
بسم الله الرحمن الرحیم

3WINTERS-IP : What has been found and published till now?

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TYPE 3 VON WILLEBRAND INTERNATIONAL REGISTRIES INHIBITOR PROSPECTIVE STUDY

No-profit, investigators initiated, multicenter, European-Iranian observational, retrospective and prospective study on patients with diagnosis of Type 3 von Willebrand Disease.
(3WINTERS-IPS, registered at www.clinicaltrial.gov as NCT02460458)

PROTOCOL VERSION: Amended version 16 MAY 2012

Amendment: Amendment 1, 16 MAY 2012

Scientific Coordination and Supervision:

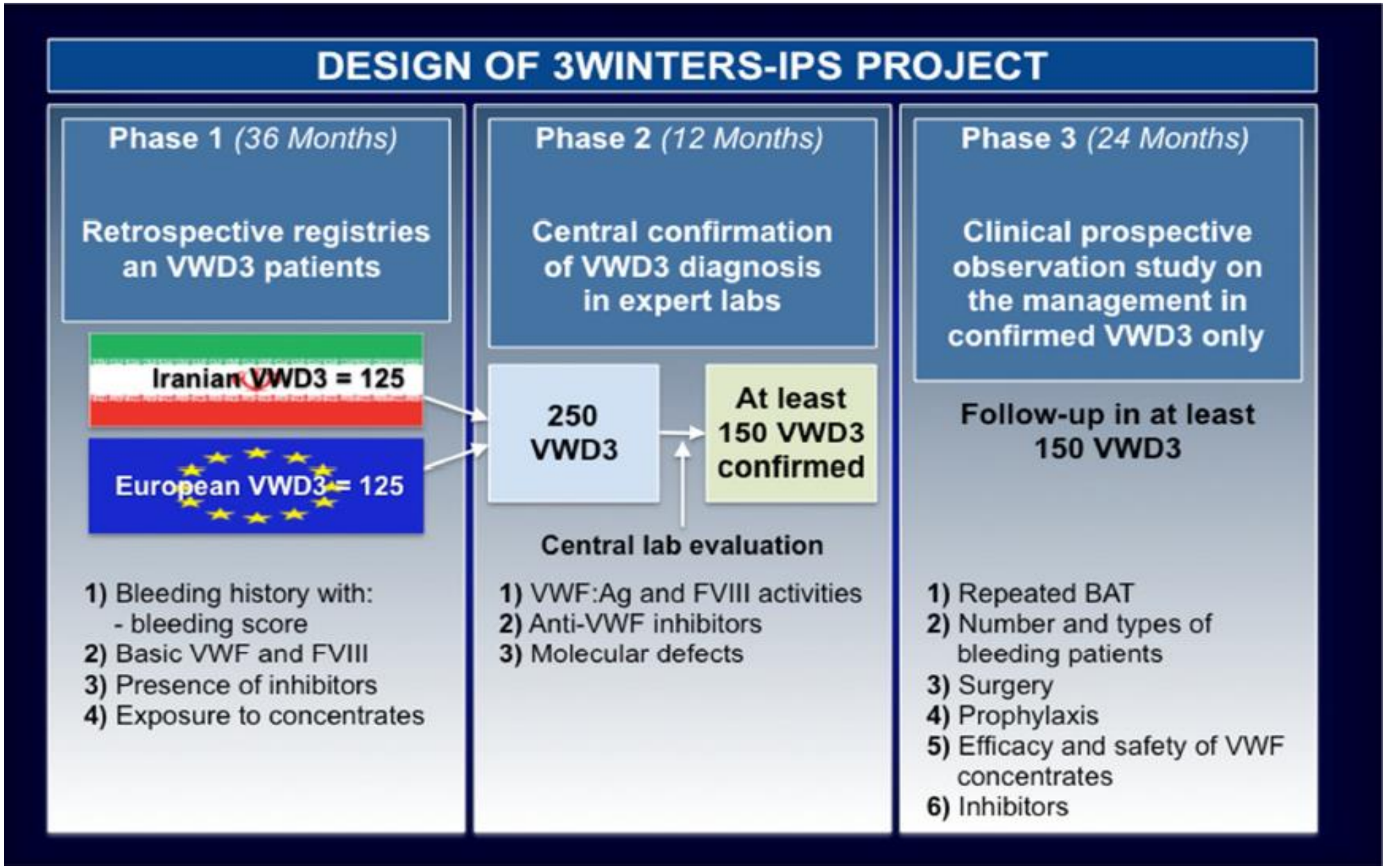
A. B. FEDERICI and P.M. MANNUCCI

Study objectives

- International network among European (125 cases) and Iranian (125 cases) Centers
- Prospective enrollment of the 250 VWD3 patients using a common database online
- Detailed information about previous bleedings and exposure to VWF concentrates
- Bleeding severity score of VWD3 calculated with a common questionnaire
- Plasma and DNA samples from all the 250 patients for centralized analyses
- Confirmation of the diagnoses using centralized tests
- VWF gene defects with VWF phenotype and risk of anti VWF inhibitors
- Common methods for anti-VWF antibody determination and for gene analyses in VWD3
- Frequency and sites of bleeding in VWD3 followed-up for 2 years
- Efficacy assessment of the VWF concentrates used to treat VWD3 using the most objective criteria for efficacy.

- **Inclusion Criteria**
  - All ages, both genders
  - Informed Consent obtained (parents will sign for children)
  - Previous documented Diagnosis of VWD3 (VWF antigen: **undetectable or <5 U/dL**)
  - Detailed information on inherited pattern, history of bleeding, previous exposure to blood products
  - Availability of plasma and DNA samples at enrolment
- **Exclusion Criteria**
  - Patient who, at the enrolment, are not available for follow-up

- A total of 16 Investigational sites will be initially involved in this project in:
  - 8 European countries: France, Germany, Hungary,Italy, Netherland, Spain, Sweden, UK and
  - other 7 sites in Iran.



ISTH2015 15ABS-2164

EXTENDED PHASE (24 months)

Additional clinical prospective observation on previously VWD3-confirmed & observed cases

