POST-ISTH:
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Malattia di von Willebrand e difetti acquisiti della coagulazione

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Summary

- Von Willebrand factor and angiogenesis
- Von Willebrand factor and risk of thrombosis
- Genetic heterogeneity of von Willebrand disease
- Treatment of von Willebrand disease
- Acquired clotting abnormalities
- The future is here

VWF and angiogenesis: what is known

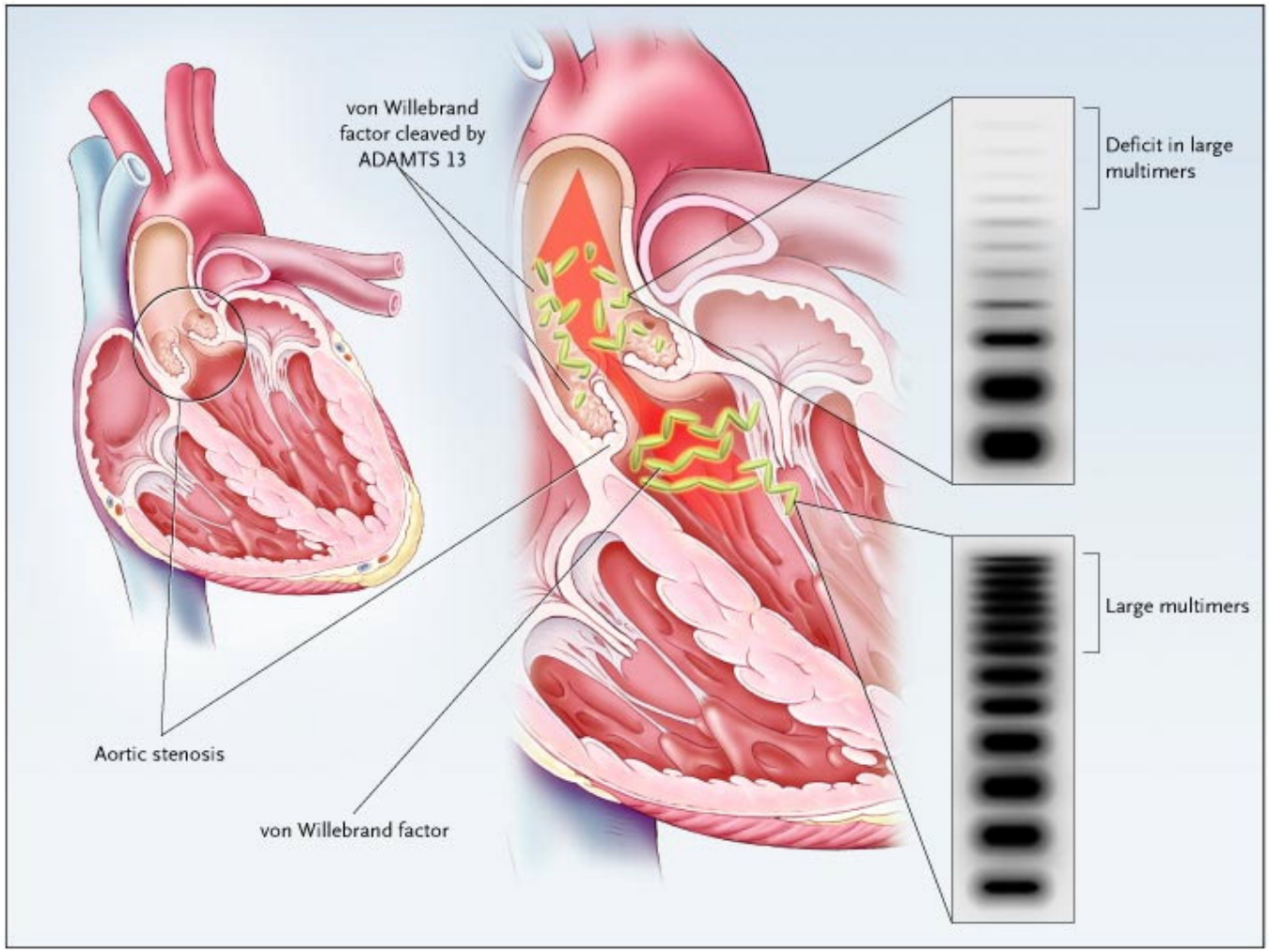
- Incidence of angiodysplasia in 4,503 VWD patients (0 % type 1, 2 % type 2, 4.5 % type 3) (Fressinaud 1993)

Number and types of bleeding episodes during 24-month follow-up

	Type 1 R1205H (n = 60)	Type 1 C1130F (n = 23)	Type 2 A (n = 46)	Type 2 M (n = 61)
Epistaxis	2	0	19	20
Menorrhagia	2	6	18	11
Oral	0	0	4	4
Gastrointestinal	1	0	53	7
Hematuria	0	0	0	3

