémorragiques personnels ou ant fam de MW
  - Taux historique VWF:Ag et/ou VWF:Act ≤ 30UI/dl
  - Type 1: VWF:Ag ou VWF:Act ≥ 5UI/dL et VWF:Act/VWF:Ag ≥ 0,70
  - 59% type 1 / 37% type 2/ 4% type 3

- **Age Médian** 45 ans (16-85)
- **Sexe** Féminin 64%
- **Gpe O :** 61% WiN study/ 68% type 1

- **BS** Tosetto simplifié autoadmin

Type*	n (%)	Median BS (range)	VWF:Ag† (IU/dl)	VWF:CB† (IU/dl)	VWF:Act† (IU/dl)	FVIII:C† (IU/dl)
Type 1	346	9 (-2–31)	39 (25–54)	45 (26–68)	48 (26–72)	68 (52–90)
Type 2	215	13 (-1–33)	25 (16–35)	8 (6–16)	8 (4–17)	37 (27–49)
Type 3	26	19.5 (1–35)	0 (0–3)	0 (0–3)	0 (0–1)	2 (1–12)

* p for trend in VWF and FVIII:C levels between type 1, type 2 and type 3 VWD were all <0.001. † median levels in IU/dl (25–75% interquartile range), pregnant patients and patients who used desmopressin or clotting factor concentrates 72 hours prior to blood sampling, were excluded (type 1 n=337, type 2 n=209, type 3 n=23). New centrally measured levels of VWF and FVIII:C were used.



De Wee, Thromb Haemost 2012;108:683-692

Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease

Eva M. de Wee[1]; Yvonne V. Sanders[1]; Eveline P. Mauser-Bunschoten[2]; Johanna G. van der Bom[3,4]; Manon E. L. Degenaar-Dujardin[5]; Jeroen Eikenboom[6,7]; Arja de Goede-Bolder[8]; Britta A. P. Laros-van Gorkom[9]; Karina Meijer[10]; Karly Hamulyák[11]; Marten R. Nijziel[12]; Karin Fijnvandraat[13]; Frank W. G. Leebeek[1]; for the WiN study group