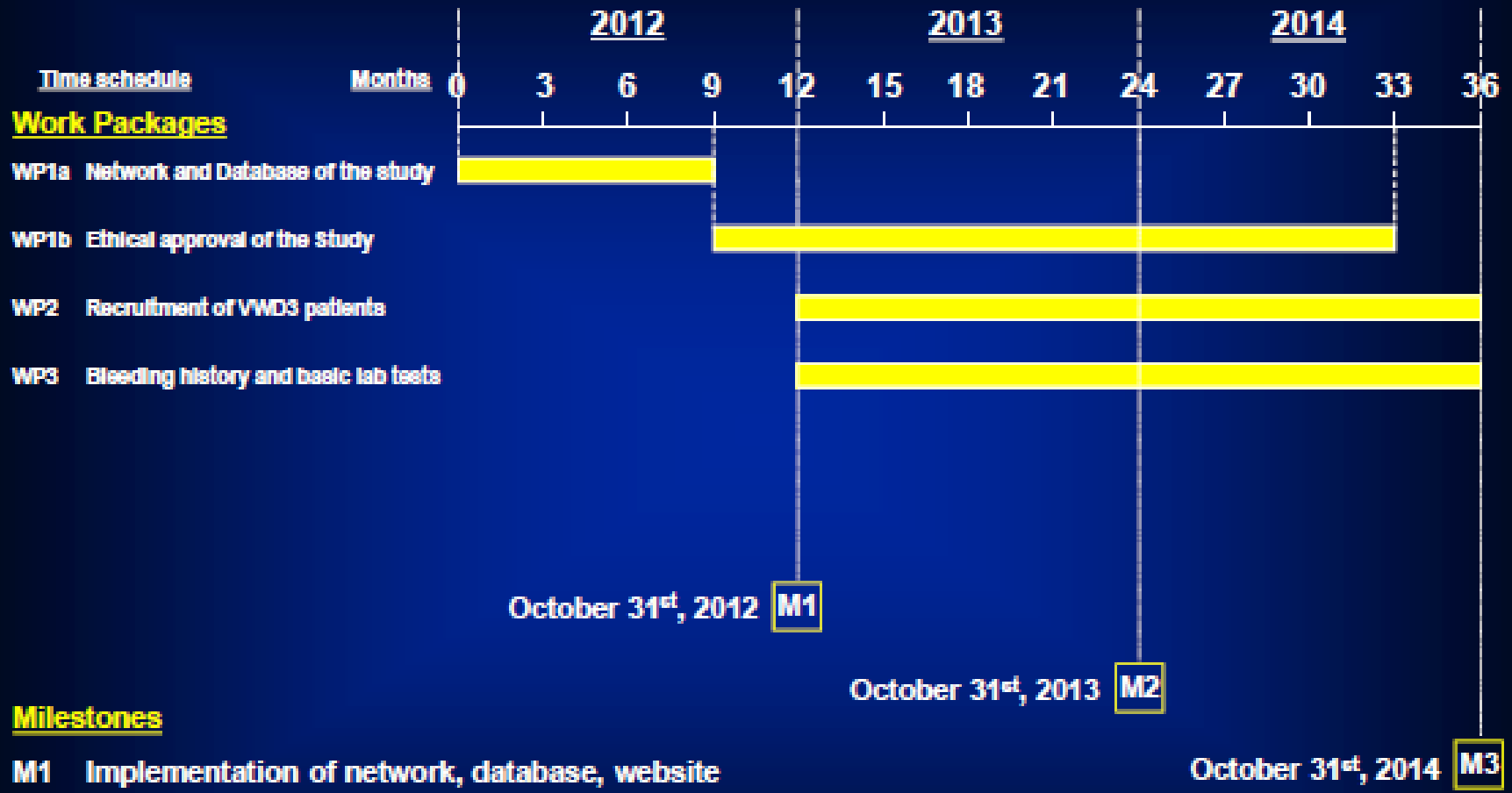
Starting VWD3 cases: 149

1. Number & type of bleeding events
2. Number & type of surgeries
3. Treatments administered (type, brand, units) with focus on efficacy & safety of VWF concentrates (recombinant / plasma-derived)

MILESTONES:2012-2022

- **M1: Implementation of network, database, website**
- **M2: Inclusion of at least 150 VWD3 patients**
- **M3: Inclusion of all the 250 VWD3 patients**
- **M4: Implementation into database of prospective CRF**
- **M5: Inclusion of confirmed VWD3 into prospective study (at least 150)**
- **M6: Report on the use of VWF concentrates (on demand versus prophylaxis) on the VWD3 patients prospectively observed for 2years(Quantities, Efficacy and Safety)**
- **M7: Ethical approvals and start of additional 2-year extension prospective phase&new database of prospective CRF for the data collection during the extension**
- **M8: Report on the use of VWF concentrates (on demand versus prophylaxis) on the VWD3 patients prospectively observed for the previous(2017–2018) 2years (Quantities, Efficacy and Safety)**
- **M9: Report on the use of VWF concentrates (on demand versus prophylaxis) on the VWD3 patients prospectively observed for the additional(2021–2022) 2years(Quantities, Efficacy and Safety)**
- **M10: Global evaluation on the use of VWF concentrates(on demand versus prophylaxis) on patients with confirmed VWD3 diagnosis prospectively observed for 4years (Quantities ,Efficacy and Safety)**