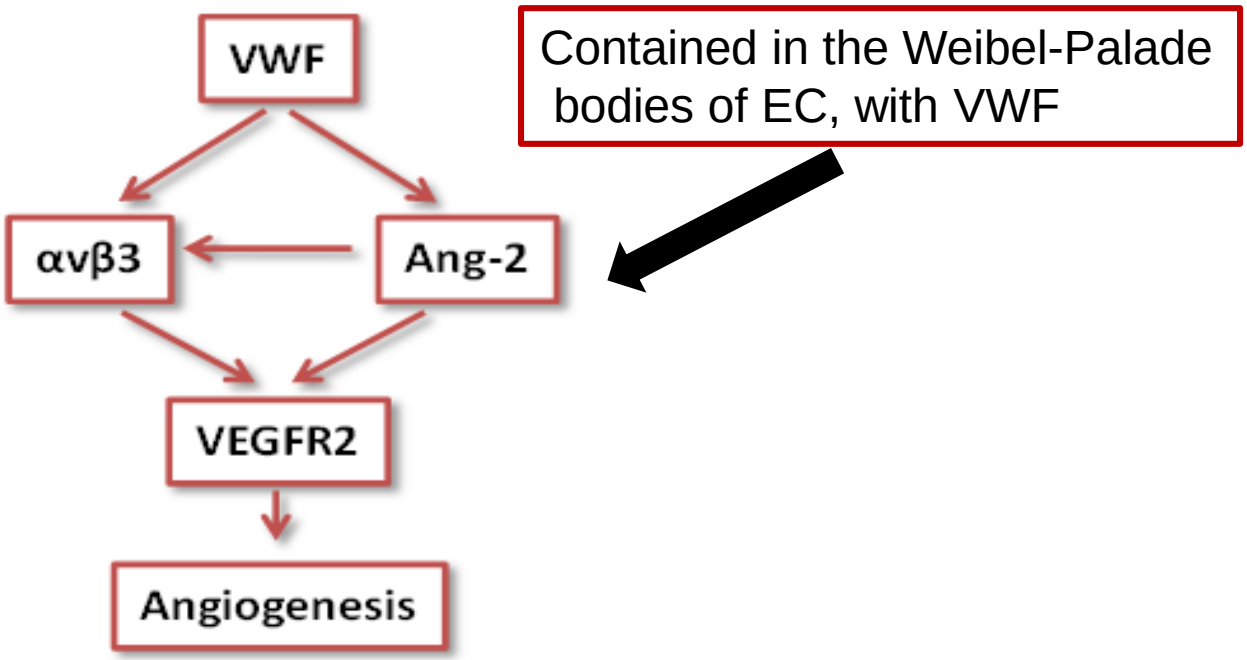
Castaman, 2011;2012

Heyde syndrome: aortic stenosis, loss of HMW VWF multimers, GI bleeding (Warkentin, 1992)



Surgical correction leads to normalization of VWF multimers and abolition of GI bleeding (Vincentelli, 2003)

VWF, ANGIODYSPLASIA AND ANGIOGENESIS

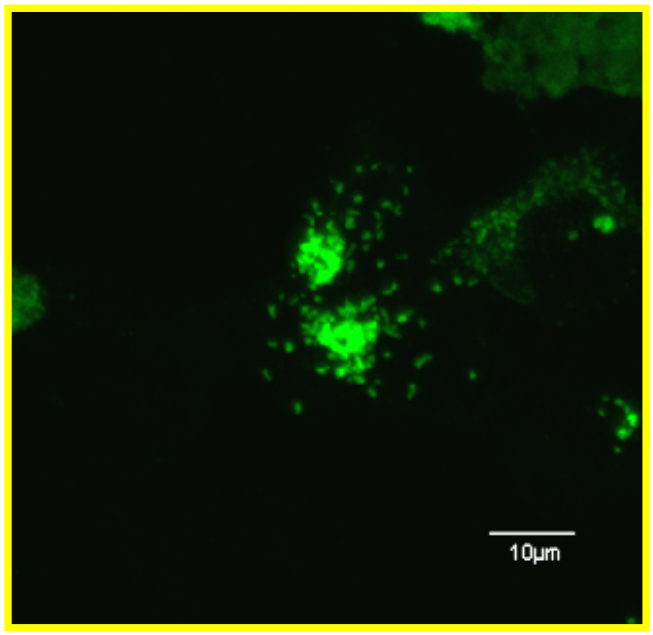


VWF controls angiogenesis through intra and extracellular pathways (Ang-2 and integrin αvβ3). Ang-2 is antagonist of Ang-1 and is reduced in VWD

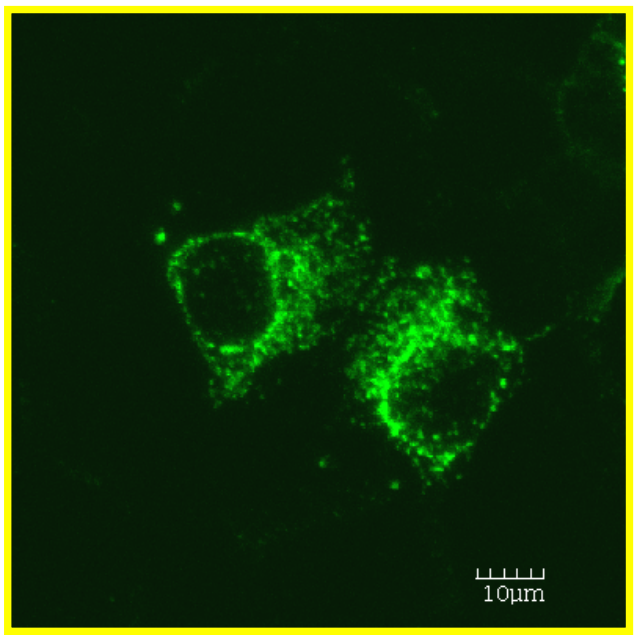
Angiogenesis is modulated through VEGF Receptor 2 signalling (Randi , 2013)