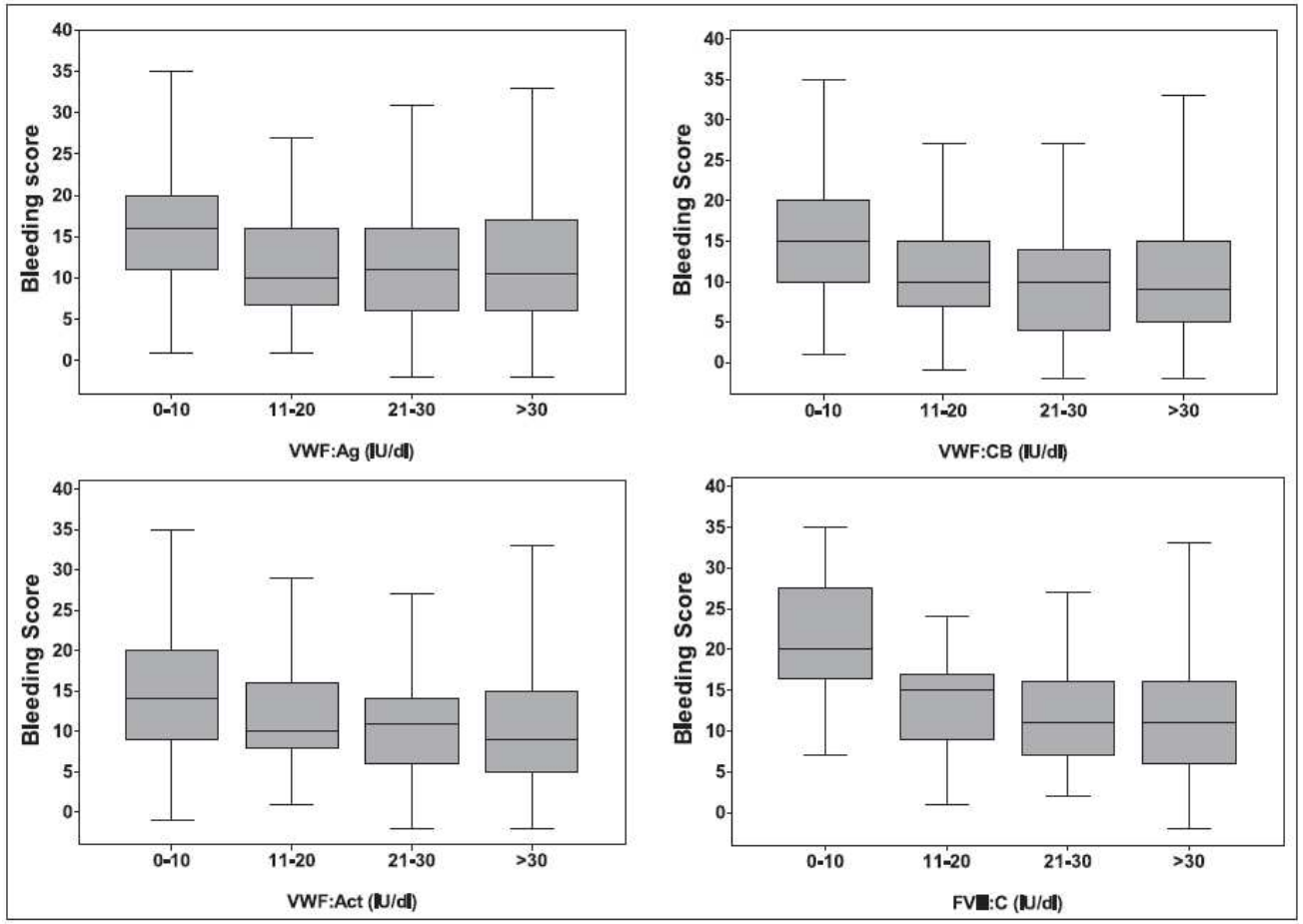


Figure 3: Bleeding score according to VWF and FVIII levels. Association between bleeding score and VWF:Ag, VWF:CB, VWF:Act and FVIII:C levels.

+10 ans = +0,8 pt BS (0,4-1,1)
F +10 ans = +1,1 pt BS (0,6-1,5)
H +10 ans: NS

De Wee, Thromb Haemost 2012;108:683-692

Mutation distribution in the von Willebrand factor gene related to the different von Willebrand disease (VWD) types in a cohort of VWD patients

Hamideh Yadegari; Julia Driesen; Anna Pavlova; Arijit Biswas; Hans-Jörg Hertfelder; Johannes Oldenburg
Institute of Experimental Haematology and Transfusion medicine, University Clinics Bonn, Germany

- **Critères d'inclusion**: 78 Cas Index Allemands avec MW
- Classés selon critères ISTH 2006
- 28 type1 / 32 type 2 / 18 type 3

- **Bio** type 1 Ag 39,5 (9-77%)

- **Age** ?
- **Sexe** ?
- **Gpe O ?**

- **Mutation chez 19 type 1** (68%)
  - 8 Ag et RCo <30UI/dL
  - 6 Ag et RCo entre 30-50UI/dL
  - 5 Ag et RCo >50UI/dL
- Abs de mutation chez 9 type 1 (32%), ts >30UI/dL
  - Soit **55% de mut si >30 vs 100% si <30**

- **BS** non

Table 2 Changes in the classification of von Willebrand disease (VWD)

Previous [1]	Current
VWD is caused by mutations at the *VWF* locus	VWD is not restricted to *VWF* gene mutations
VWD type 1 includes partial quantitative deficiency of VWF. The multimers distribution and structure of plasma VWF is indistinguishable from normal.	VWD type 1 includes partial quantitative deficiency of VWF. Plasma VWF may contain mutant subunits, but has normal functional activity relative to antigen level. The proportion of large multimers is not decreased significantly.