Phase 1 of the study *(October 2011-October 2014)*



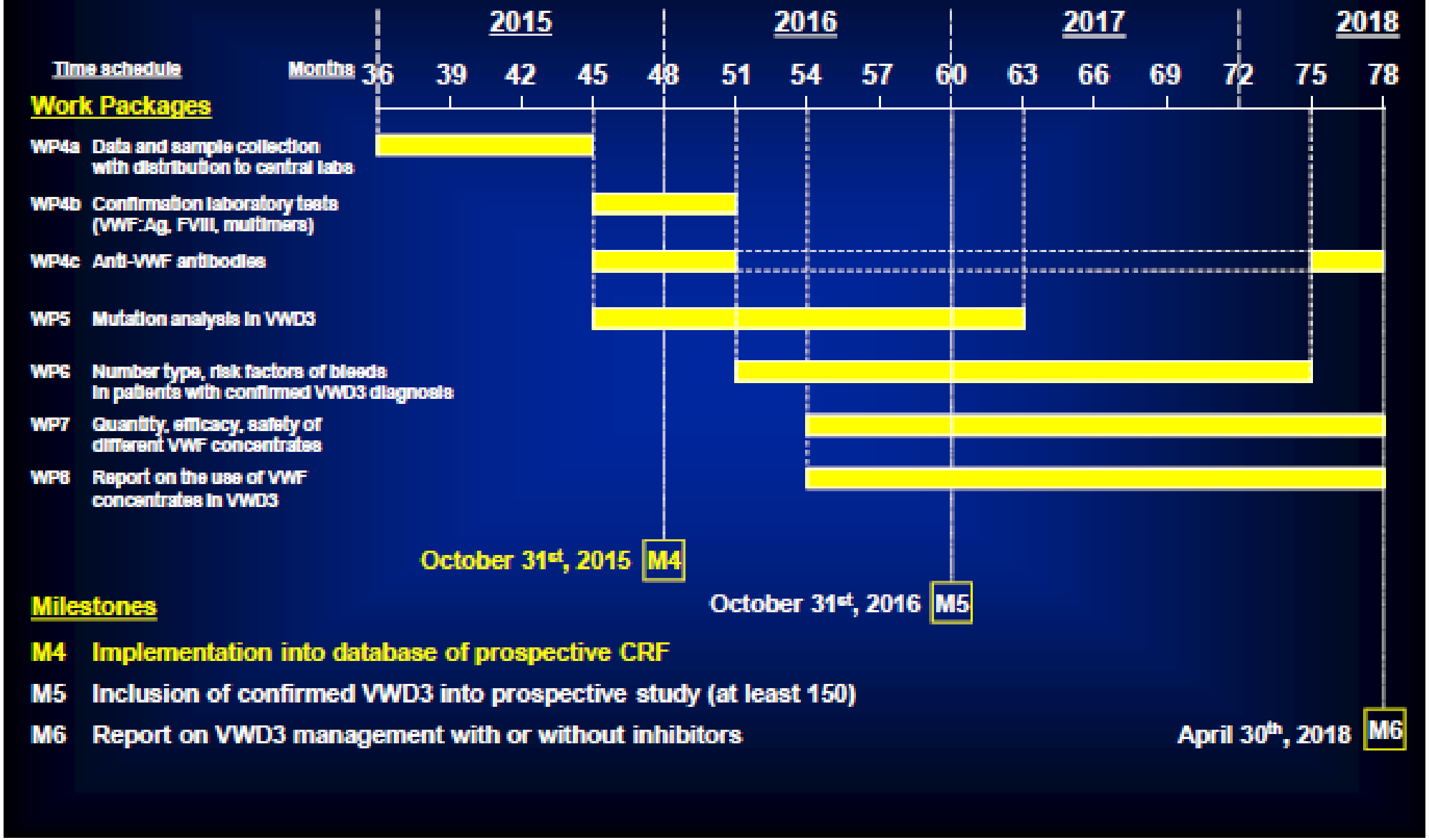
Milestones

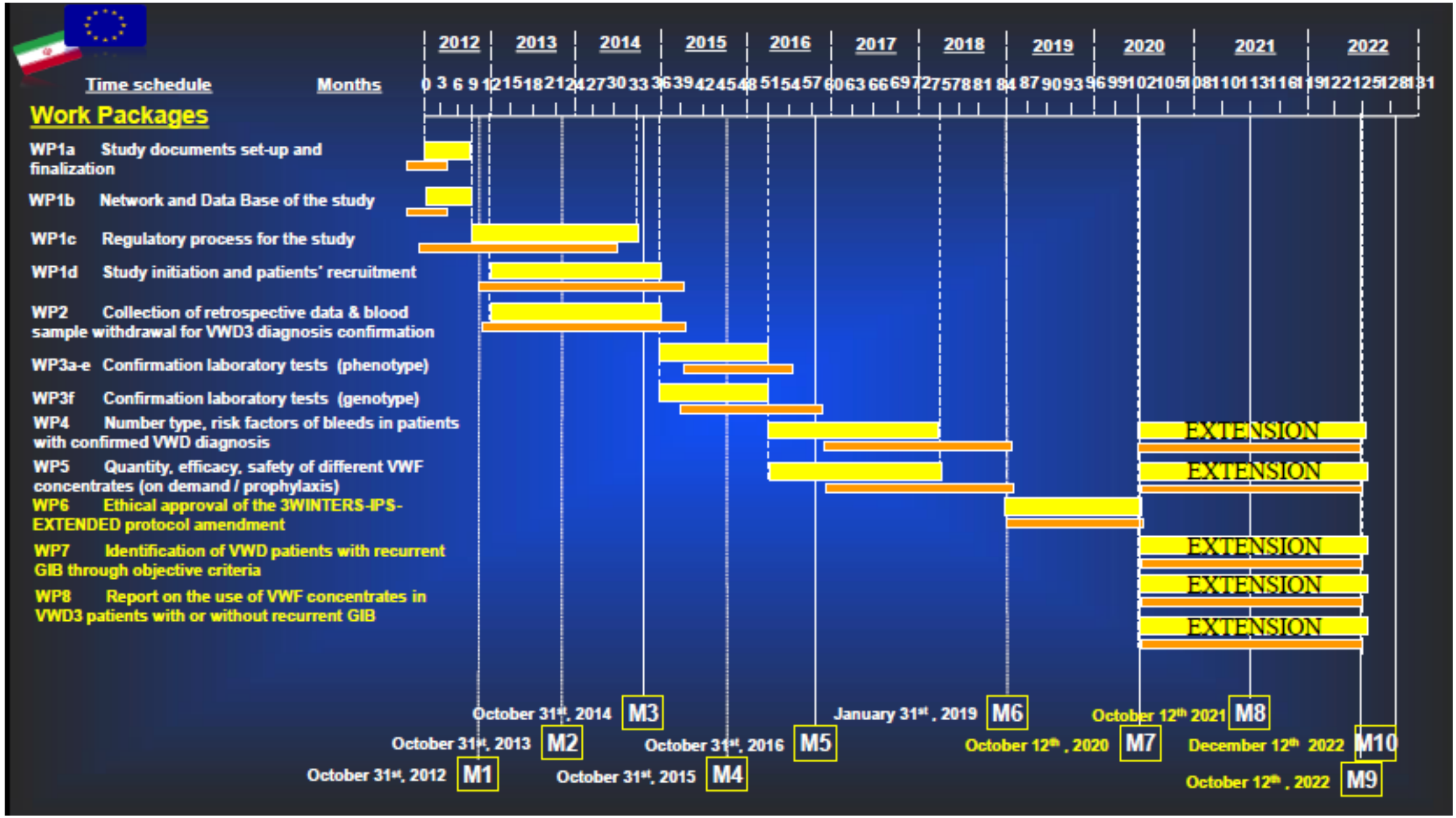
M1 Implementation of network, database, website

M2 Inclusion of at least 150 VWD3 patients

M3 Inclusion of all the 250 VWD3 patients

Phases 2 and 3 of the study *(October 2015-April 2018)*




Time schedule
Months
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69 72 75 78 81 84 87 90 93 96 99 102 105 108 111 114 117 120 123 126 129 131
Work Packages
WP1a Study documents set-up and finalization
WP1b Network and Data Base of the study
WP1c Regulatory process for the study
WP1d Study initiation and patients' recruitment
WP2 Collection of retrospective data & blood sample withdrawal for VWD3 diagnosis confirmation
WP3a-e Confirmation laboratory tests (phenotype)
WP3f Confirmation laboratory tests (genotype)
WP4 Number type, risk factors of bleeds in patients with confirmed VWD diagnosis
WP5 Quantity, efficacy, safety of different VWF concentrates (on demand / prophylaxis)
WP6 Ethical approval of the 3WINTERS-IPS-EXTENDED protocol amendment
WP7 Identification of VWD patients with recurrent GIB through objective criteria
WP8 Report on the use of VWF concentrates in VWD3 patients with or without recurrent GIB
EXTENSION
EXTENSION
EXTENSION
EXTENSION
EXTENSION
October 31st, 2012 M1
October 31st, 2013 M2
October 31st, 2014 M3
October 31st, 2015 M4
October 31st, 2016 M5
January 31st , 2019 M6
October 12th , 2020 M7
October 12th 2021 M8
October 12th , 2022 M9
December 12th 2022 M10

	Investigator	Site	Country
DE02	J. Oldenburg	Bonn	Germany
DE03	A. Tiede	Hannover	Germany
ES01	M.F. Lopez Fernandez	A Coruña	Spain
FI01	R. Lassila	Helsinki	Finland
FR01	J. Goudemand	Lille	France
FR03	M. Troassaert	Nantes	France
GB01	C. Hay	Manchester	UK
HU01	I. Bodo	Budapest	Hungary
IR01	P. Eshghi	Tehran	Iran
IR02	M. Karimi	Shiraz	Iran
IR04	M. Baghaipour	Tehran	Iran
IR05	B. Keikhaei	Ahvaz	Iran
IR06	Z. Badiee	Mashad	Iran
IR07	M. Ghanavat	Esfahan	Iran
IT01	F. Peyvandi	Milano	Italy
IT02	A. Tosetto	Vicenza	Italy
IT03	G. Castaman	Firenze	Italy
IT04	R. Marino	Bari	Italy
NL01	J. Eikenboom	Lieden	The Netherlands
NL02	F. Leebeek	Rotterdam	The Netherlands
SE01	E. Zetterberg	Malmö	Sweden

WHAT HAS BEEN PUBLISHED OR PRESENTED TILL 10-2022?

Background: Von Willebrand disease type 3 (VWD3) is of major interest because of severe clinical presentation, need for replacement therapy with VWF/FVIII concentrates and the risk of anti-VWF inhibitors developing after treatment.
Aims: To evaluate in large cohort of VWD patients the relationship between standardised phenotypic, genotypic, clinical data and bleeding tendency, response to therapy with VWF/FVIII concentrates and the risk of anti-VWF inhibitor development.
Methods: 3WINTERS-IPS is a multicenter, European and Iranian observational, retrospective and prospective study on patients with VWD3. Patients meeting the enrolment criteria were enrolled at each participating centre and data entered into the project database.
Results: 251 VWD3 cases are included on the database with a gender distribution 106/145 (M/F); median age 27 (1-75) yr and median bleeding score (BS) 12 (1-33). Median (range) of local lab test were: VWF:Ag 1.9 (<1-7) IU/dL; FVIII:C 2.3 (<1-15) IU/dL. Anti-VWF antibodies are reported present in 11. Molecular genetic analysis was undertaken at local sites in 55 patients all from EU sites. Of these, 31 (56%) are compound heterozygous (CH), 19 (35%) are homozygous (H) and 5 (9%) are apparently heterozygous with only one mutation found. In the CH group, there is a full range of mutation types including large deletions, small deletions/insertions, missense and nonsense mutations and splice site changes. One CH case had 2 missense mutations, both resulting in loss of a cysteine (p.C1227R and p.C2283R). Of the H group, 6 (31%) had splice and 5 (26%) had nonsense mutations. Of the 4 H with missense mutations, 2 resulted in loss of cysteines p.C2212R and p.C2362F and 2 had p.N2546Y. One H case had a gene conversion involving p.Q1311*.
Conclusion: This initial data confirms that VWD3 is phenotypically and genotypically heterogeneous.