REDUCED VON WILLEBRAND FACTOR SECRETION IS ASSOCIATED WITH LOSS OF WEIBEL-PALADE FORMATION

WT-VWF



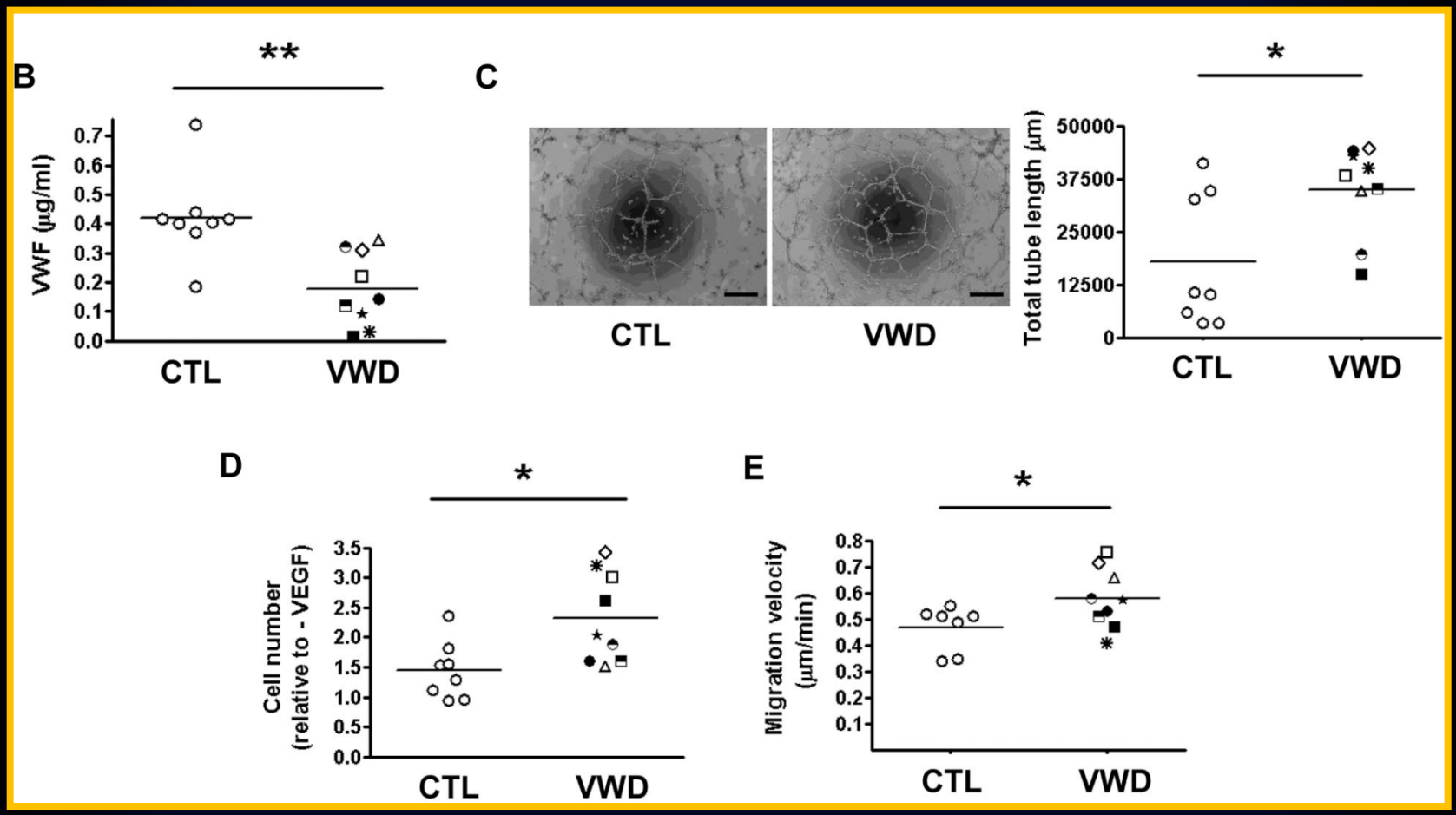
R854W-VWF



Normal VWF is required for Weibel-Palade bodies formation

Castaman et al, JTH 2010

Endothelial von Willebrand factor regulates angiogenesis



Blood outgrowth ECs from patients with VWD show increased in vitro angiogenesis, proliferation, and migration

Starke et al, Blood 2011

VWF regulates angiogenesis
(Randi, AS061)

- Endothelial VWF modulates the process of new vessel formation by exerting an inhibitory effect

- VWF deficiency resulted in enhanced pro-angiogenic signalling through vascular endothelial growth factor receptor-2 (VEGFR2), one of the most potent activators of angiogenesis

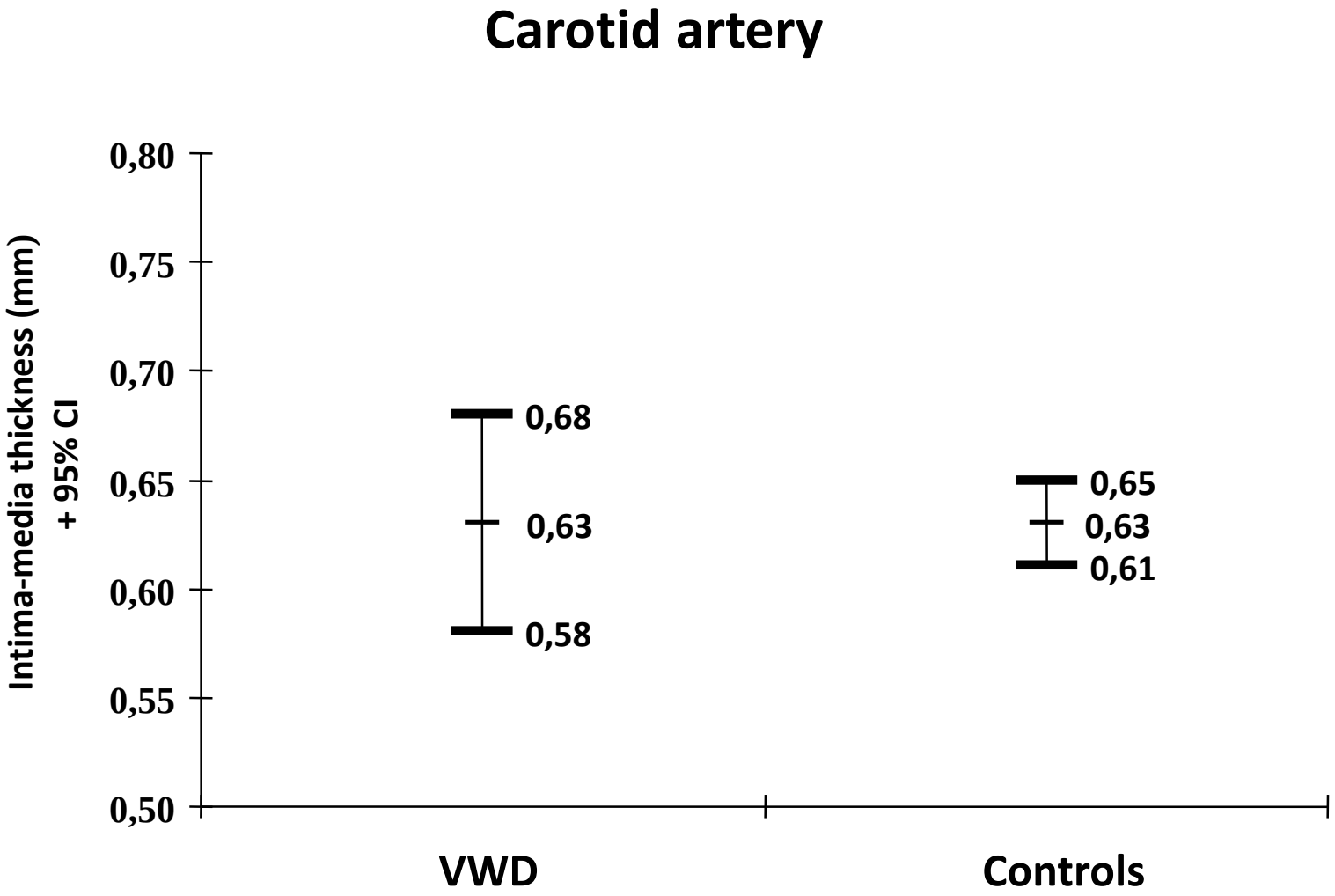
VWF regulates angiogenesis

(Casey, OR023; Groeneveld OR027)