Yadegari, Thromb Haemost 2012;108:662-671

Journal of Thrombosis and Haemostasis, **12**: 1238–1243 DOI: 10.1111/jth.12594

IN FOCUS

Quantitative impact of using different criteria for the laboratory diagnosis of type 1 von Willebrand disease

T. QUIROGA,* M. GOYCOOLEA,* S. BELMONT,† O. PANES,† E. ARANDA,† P. ZÚÑIGA,‡ J. PEREIRA† and D. MEZZANO†

- 4729 évaluations biologiques de 4425 patients adressés pour saignements cutanéo muqueux
  - Mesures FVIII:C VWF:Ag VWF:Rco VWF:CB
  - Pas de données cliniques ou familiales
  - 101 HA ou B ou conductrices exclus
  - 3 MW type 3 exclus
  - 23 MW type 2 exclus

Table 1 Age and sex of the 4298 study patients*

Age	Females, n	Males, n	Total
0.1–10 yrs	544 (13%)	699 (16%)	1243 (29%)
11–81 yrs	2410 (56%)	645 (15%)	3055 (71%)
Total	2954 (69%)	1344 (31%)	4298

*Median age (range) of all the patients: 17 (0.1–81) years.

Guidelines	Critères diagnostiques type 1
NHLBI (US) 2008 Nichols *Haemophilia*	VWF<30UI/dL/ taux bas 30-50 UI/dL
ISTH-SSC modification 2012 Branchford *Hematology Am Soc Hematol Educ Program*	VWF:Rco et VWF:Ag <2DS de la moyenne et MM normaux
EUVWD (EU) 2013 Castaman *Haematologica*	VWF:RCo (ou VWF:CB) <40UI/dL
ZPMCBVWD (US) 2013 Montgomery *Blood*	VWF:RCo ou VWF:Ag <40UI/dL
Chili	2 mesures/3<2,5è percentile (VWF:Ag<42 VWF:Rco<37 VWF:CB<39): MW t1 1 mesure/3<2,5è percentile : possible MW type 1 2 ou 3 entre 2,5è et 7,5è percentile (VWF:Ag<51 VWF:Rco<46 VWF:CB<48) : VWF limites basses de la N

CRMW Quiroga, J Thromb Haemost 2014;12:1238-43

Journal of Thrombosis and Haemostasis, **12**: 1238–1243 DOI: 10.1111/jth.12594

IN FOCUS

Quantitative impact of using different criteria for the laboratory diagnosis of type 1 von Willebrand disease

T. QUIROGA,* M. GOYCOOLEA,* S. BELMONT,† O. PANES,† E. ARANDA,† P. ZÚÑIGA,‡ J. PEREIRA† and D. MEZZANO†

Table 2 Laboratory diagnosis of type 1 VWD using four different criteria

Criteria	Diagnosis	No. of patients ($N = 4298$)
NHLBI recommendation	Type 1 VWD	122 (2.8%)
	Possible type 1; 'low VWF'	706 (16.4%)
	Normal VWF	3470 (80.8%)
EUVWD	Type 1 VWD	339 (7.9%)
	Normal	3959 (92.1%)
ZPMCBVWD	Type 1 VWD	357 (8.3%)
	'Low VWF' + normal*	3941 (93.7)
≤ 2.5th percentile	Type 1 VWD	280 (6.5%)
	Possible type 1 VWD	169 (3.9%)
	'Low VWF'	181 (4.2%)
	Normal VWF	3668 (85.4%)

*Includes 'Low VWF' and patients with normal VWF.