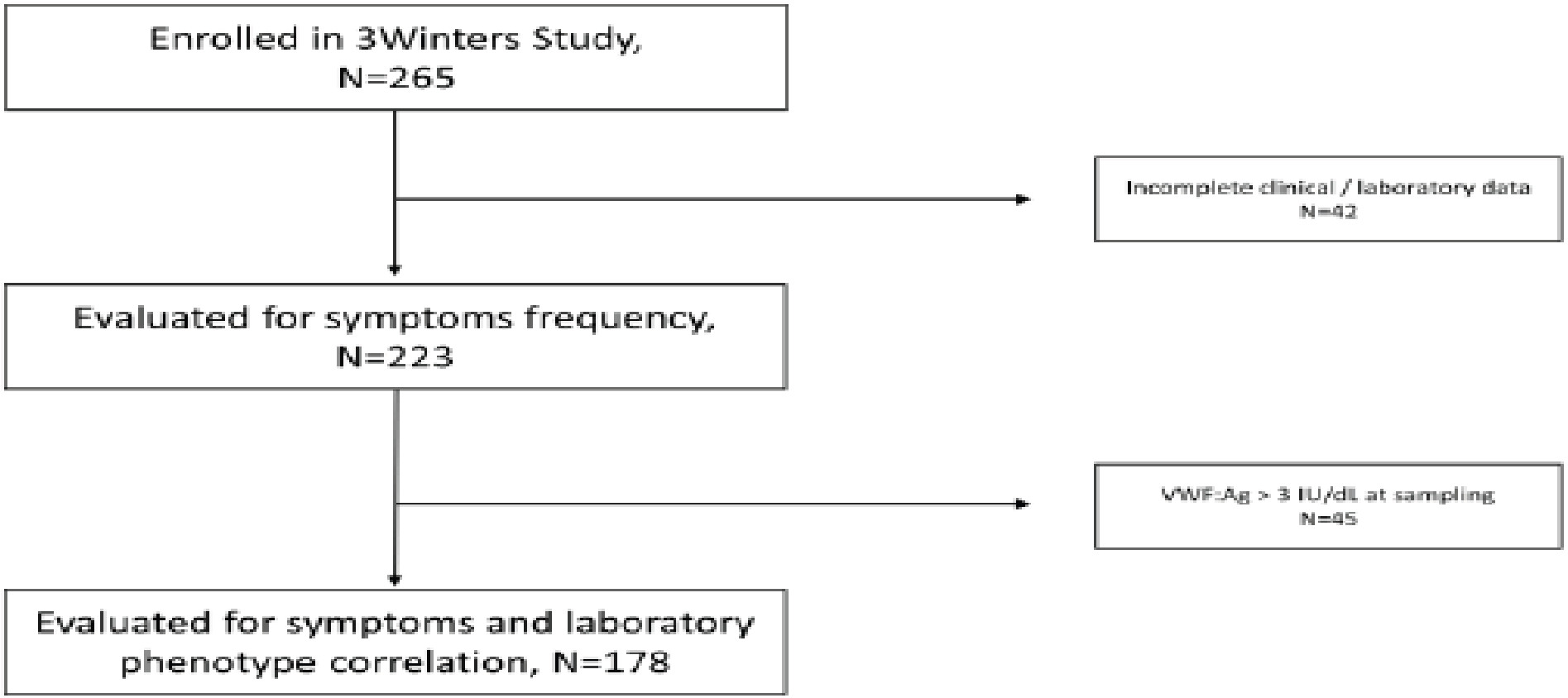
J Thromb Haemost. 2020 Sep;18(9):2145-2154. doi: 10.1111/jth.14886. Epub 2020 Aug 25.

Bleeding symptoms in patients diagnosed as type 3 von Willebrand disease: Results from 3WINTERS-IPS, an international and collaborative cross-sectional study

Alberto Tosetto [1], Zahra Badiee [2], Mohammad-Reza Baghaipour [3], Luciano Baronciani [4], Javier Battle [5], Erik Berntorp [6], Imre Bodó [7], Ulrich Budde [8], Giancarlo Castaman [9], Jeroen C J Eikenboom [10], Peyman Eshghi [11], Cosimo Ettorre [12], Anne Goodeve [13], Jenny Goudemand [14], Charles Richard Morris Hay [15], Hamid Hoorfar [16], Mehran Karimi [17], Bijan Keikhaei [18], Riitta Lassila [19], Frank W G Leebeek [20], Maria Fernanda Lopez Fernandez [5], Pier Mannuccio Mannucci [4], Maria Gabriella Mazzucconi [21], Massimo Morfini [9], Johannes Oldenburg [22], Ian Peake [13], Rafael Parra Lòpez [23], Flora Peyvandi [4] [24], Reinhard Schneppenheim [25], Andreas Tiede [26], Gholamreza Toogeh [27], Marc Trossaert [28], Omidreza Zekavat [29], Eva M K Zetterberg [6], Augusto B Federici [30]

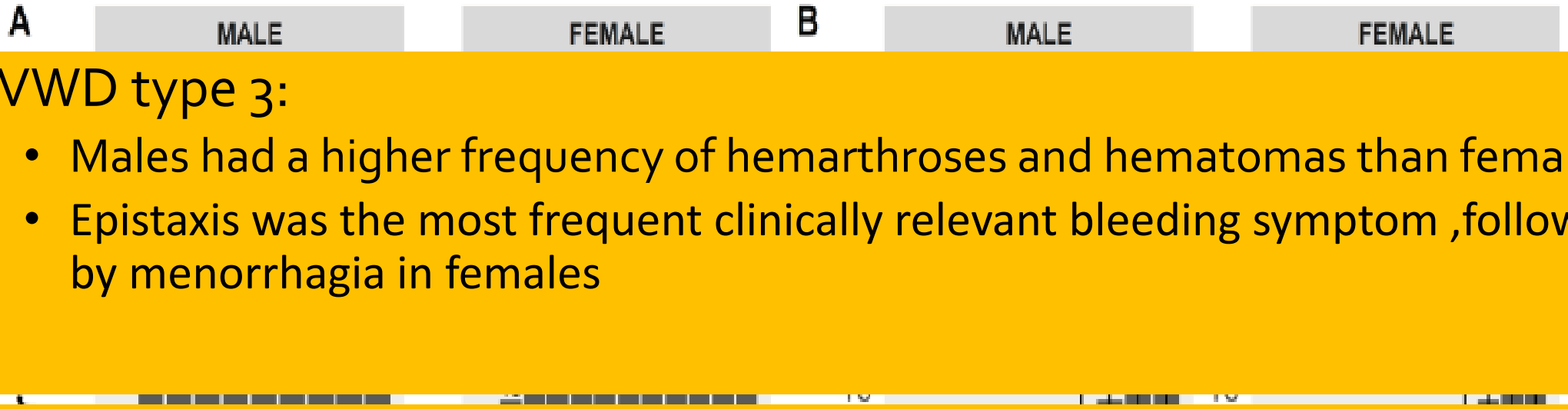
Affiliations + expand

- The 3WINTERS-IPS is the first extensive, multicenter investigation of type 3 patients that systematically collects clinical and laboratory phenotypic data
- Aims and method of study:
  - Bleeding symptoms in VWD type 3 patients :
    - Frequency and the Severity across age and sex groups
    - Compare with type I
    - To investigate any possible clustering of bleeding symptoms
  - Bleeding score (BS) using the MCMDM-1VWD bleeding questionnaire



- 106 patients of Iranian descent

Bleeding symptoms



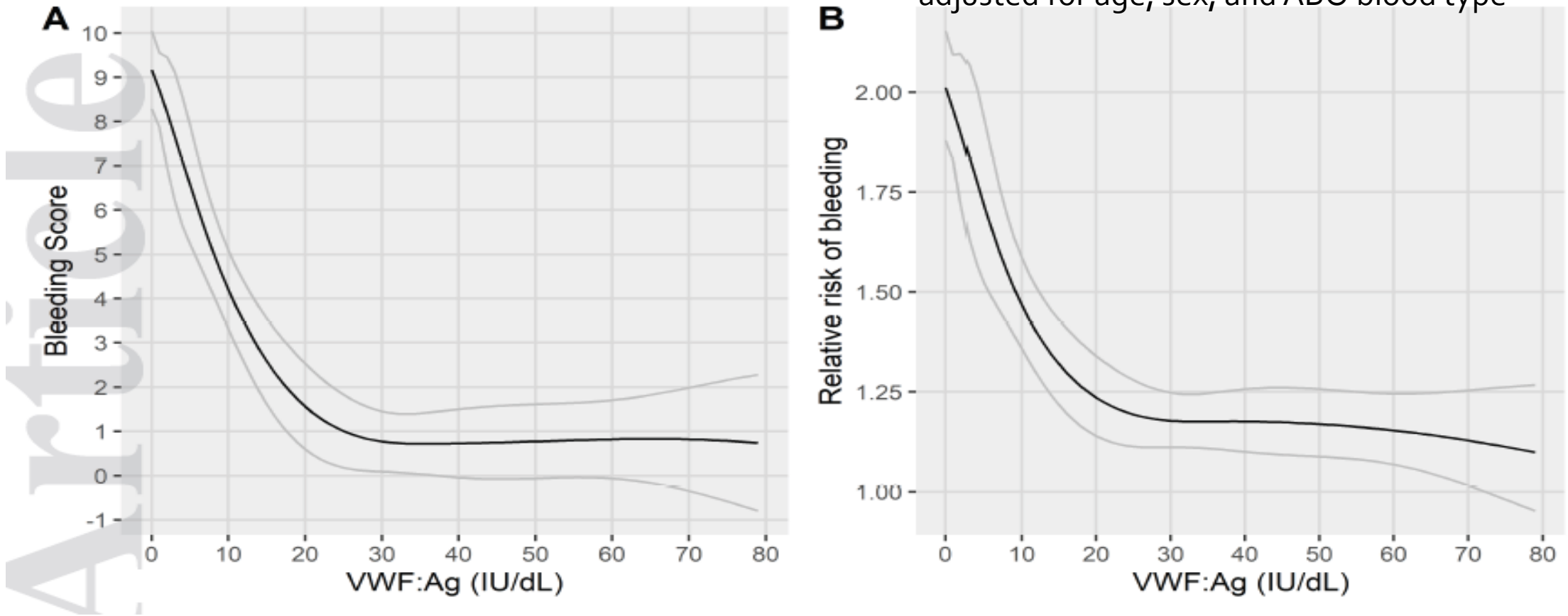
- VWD type 3:
  - Males had a higher frequency of hemarthroses and hematomas than females
  - Epistaxis was the most frequent clinically relevant bleeding symptom ,followed by menorrhagia in females

- VWD type3 comparing with type 1:
  - Surgical, post-extraction and post-partum bleeding, and menorrhagia were not specifically over-represented in type 3 VWD.
  - Deep hematomas, hemarthroses, oral cavity, and CNS bleeding were overrepresented (>five-fold) in type 3 VWD.