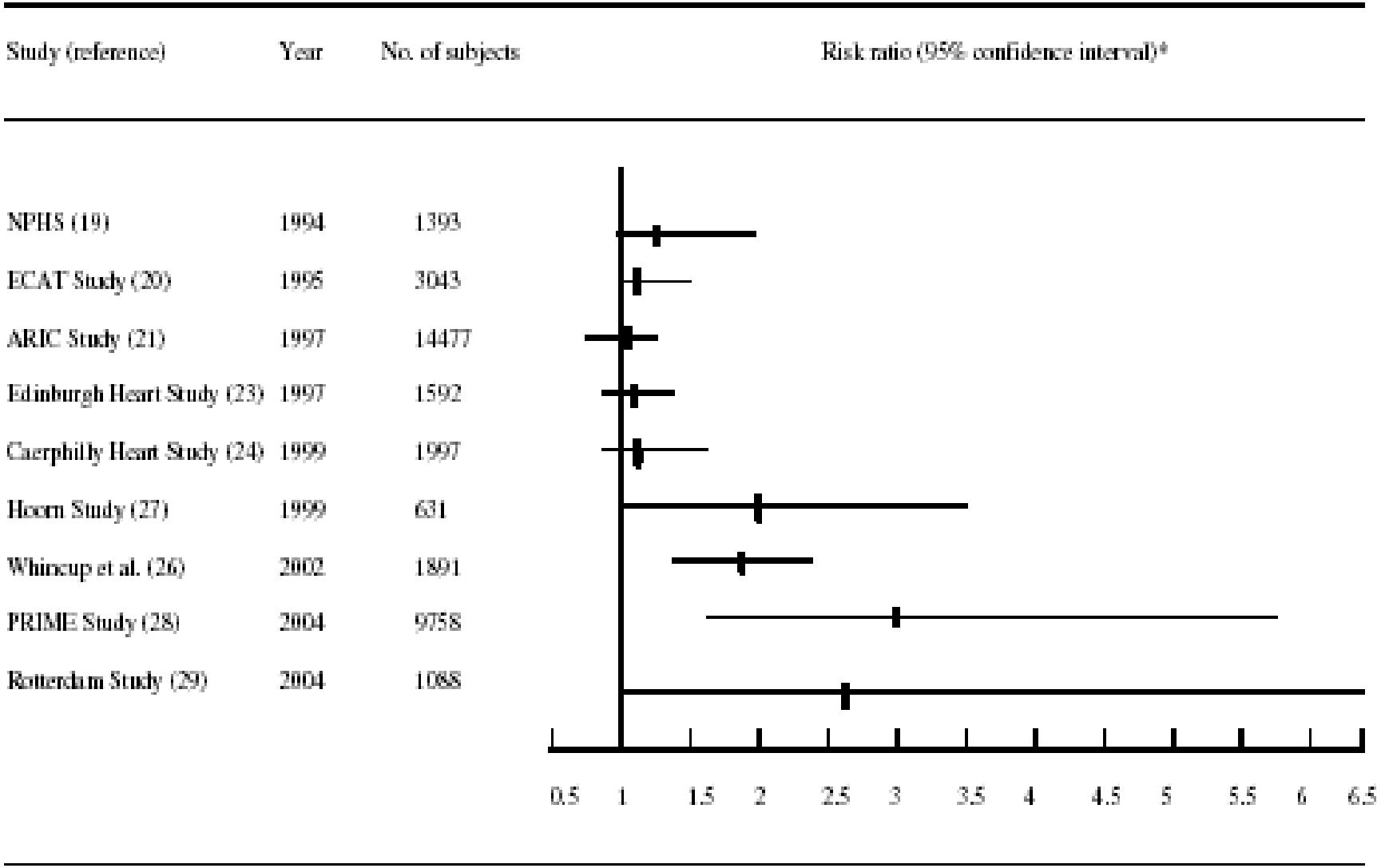
- Secretion of Ang-1 and VEGF increased in VWD, Ang-2 reduced
- BOEC proliferation is increased in type 2 A and 2 B supporting the increased GI bleeds in these patients
- Cultured cells may have migrating abnormalities

Von Willebrand factor and the risk of thrombosis: what is known

Patients with type 3 severe von Willebrand disease are not protected against atherosclerosis: results from a multicenter study in 47 patients (Sramek, 2004)



Prospective studies on the role of VWF in coronary disease



Association between FVIII/VWF levels and risk of VTE

	VWF	FVIII
Case-control studies		
- LETS, 1995	-	+
- Lowe, 1999		-
- Kraaijenhagen, 2000		+
Prospective studies		
- Kyrle, 2000		+
- LITE, 2002	+	+

Von Willebrand disease and cardiovascular risk

- WIN study: retrospective Dutch study in 635 adult VWD patients (VWF ≤ 30 U/dL)

- Global prevalence of AMI, stroke and coronary disease 39-63 % less than 2 reference populations

- Standard morbidity ratio vs general population:
  - Coronary disease 0.6 (95% CI, 0.32-0.98)
  - AMI 0.4 (95% CI, 0.13-0.83)
  - Stroke 0.33-0.65 (95% CI, 0.06-1.59)

Sanders, 2013

Rotterdam Study

(Sonneveld et al,AS181)

- Background: Recent studies have shown correlation between VWF and ADAMTS-13 levels and ischemic stroke and AMI

- Prospective Dutch population-based study in 6,511 subjects aged ≥ 55 years

- Median Follow-up 11.3 years, 442 deaths (7.2 %) from cardiovascular disease

	Low ADAMTS-13 activity HR (CI 95%)	High VWF:Ag HR (CI 95%)
Death from overall causes	1.46 (1.26-1.69)	1.21 (1.06 – 1.38)
Death from cardiovascular cause	1.46 (1.09-1.96)	1.29 (0.98 – 1.7)

Low risk of cardiovascular events in VWD
(Seaman et al, OR201)

- Retrospective USA study based on discharge data diagnosis 2009-2011 of ~ 20,000,000 patients

- CVD = ischemic heart disease, AMI, ischemic cerebrovascular disease, peripheral vascular disease

- Multivariable logistic regression to estimate the odds of CVD in patients with VWD after adjustment for age, gender, and CVD risk factors (hypertension, hyperlipidemia, diabetes mellitus).