Table 3 Quantitative contribution of VWF:RCo in the diagnosis of 280 patients with type 1 VWD

VWF:Ag ≤ 42 IU dL^{-1}	VWF:RCo ≤ 37 IU dL^{-1}	VWF:CB* ≤ 39 IU dL^{-1}	Number of patients
+	+	+	173
+	+	–	42
+	–	+	61
–	+	+	4
276	219	238	280

VWF, von Willebrand factor; VWD, von Willebrand disease; Ag, antigen; RCo, ristocetin cofactor; CB, collagen binding.
*Inclusion of VWF:CB assay allowed diagnosing 65 additional patients.

Quiroga, J Thromb Haemost 2014;12:1238-43

Journal of Thrombosis and Haemostasis, 13: 228–236 DOI: 10.1111/jth.12799

ORIGINAL ARTICLE

Predictors of von Willebrand disease diagnosis in individuals with borderline von Willebrand factor plasma levels

P. BUCCIARELLI,* S. M. SIBONI,* F. STUFANO,* E. BIGUZZI,* M. T. CANCIANI,* L. BARONCIANI,* M. T. PAGLIARI,* S. LA MARCA,* C. MISTRETTA,* F. R. ROSENDAAL†‡ and F. PEYVANDI*

- 785 patients adressés au centre ABBHTC de Milan pour un épisode hémorragique
- et 165 pour allongement du TCA,
- avec NFS, TP, TCA, FVIII:C, VWF:RCo, VWF:Ag
  - Dont 96 (10%) avec VWF:RCo entre 30-60UI/dL
  - Exclusion 1 HAMin et 2 AVWS
  - 70/93 adressés pour un épisode hémorragique
  - 93 avec données cliniques, BS, et tests de second niveau : VWF:CB, VWF MM, liaison FVIII, RIPA, VWF intraplaquettaire

- MW: au moins 1 critère
  - Diminution VWF plaquettaire
  - VWF:RCo/VWF:Ag ou VWF:CB/VWF:Ag

  ou FVIII:C/VWF:Ag ≥ 0,60 ou MM anormaux (Type 2)
  - RIPA positive (Type 2B New York)
  - ou si pas de ccl avec les tests de second niveau

  antécédent familial de VWD

Table 1 Baseline characteristics of the 93 individuals with borderline von Willebrand factor (VWF) plasma levels

	VWD	
	Yes (n = 45)	No (n = 48)
Sex (M/F)	10/35	21/27
Age (years)	27 (15–41)	28 (15–43)
Type of selection, no. (%)		
Bleeding	36 (80)	34 (71)
Only prolonged APTT	9 (20)	14 (29)
Bleeding score	6 (3–9)	4 (2–7)
Positive family history, no. (%)	13 (29)	12 (25)
Blood group O, no. (%)	33 (73)	35 (73)
VWF:RCo (IU dL^{-1})	39 (34–49)	53 (48–57)
VWF:Ag (IU dL^{-1})	46 (41–52)	61 (56–67)
Factor VIII:C (IU dL^{-1})	60 (51–72)	70 (58–85)

Bucciarelli, J Thromb Haemost 2015;13:228-36

Journal of Thrombosis and Haemostasis, 13: 228–236 DOI: 10.1111/jth.12799

ORIGINAL ARTICLE

Predictors of von Willebrand disease diagnosis in individuals with borderline von Willebrand factor plasma levels

P. BUCCIARELLI,* S. M. SIBONI,* F. STUFANO,* E. BIGUZZI,* M. T. CANCIANI,* L. BARONCIANI,* M. T. PAGLIARI,* S. LA MARCA,* C. MISTRETTA,* F. R. ROSENDAAL†‡ and F. PEYVANDI*

Table 3 Likelihood ratios (LRs) of von Willebrand disease (VWD) diagnosis according to von Willebrand factor ristocetin cofactor activity (VWF:RCo) plasma levels

VWF:RCo (IU dL^{-1})	VWD$^+$, no.(%)	VWD$^-$, no.(%)	LR$^+$ (95% CI)	LR$^-$ (95% CI)
30–40	23 (51)	0 (–)	∞	0.49 (0.37–0.66)
41–50	13 (29)	19 (40)	0.73 (0.41–1.30)	1.18 (0.88–1.58)
51–60	9 (20)	29 (60)	0.33 (0.18–0.62)	2.02 (1.38–2.95)
Total	45 (100)	48 (100)	–	–

CI, confidence interval. In the VWD+ and VWD– columns, all percentages are calculated according to the total numbers of VWD+ and VWD–.