Increased bleeding scores were evident for all age-classes and even in pediatric cases

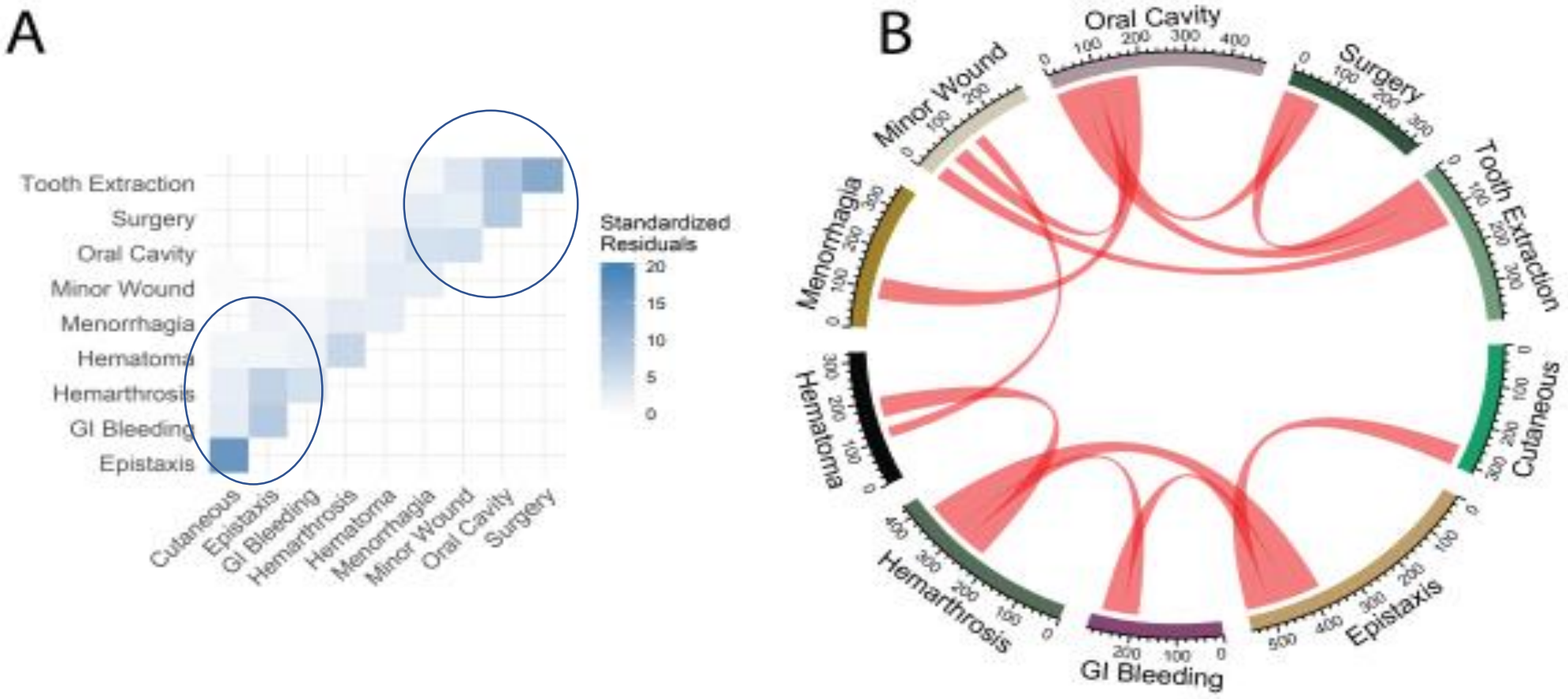
Relationship between bleeding severity and VWF:Ag in the two merged cohorts

adjusted for age, sex, and ABO blood type



Article

Bleeding symptom clusters



- The 3WINTERS-IPS and the MCMDM-1 VWD cohorts were:
  - Similar as for sex distribution
  - Differed significantly in terms of **age of diagnosis** and **severity** of clinical presentation.
  - The **ABO composition** was also noticeably different, with an excess of blood O group patients in the type 1 MCMDM-1 VWD cohort

- Severity:
  - the BS emphasizes the importance of a bleeding disorder as a determinant of the “severity” (e.g., amount of blood loss) of a single symptom.
  - total number of bleeding symptoms gives more importance to disease as a risk factor for “bleeding tendency” in all body tissues.

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DOI: 10.1111/jth.15658

ORIGINAL ARTICLE

Von Willebrand factor propeptide and pathophysiological mechanisms in European and Iranian patients with type 3 von Willebrand disease enrolled in the 3WINTERS-IPS study

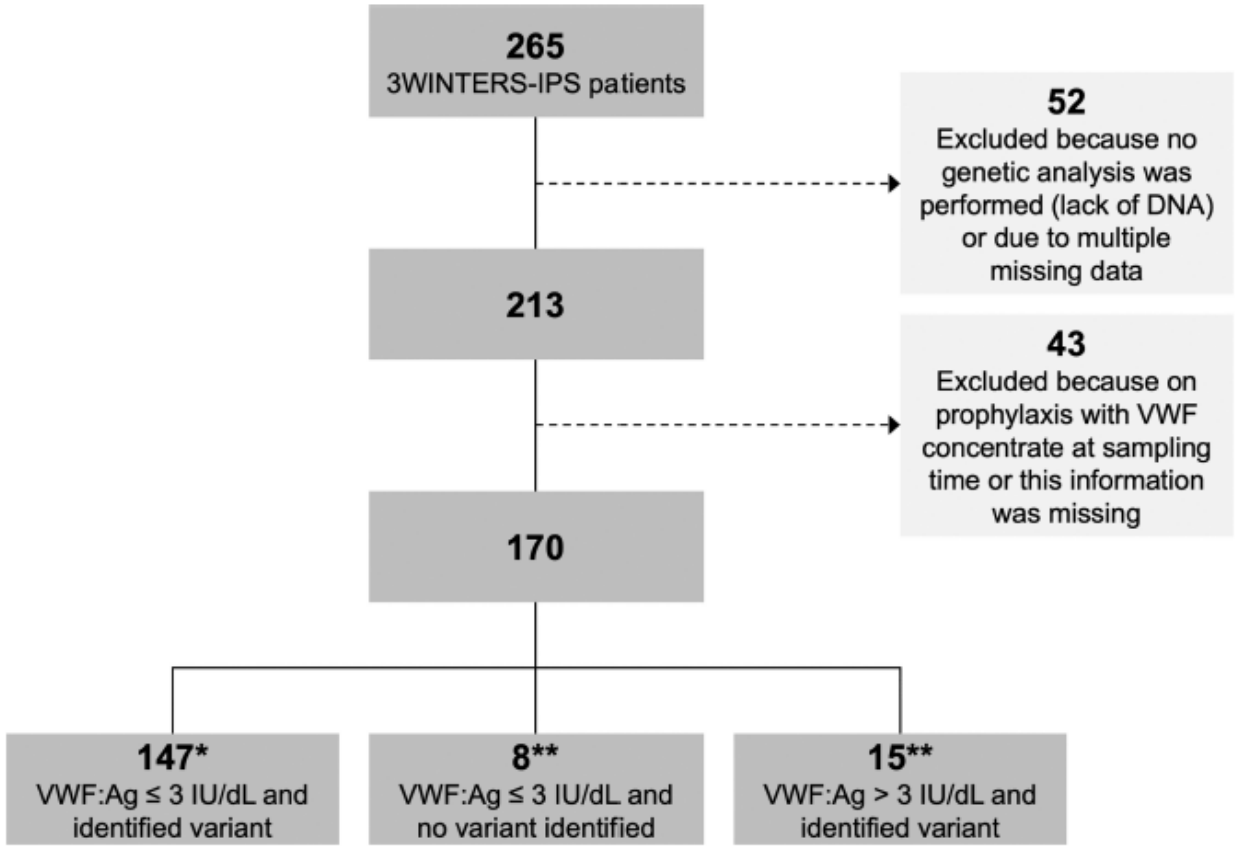
Maria Teresa Pagliari[1] | Frits R. Rosendaal[2] | Minoo Ahmadinejad[3,4] | Zahra Badiee[5] | Mohammad-Reza Baghaipour[6] | Luciano Baronciani[7] | Olga Benítez Hidalgo[8] | Imre Bodó[9] | Ulrich Budde[10] | Giancarlo Castaman[11] | Peyman Eshghi[4] | Jenny Goudemand[12] | Mehran Karimi[13] | Bijan Keikhaei[14] | Riitta Lassila[15] | Frank W. G. Leebeek[16] | Maria Fernanda Lopez Fernandez[17] | Pier Mannuccio Mannucci[7] | Renato Marino[18] | Johannes Oldenburg[19] | Ian Peake[20] | Cristina Santoro[21] | Reinhard Schneppenheim[22] | Andreas Tiede[23] | Gholamreza Toogeh[24] | Alberto Tosetto[25] | Marc Trossaert[26] | Hamideh Yadegari[19] | Eva M. K. Zetterberg[27] | Flora Peyvandi[7,28] | Augusto B. Federici[29] | Jeroen Eikenboom[30]