Low risk of cardiovascular events in VWD
(Seaman et al, OR201)

	VWD patients (n = 7,556)	Non-VWD patients (n = 19,918,970)	P
Prevalence of cardiovascular disorders	15 %	26 %	< 0.001
Ischemic heart disease	11.5 %	20.6 %	< 0.001
AMI	3.38 %	7.24 %	< 0.001

- VWD was associated with a **decreased risk of CVD**
  OR = 0.84, 95% CI: 0.78 - 0.90

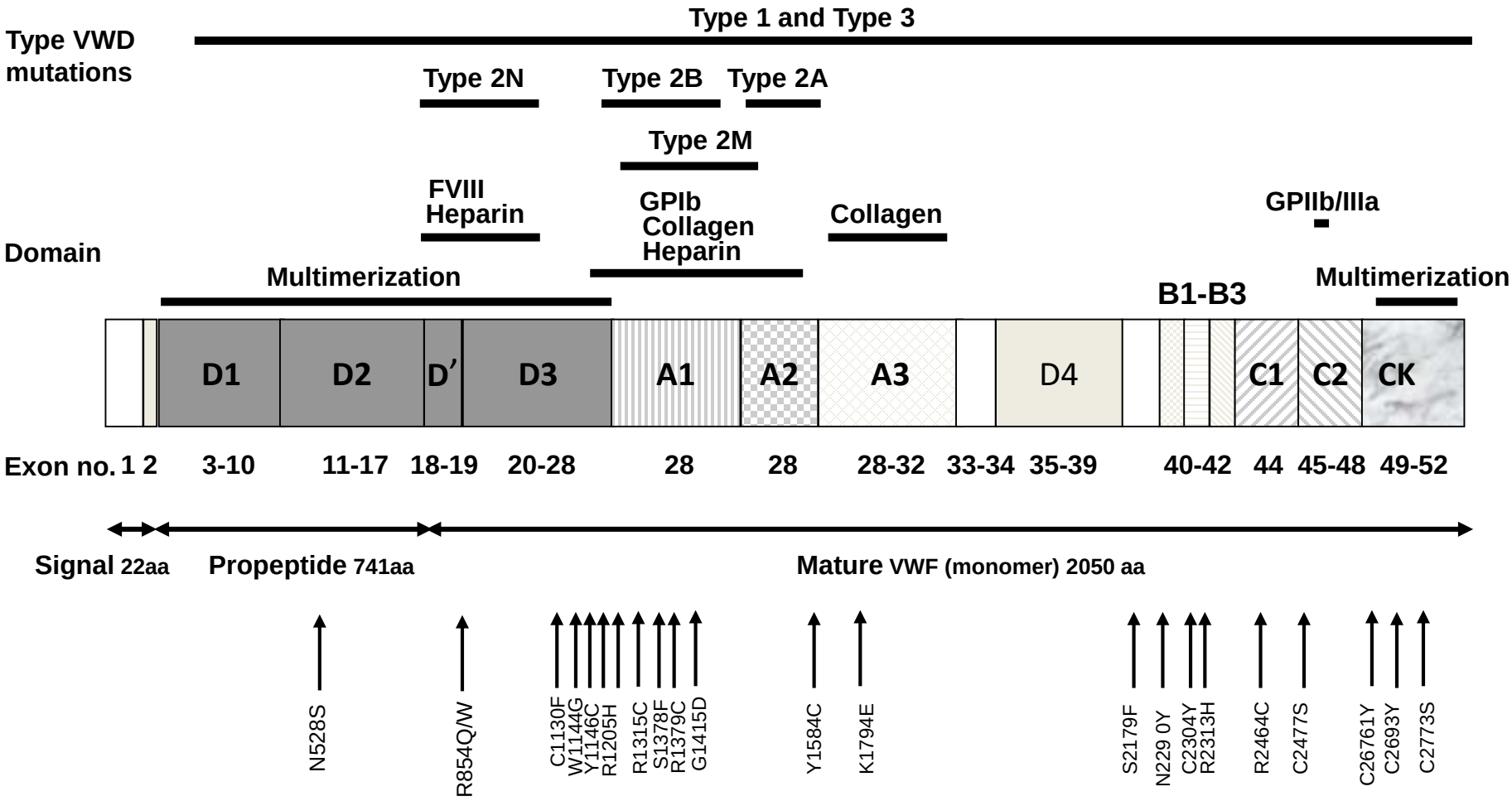
- The risk of IHD was **less**:
  OR = 0.85, 95% CI: 0.79 - 0.92

- The risk of AMI was **less**
  OR = 0.68, 95% CI: 0.60 - 0.77

miRNA, VWF levels and diabetes
(Xiang et al, PO673)

- High risk of arterial thrombosis in diabetes associated with high VWF levels
- MicroRNAs (miRNAs) are small 19–23 nucleotide RNA molecules that negatively regulate the translation of their target mRNAs
- Hyperglycemia-induced repression of microRNA-24 (miR-24) increases VWF expression and secretion in diabetes patients and in a mouse model
- Increasing miR-24 represents a novel therapeutic target to prevent adverse thrombotic events in diabetic patients

Genetic heterogeneity of von Willebrand disease: what is known



Genetic heterogeneity of von Willebrand disease (Boisseau et al, OR025)

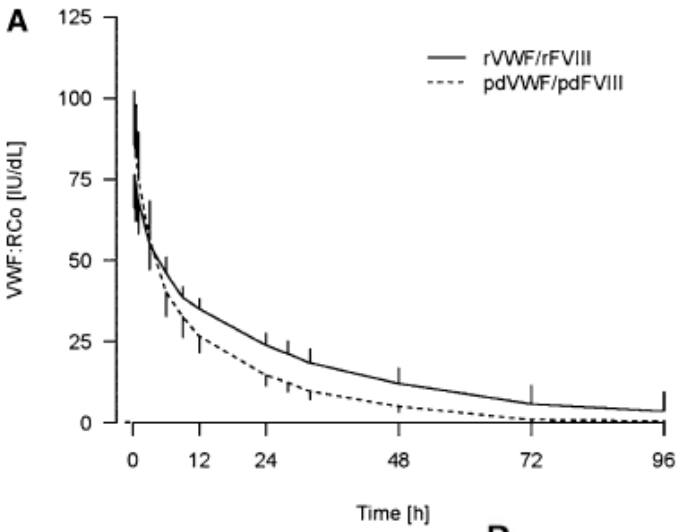
- French study of 75 type 3 VWD patients
- 72 different mutations (65 % novel) in 88% of cases
- Deep intronic mutations in 12 % of cases, as in afibrinogenemia and mild hemophilia A (Duga et al, 2009; Castaman et al, 2011)
- Bleeding severity and need for prophylaxis significantly higher in those with with FVIII < 5 U/dL and VWF < 1 IU/dL