- 27% très haute proba MW : tests 2e niv.
  - 30 - 40 IU dL
  - femmes 41-50 non-O
- 25% proba MW<20% : pas de tests 2e niv
  - hommes 51-60
  - hommes 41-50 gpe O
- 48% zone grise
  - femmes 41-50 gpe O,
  - femmes 51-60,
  - hommes 41-50 non-O

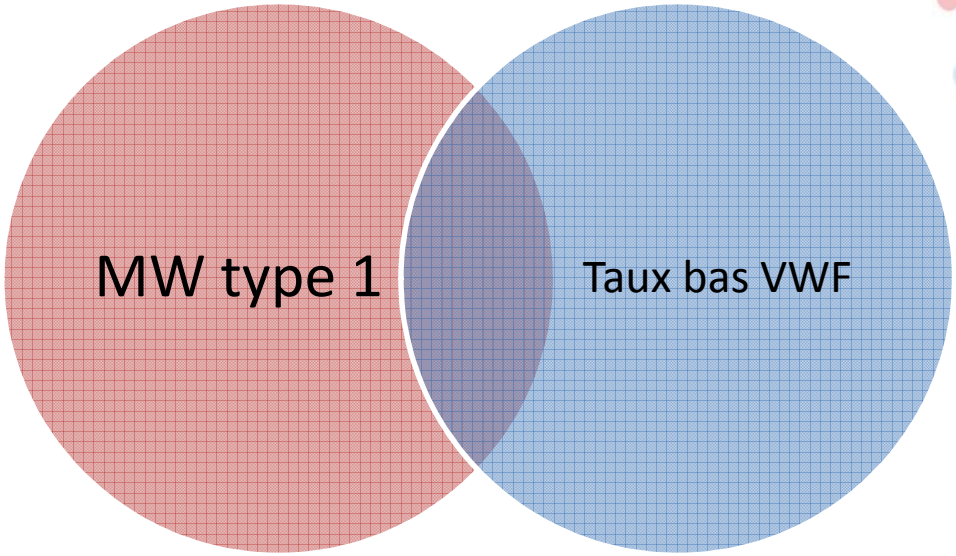
Table 2 Risk of von Willebrand disease (VWD) diagnosis according to different predictors

Predictors	VWD, no. (%) Yes (n = 45)	VWD, no. (%) No (n = 48)	OR_{adj} (95% CI)*
Bleeding score†	–	–	1.17 (0.57–2.39)
Positive family history			
No	32 (71)	36 (75)	1 (Reference)
Yes	13 (29)	12 (25)	1.23 (0.34–4.44)
Age‡	–	–	0.96 (0.67–1.38)
Female sex	35 (78)	27 (56)	5.76 (1.47–22.53)
VWF:RCo§,¶			
For blood group O			3.14 (1.70–5.82)
For blood group non-O			7.00 (1.48–33.11)

CI, confidence interval; OR, odds ratio; VWF:RCo, von Willebrand factor ristocetin cofactor activity. *Odds ratios adjusted for the effect of all the other variables and for that of ABO blood group. †OR for every 5-point increase in bleeding score. ‡OR for every 10-year increase in age. §OR for every 5 IU dL–1 decrease in VWF:RCo. ¶The OR for VWF:RCo was calculated by taking into account its interaction with ABO blood group.

Bucciarelli, J Thromb Haemost 2015;13:228-36

Au total



	Type 1	Taux bas
Taux	<30	30-50
Mutation délétère	75-100%	44-55%
Score hémorragique	augmenté	Parfois augmenté
Antécédents familiaux	présents	moins
Proportion de sujets O	+ élevée	+++ élevée