J Thromb Haemost. 2022;20:1106–1114. doi:10.1111/jth.15658

Introduction

- Objectives:
  - To investigate the VWFpp/VWF:Ag and FVIII:C/VWF:Ag ratios on the pathophysiological mechanism underlying type 3 VWD
  - Association of VWFpp with bleeding severity
- Defentions:
  - type 3 VWD :confirmed by a centrally measured VWF:Ag ≤ 3 IU/dl
  - **Missense defects** included missense variants, gene conversions (not leading to null variants), small insertions and small deletions that **do not alter the reading frame.**
  - **Null defects** included variants that introduce a stop codon, splice variants, large deletions, large insertions, small insertions, small deletions, indels, or small duplications which alter the reading frame and thereby **cause a premature stop codon.**
  - **Other mutations:** partial molecular diagnosis(excluded from the statistical analysis)
- Groups:
  - Homozygous/compound heterozygous for missense variants OR for null variants,
  - Compound heterozygous for null/missense variants
- Analyses were repeated by considering European and Iranian patients separately

Participants



** were considered separately for secondary analyses

TABLE 3 Main study group stratified by type of *VWF* variants in European and Iranian patients

European type 3 VWD patients, *n* (%)[a]	VWF:Ag (IU/dl)	FVIII:C (IU/dl)	VWFpp (IU/dl)	FVIII:C/VWF:Ag	VWFpp/VWF:Ag	BS
Homozygous/compound heterozygous for missense variants, 8 (13.3)	0.5 (0.5 to 1.8)	2.6 (2.2 to 4.0)	3.7 (3.0 to 7.3)	4.0 (2.8 to 4.9)	4.7 (1.7 to 12.7)	16.0 (15.0 to 24.3)
Homozygous/compound heterozygous for null variants, 43 (71.7)	0.5 (0.5 to 0.5)	2.4 (2.0 to 3.2)	1.2 (0.6 to 5.2)	4.4 (3.4 to 5.8)	2.4 (1.2 to 6.7)	18.0 (13.5 to 23.5)
Compound heterozygous for missense-null variants, 5 (8.3)	0.5 (0.5 to 1.5)	2.9 (2.0 to 7.8)	4.1 (1.1 to 8.2)	4.5 (4.0 to 7.3)	2.7 (2.2 to 13.6)	19.0 (10.5 to 24.5)
Other, 4 (6.7)	0.5 (0.5 to 1.8)	2.1 (1.8 to 2.7)	3.9 (1.2 to 11.9)	4.1 (1.5 to 5.4)	5.5 (2.4 to 9.7)	18.5 (8.8 to 20.8)
Median difference (95% CI), P missense vs. null	—	0.3 (−0.4 to 1.1) 0.414	2.3 (−0.8 to 3.6) 0.190	−0.8 (−2 to 0.4) 0.228	1.0 (−2.0 to 5.5) 0.483	0 (−6.0 to 6.0) 0.989
Median difference (95% CI), P missense vs. compound missense-null	—	−0.2 (−7.0 to 14.0) 0.712	0 (−0.6 to 1.4) 0.865	0.4 (−5.1 to 6.0) 0.122	−0.1 (−11.0 to 11.8) 1	−2.0 (−11.0 to 13.0) 0.607
Iranian type 3 VWD patients, n (%)[b]	**VWF:Ag (IU/dl)**	**FVIII:C (IU/dl)**	**VWFpp (IU/dl)**	**FVIII:C/VWF:Ag**	**VWFpp/VWF:Ag**	**BS**
Homozygous/compound heterozygous for missense variants, 12 (13.8)	0.5 (0.5 to 0.5)	2.6 (1.6 to 3.3)	2.7 (1.2 to 4.7)	5.2 (3.2 to 6.6)	5.4 (2.4 to 9.3)	7.5 (4.3 to 12.3)
Homozygous/compound heterozygous for null variants, 73 (83.9)	0.5 (0.5 to 0.5)	2.2 (1.7 to 2.6)	1.2 (0.6 to 2.7)	4.2 (3.5 to 5.2)	2.4 (1.2 to 5.4)	11.0 (4.0 to 17.0)
Compound heterozygous for missense-null variants, 1 (1.1)	0.5	3.7	2.6	7.4	5.2	15.0
Other, 1 (1.1)	0.5	1.4	3.1	2.8	6.2	—
Median difference (95% CI), P missense vs. null	—	0.3 (−03 to 0.8) 0.271	0.8 (−0.1 to 2.9) 0.072	0.6 (−0.4 to 1.8) 0.229	1.6 (−0.2 to 5.8) 0.062	−3.5 (−7.0 to 2.0) 0.283
P missense vs. compound missense-null[c]	—	0.178	1	0.178	1	0.284

Results & conclusion

- The VWFpp level as well as the VWFpp/VWF:Ag ratio were Clearly higher in patients with missense variants > heterozygous for a null and a missense variant > null variants.So in the patients with missense variants:
  - Increased clearance of secreted mature VWF plays a role in the pathogenesis
  - An increased VWFpp/VWF:Ag ratio is indicative of the presence of missense variants
- Strongly reduced levels of VWF measurements (VWF:Ag and VWFpp) were seen in all groups :
  - In the patients with missense variants there is a combination of intracellular retention, secretion defect, or fast clearance of mutant protein from the circulation
- Higher than the normal reference range without any difference between patients with homozygous/compound heterozygous for null or missense variants in FVIII:C/VWF:Ag ratio :
  - FVIII:C/VWF:Ag ratio does not discriminate missense from null alleles

Results & conclusion

- Patients with missense variants:
  - Milder bleeding phenotype with a slightly lower BS than patients homozygous/compound heterozygous for null variants (11.5 vs. 14.0; *P* = .501).
- However, there was no association between VWFpp level and the bleeding symptoms represented by the BS in none of the genetic groups . (*r* = .024; *P* = .778)
- the European population showed the highest number of different variants, which were distributed along the VWF, whereas the Iranian population has the highest number of homozygous carriers of variants, which were mainly localized at the VWF amino-terminal end

REGULAR ARTICLE

blood advances

Genotypes of European and Iranian patients with type 3 von Willebrand disease enrolled in 3WINTERS-IPS

Luciano Baronciani,[1] Ian Peake,[2] Reinhard Schneppenheim,[3] Anne Goodeve,[2] Minoo Ahmadinejad,[4,5] Zahra Badiee,[6] Mohammad-Reza Baghaipour,[7] Olga Benitez,[8] Imre Bodó,[9] Ulrich Budde,[10] Andrea Cairo,[1] Giancarlo Castaman,[11] Peyman Eshghi,[5] Jenny Goudemand,[12] Wolf Hassenpflug,[3] Hamid Hoorfar,[13] Mehran Karimi,[14] Bijan Keikhaei,[15] Riitta Lassila,[16] Frank W. G. Leebeek,[17] Maria Fernanda Lopez Fernandez,[18] Pier Mannuccio Mannucci,[1] Renato Marino,[19] Nikolas Nikšić,[2] Florian Oyen,[3] Cristina Santoro,[20] Andreas Tiede,[21] Gholamreza Toogeh,[22] Alberto Tosetto,[23] Marc Trossaert,[24] Eva M. K. Zetterberg,[25] Jeroen Eikenboom,[26] Augusto B. Federici,[27] and Flora Peyvandi[1,28]