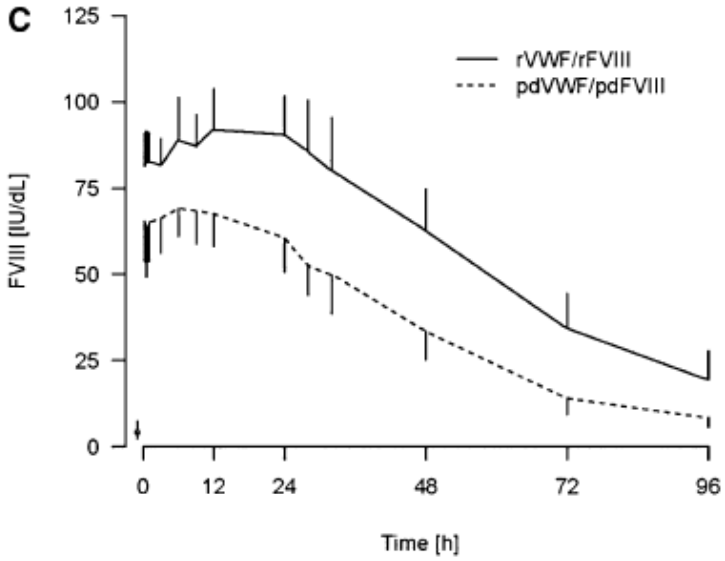
Genetic heterogeneity of von Willebrand disease (Goudemand et al, OR024)

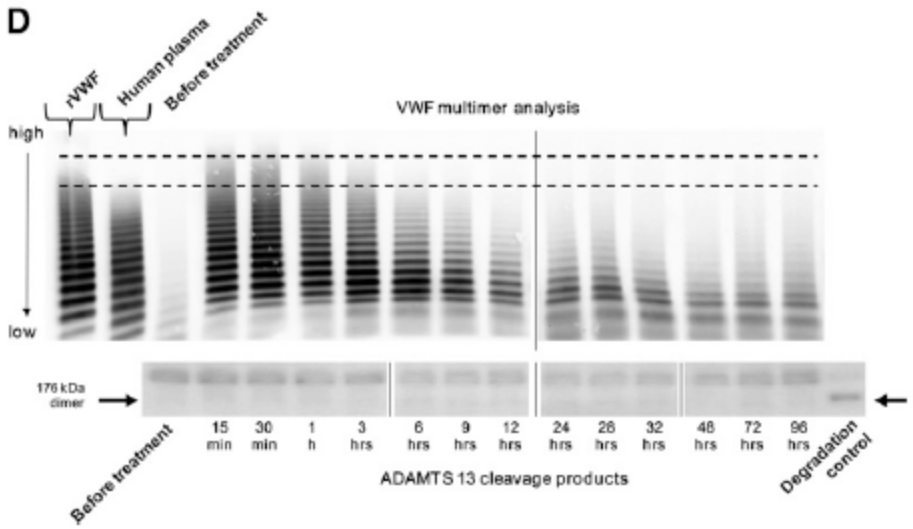
- French study of 88 families with type 2 N VWD
- R854Q present in 93/102 (91%)
- Homozygotes have on average higher FVIII levels and milder clinical phenotype than compound heterozygotes

blood
2013 122: 648-657
doi:10.1182/blood-2013-01-479527 originally published online June 18, 2013

Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial







Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease

Joan C. Gill,[1,2] Giancarlo Castaman,[3,4] Jerzy Windyga,[5] Peter Kouides,[6,7] Margaret Ragni,[8,9] Frank W. G. Leebeek,[10] Ortrun Obermann-Slupetzky,[11] Miranda Chapman,[11] Sandor Fritsch,[11] Borislava G. Pavlova,[11] Isabella Presch,[11] and Bruce Ewenstein[12]

Blood. 2015;126(17):2038-2046

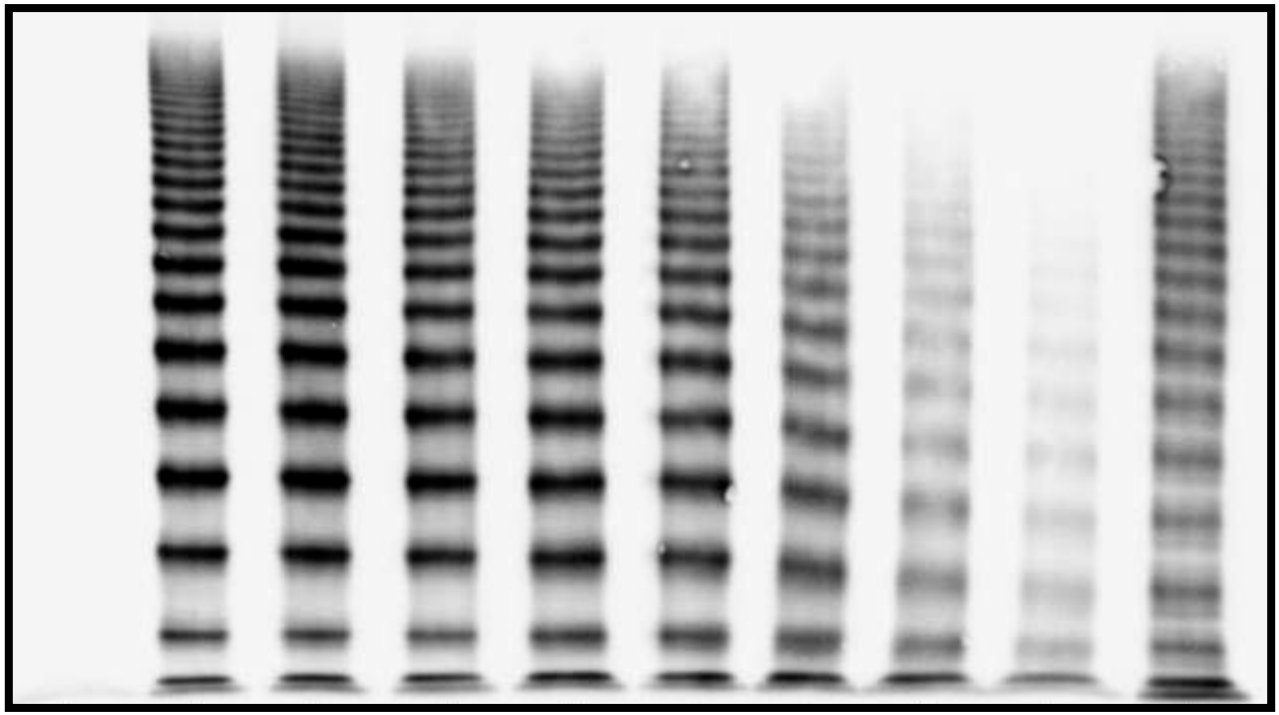
- The treatment success rate (mean efficacy score of < 2.5) was 100% (90% CI: 87.3 to 100.0) (n = 22: 17 type 3, 4 type 2A, 2 type 2N; 192 bleeds: 122 minor, 61 moderate, 7 major, 2 unknown).

- Treatment was good (3.1%) or excellent (96.9%) in all bleeds

- The rVWF PK profile was unaffected by rFVIII (mean VWF:RCo terminal halflife = 21.9 h [rVWF] and 19.6 h [rVWF:rFVIII])

OR088

VWF multimers and degradation products pre- and post-infusion of rVWF in a subject with type 3 VWD (Gill, OR088)



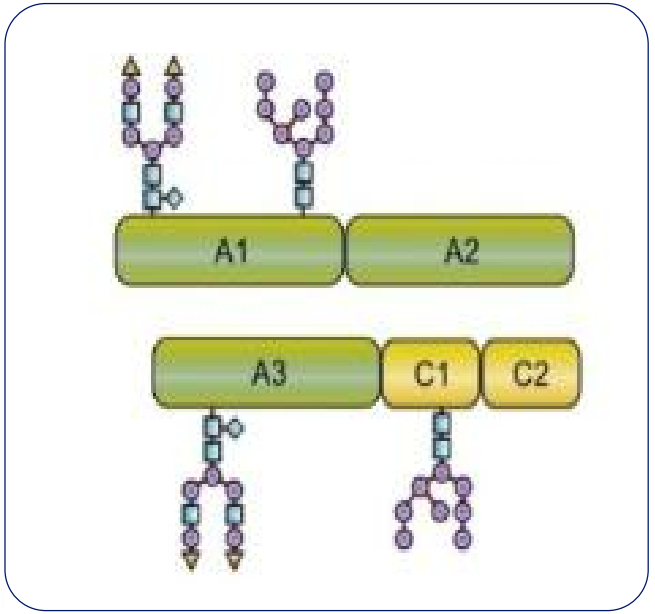
Treatment summary of all bleeding episodes

	No. bleeding episodes	Total no. infusions	Median (range) no. infusions/ bleed	Median (range) VWF:RCo dose (IU/kg)/ infusion	Median (range) rFVIII dose (IU/kg)/ infusion	% bleeds (N=192) rated* excellent or good (n excellent / good)
Subject VWF type						
Type 3	175	219	1 (1-4)	48.2 (23.8-184.9)	33.6 (16.6-129.3)	100% (171 / 4)
Type 2A	16	18	1 (1-2)	50.2 (32.9-90.2)	32.5 (23.7-38.6)	100% (14 / 2)
Type 2N	1	1	1 (1-1)	54.3 (54.3-54.3)	NA†	100% (1 / 0)
Bleed severity						
Minor	122	132	1 (1-3)	43.3 (25.2-158.2)	33.5 (17.6-86.2)	100% (119 / 3)
Moderate	61	89	1 (1-4)	52.7 (23.8-184.9)	36.9 (16.6-129.3)	100% (59 /2)
Major/severe	7	15	2 (1-3)	100.0 (57.5-135.0)	39.0 (25.0-42.3)	100% (6 / 1)
Unknown	2	2	1 (1-1)	33.4 (33.1-33.8)	23.3 (23.1-23.6)	100% (2 / 0)
Bleed site‡						
Joint	59	66	1 (1-3)	48.2 (23.8-139.6)	34.9 (16.6-129.3)	100% (57 / 2)
GI	6	10	1 (1-2)	60.0 (53.6-121.1)	33.2 (19.3 -49.4)	100% (5 / 1)
Mucosal	106	121	1 (1-4)	43.3 (23.8-184.9)	30.6 (16.6-61.3)	100% (103 / 3)
Other§	37	57	1 (1-4)	52.2 (25.2-184.9)	36.8 (17.6 -86.2)	100% (36 / 1)

Acquired coagulation abnormalities

Molecular structure of OBIZUR®

- Porcine B-domain deleted rFVIII; 24 amino acid linker left from B-domain
- 1448 total amino acids
- ~170 kDa Molecular mass[2]
- Despite B-domain truncation, activated OBIZUR® is similar to endogenous porcine FVIII and retains its pro-coagulant activity[3]



1. Thompson AR. Semin Thromb Hemost 2003;29(1):11–22.
2. Wojchiechowski P. Poster (PT228) presented at WFH. 2014
3. Lai, C., A. Tse, S. Sivakollundu, M. Patel, S. Vangala, L. Zhang, et al., Poster (PT223) presented at WFH, 2014, Melbourne. Elucidation of structure and functional characteristics of OBIZUR, a recombinant porcine sequence FVIII. 2014.

Perioperative management of bleeds with rec porcine FVIII in acquired hemophilia A (Novack, OR028)

- Phase 2/3 open-label clinical trial investigating the efficacy and safety of rpFVIII in the treatment of serious bleeds in 28 AHA subjects

- Response to rpFVIII treatment at 24 h was the primary endpoint (e.g. effective, partially effective)

- Treatment began with a 200 U kg^{-1} dose of rpFVIII; further doses were based on the subject's target FVIII levels, anti-pFVIII titer, and clinical status

Perioperative management of bleeds with rec porcine FVIII in acquired hemophilia A (Novack, OR028)

- Recombinant pFVIII was used perioperatively for 3 major surgical interventions (1 hemicolectomy, 1 endoscopic retrograde cholangiopancreatography, 1 emergency tracheotomy) and up to 10 days post-surgery for management of a limb compartment syndrome in 2 other patients

- All had a positive response to treatment at 24 h post-infusion.
- After treatment, 2 subjects developed anti-pFVIII inhibitors de novo.
- No SAEs or thrombotic events related to rpFVIII treatment occurred
- 1 late death for bleeding while on treatment with by-passing agent

Risk of relapse in acquired hemophilia

- Relapse in about 20 % after a median of 7.5 months (Collins, 2007)

- EACH-2 : 18 % treated with steroids only,

  12 % steroids + cyclofosfamide,

  1 % rituximab

  after a median of 4 months (Collins, 2012)

- 70 % achieved a second remission

Relapse pattern and long term outcomes in 111 subjects with acquired hemophilia A (Mizrahi OR217)

- Between 2000 and 2012, 100/111 Canadian registered patients (90%), median age 73 years, achieved CR within a median of 45 days and were followed up for a median time of 25.6 months
- Of those, 14% presented one or more relapses (median time to first relapse 13.4 months [4.1–53.3 months])
- Patients with relapse were older (P = 0.054), mostly male (P = 0.083) and more frequently suffering from auto-immune or lymphoproliferative disease (P = 0.008)
- All but one relapsing patients achieved a subsequent remission and only one patient had a fatal bleed during an episode of relapse