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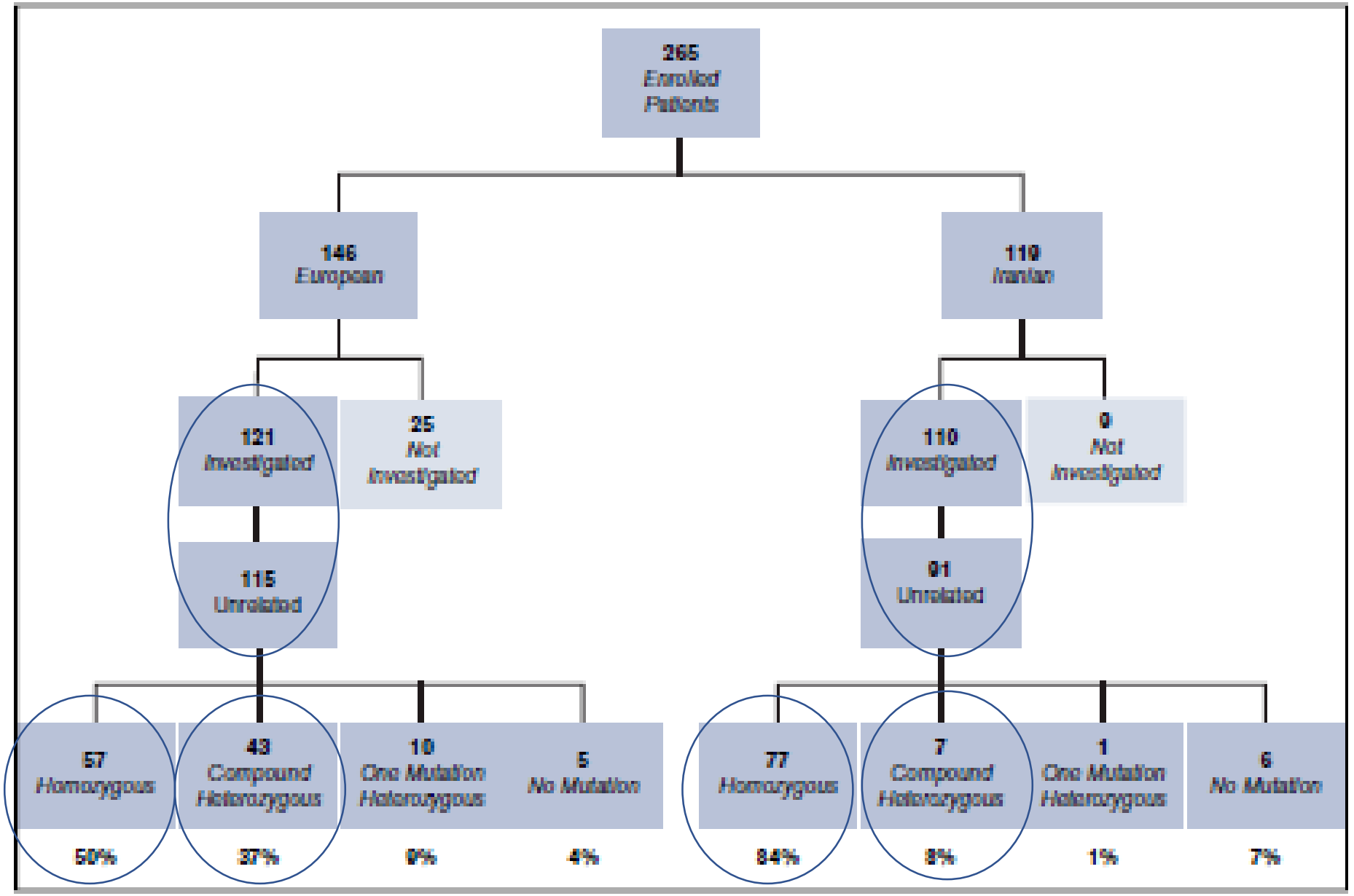
265
Enrolled
Patients
146
European
119
Iranian
121
Investigated
25
Not
Investigated
110
Investigated
9
Not
Investigated
115
Unrelated
91
Unrelated
57
Homozygous
43
Compound
Heterozygous
10
One Mutation
Heterozygous
5
No Mutation
77
Homozygous
7
Compound
Heterozygous
1
One Mutation
Heterozygous
6
No Mutation
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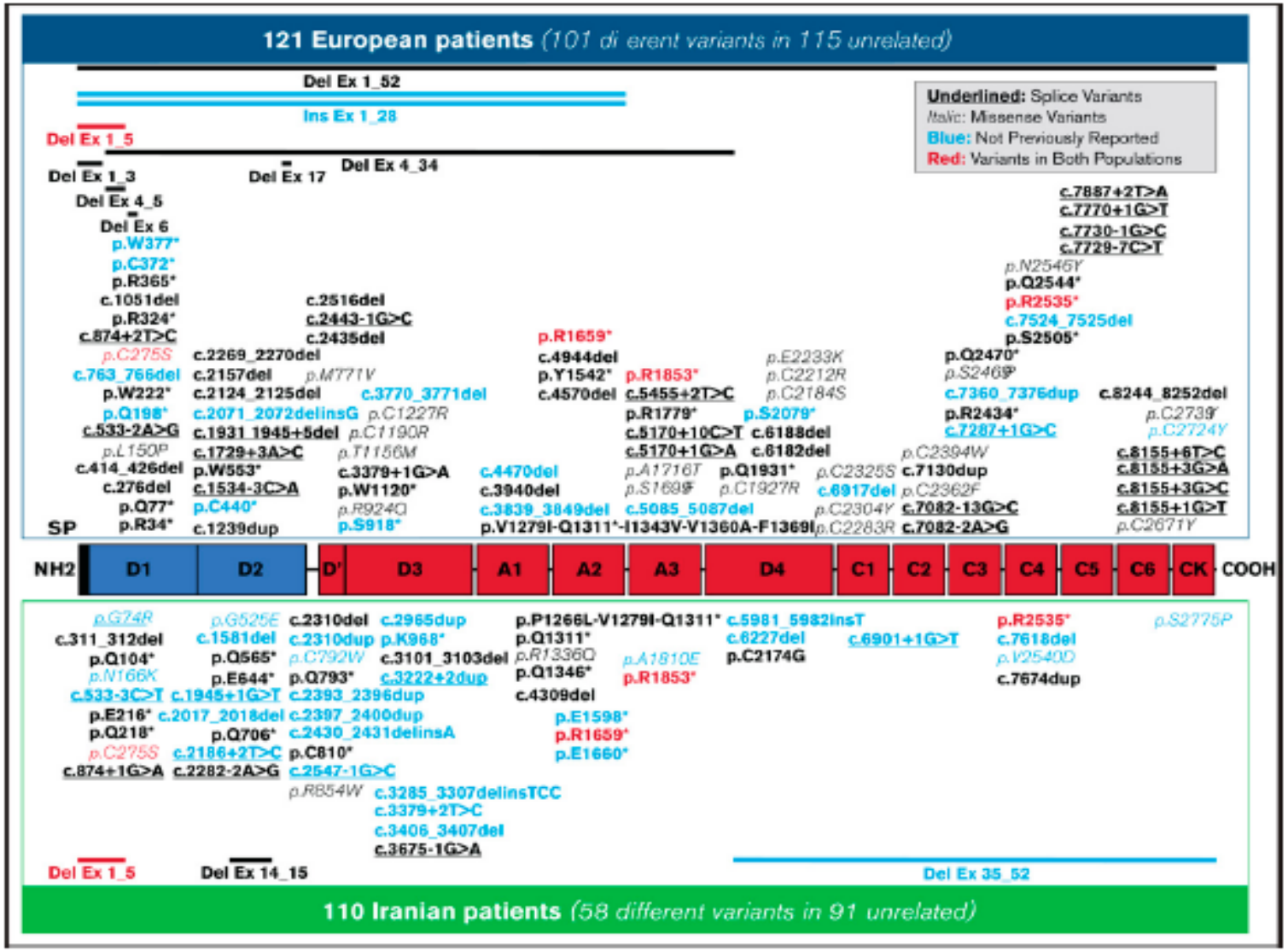
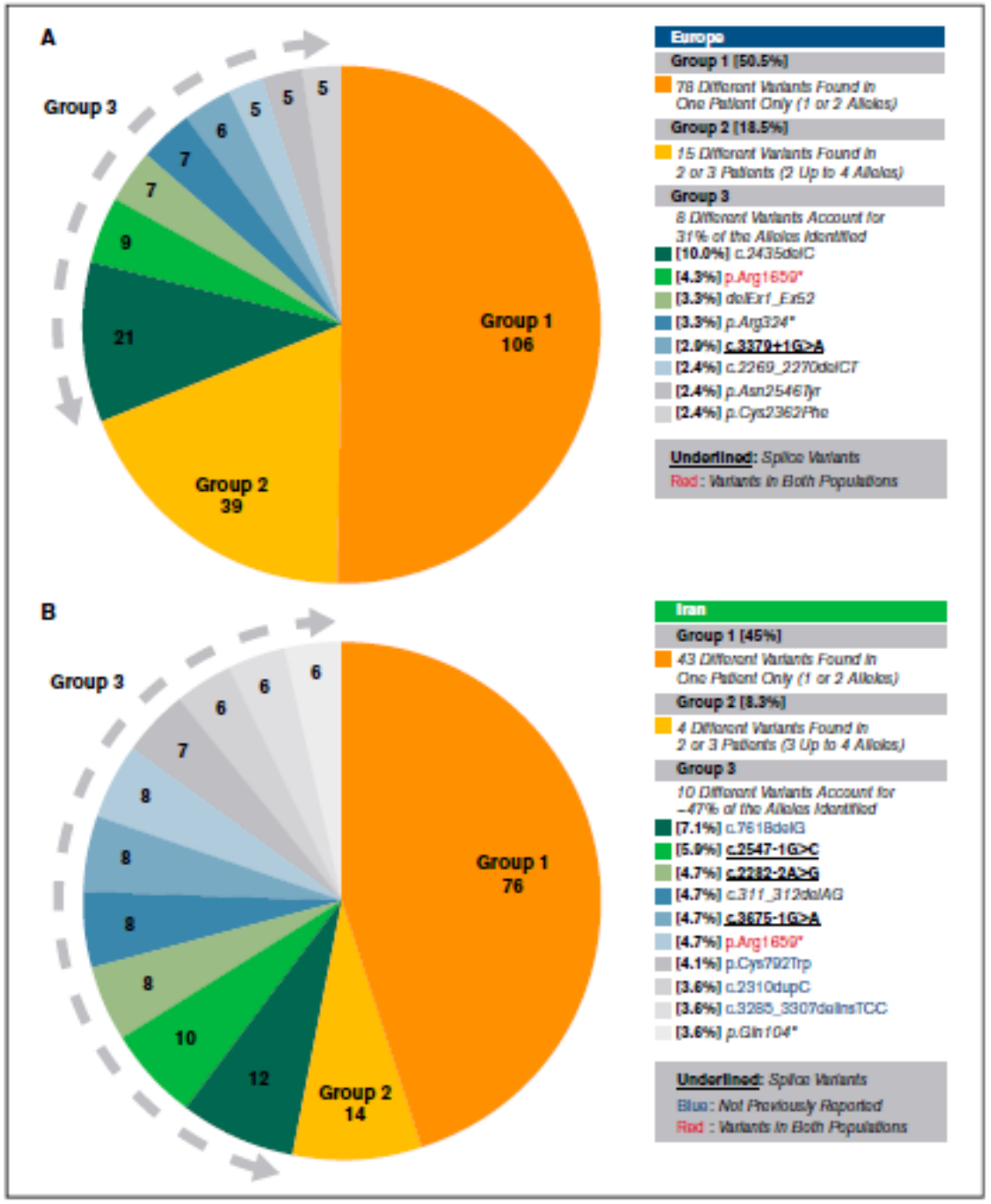
9%
4%
84%
8%
1%
7%