Hemophilia: the future

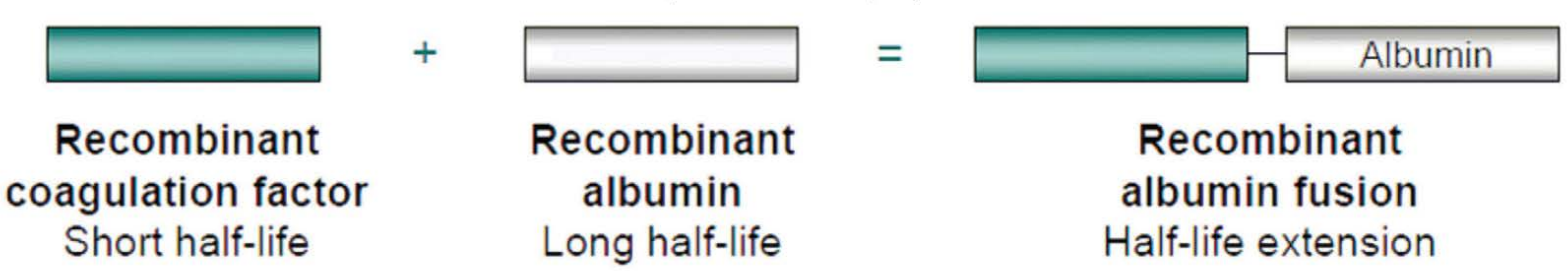
Novel products

- Development wholly based on recombinant technology

- Products under development and clinical trials include:
  - Long-acting factor VIII
  - Long-acting factor IX
  - Long-acting activated factor VII and more potent analogue
  - Anti-TFPI

Albumin fusion products

- Marketed as “natural alternative” to PEG, which is not entirely biodegradable
- DNA construct encoding both target protein and albumin in a single recombinant molecule
- Short linker in between to avoid problems due to steric hindrance and ensure retention of maximum potency



blood
2012 120: 2405-2411
Prepublished online August 2, 2012;
doi:10.1182/blood-2012-05-429688

Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

Elena Santagostino, Claude Negrier, Robert Klamroth, Andreas Tiede, Ingrid Pabinger-Fasching, Christine Voigt, Iris Jacobs and Massimo Morfini

Parameter (unit) baseline-corrected	rIX-FP			Previous FIX	
	25 IU/kg (n = 7)	50 IU/kg (n = 13)	75 IU/kg (n = 8)	rFIX (n = 8)	pdFIX (n = 4)
Half-life, h					
Mean	104.71	91.57	98.82	17.23	14.59
SD	55.08	20.74	17.48	2.28	1.73

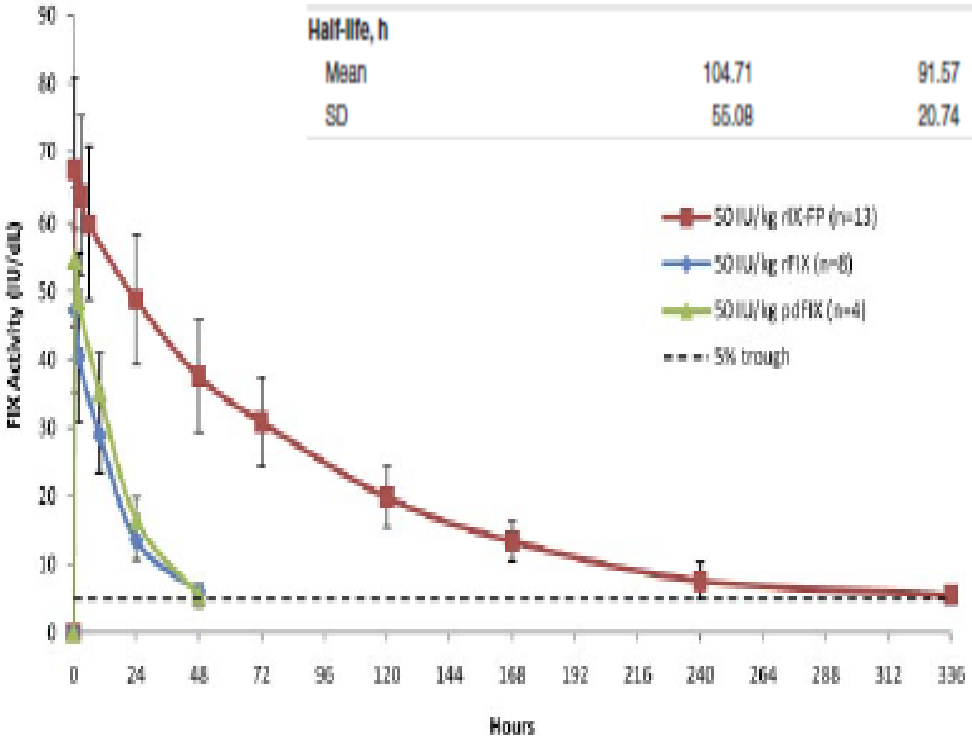


Figure 1. Linear plot of baseline-corrected FIX activity level after the infusion of 50 IU/kg of rIX-FP and previous FIX product (PK population). Mean FIX activity levels of 50 IU/kg rIX-FP, 50 IU/kg rFIX, and 50 IU/kg pdFIX were measured in International units per deciliter. Vertical bars represent SD. A horizontal dotted line represents the 5-IU/dL FIX activity level.

Long acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial

E. Santagostino, U. Martinowitz, T. Lissitchkov3,B. Pan-Petesch, Hideji Hanabusa, J. Oldenburg, L. Boggio, C. Negrier, I. Pabinger, M. von Depka Prondzinski, C. Altisent, G. Castaman, K. Yamamoto, C. Voigt, and Iris Jacobs

Blood Jan 11, 2016; OR347

- A total of 63 subjects were enrolled . In the on-demand arm, 19/23 subjects switched to 7- day PT after completing 6 months ODT, the other continued prophylaxis at 7-, 10- and 14-day .

- The median (Q1, Q3) AsBR during ODT and PT was 15.43 (7.98, 17.96) and 0.00 (0.00, 0.96), respectively, a reduction of 100% ($P < 0.0001$). Ù

- All PT subjects (n = 40) on 7-, 10- and 14-day PT had a median AsBR of 0.00.

- Subjects on 14-day PT (50–75 IU kg 1) reduced consumption by 50% over their prior FIX product