- **In 22 patients, no or only one variant was found.**
- **48 /154 different variants were novel, more in iranian (EU/IR = 18/30) .**

- **5 variants (p.Arg1659, p.Arg1853, p.Arg2535, p.Cys275Ser, and delEx1_Ex5) were found in both European and Iranian VWD3 patients**

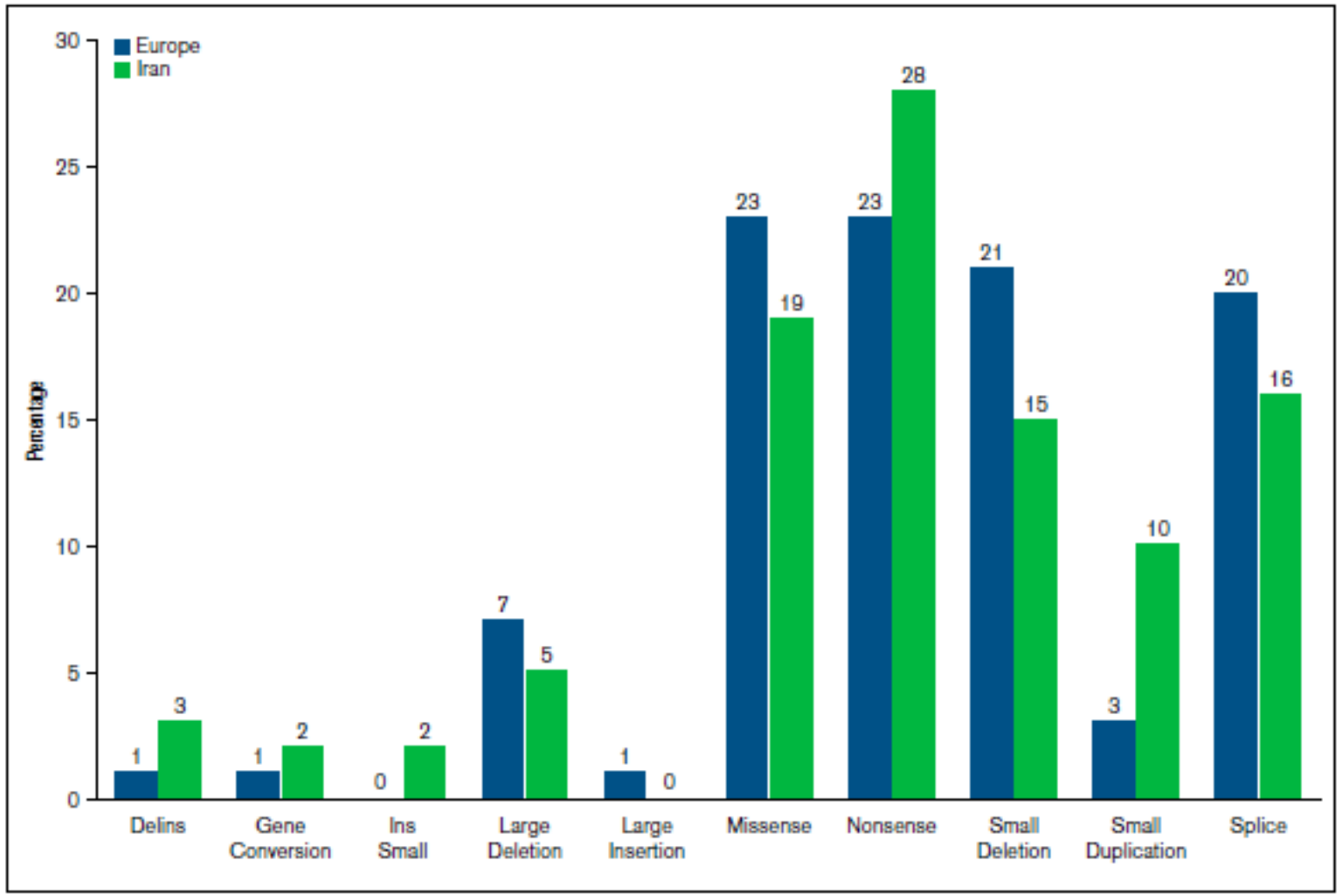


Distribution of alleles among the 154 different unique variants (EU/IR = 101/58) were divided into 3 groups:

G1: found only in a single patient, either in the heterozygous or homozygous state (1 or 2 alleles)

G2: found in 2 or 3 patients (up to 4 alleles)

G3: found in more than 3 patients (5 or more alleles)


Europe
Iran
Percentage
30
25
20
15
10
5
0
1
3
1
2
0
2
7
5
1
0
23
19
23
28
21
15
3
10
20
16
Delins
Gene Conversion
Ins Small
Large Deletion
Large Insertion
Missense
Nonsense
Small Deletion
Small Duplication
Splice