Webinars

Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Congenital TTP: diagnosis and future management

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30 June 2021

Co-funded by the Health Programme of the European Union

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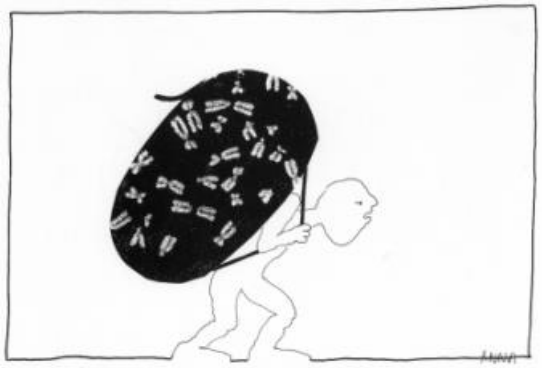
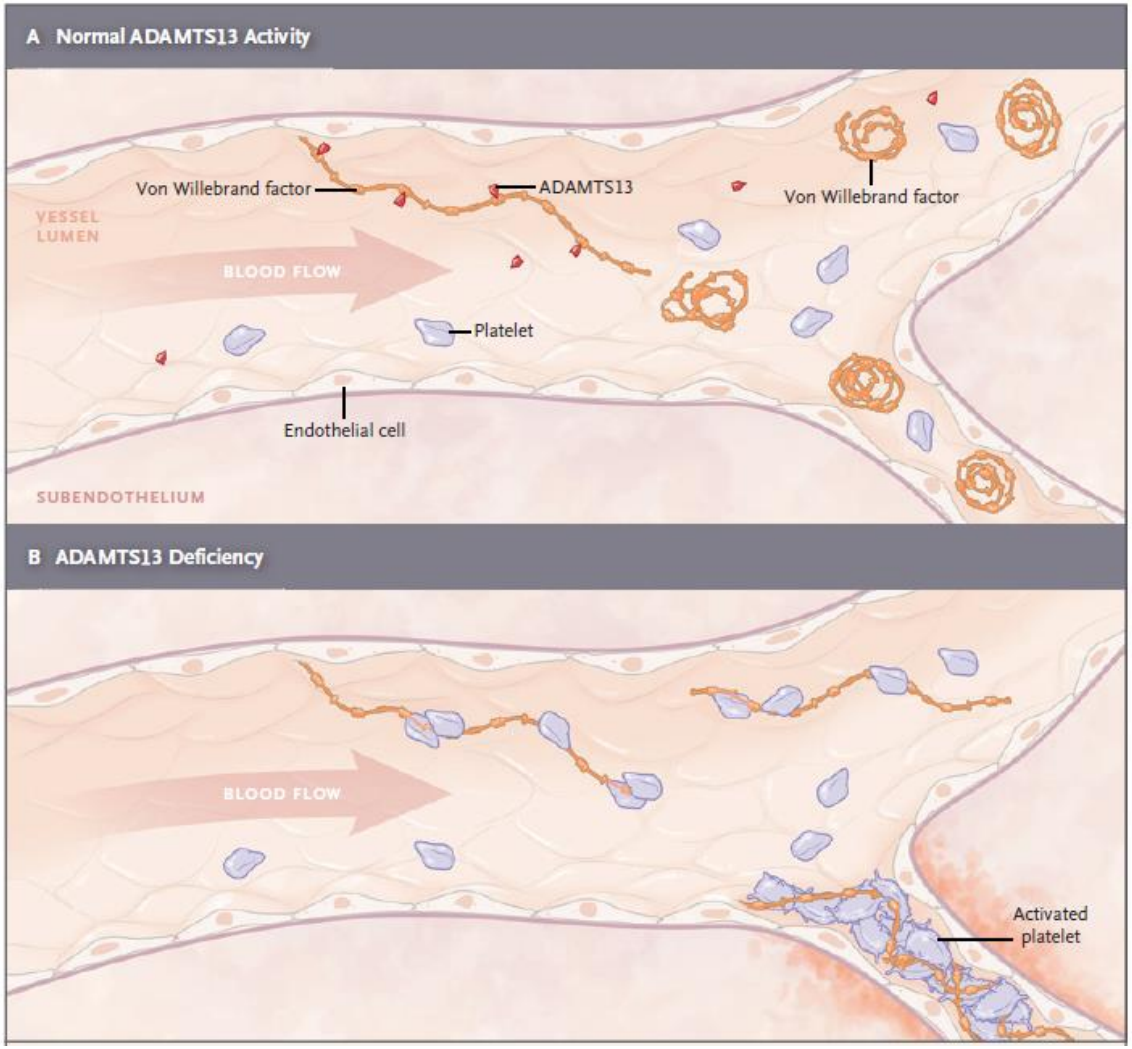
European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Employment	-
Research Support	Baxter/Takeda (IIR Grant for the “hereditary TTP registry” www.ttpregistry.net)
Advisory boards	Shire/Takeda – rADAMTS13 Ablynx/Sanofi – Caplacizumab Bayer, NovoNordisk, Octapharma, Shire, Sobi, Roche – Hemophilia
Consultancy	Federal Office of Public Health
Speakers bureau	Roche, Sanofi, Shire/Takeda, Siemens
Major stockholder	-
Other	Interprofessional Hemophilia Consultation EHCCC Inselspital (Bayer, CSL Behring, NovoNordisk, Octapharma, Sobi, Roche)

1. Recognizing hTTP
   - ❖ Presentation / Diagnosis
2. Epidemiology
3. Understand the burden of hTTP
4. Management
   - ❖ Plasma treatment
   - ❖ New developments

- Hereditary / congenital TTP = Upshaw-Schulman syndrome (OMIM #274150)
- A specific form of thrombotic microangiopathy (TMA)
- Characterized by severe congenital ADAMTS13 deficiency
- Autosomal recessive inheritance
  - Caused by mutations in the *ADAMTS13* gene (Chr. 9q34)
    >200 causative mutations known
- Ultra-rare disease





Kremer Hovinga JA & George JN.
N Engl J Med 2019;381:1653-62

SYLVIA

- 38-yr-old, previously healthy
  - 1st pregnancy, preeclampsia, IUFD* GA 26 2/7 wks
- 2nd pregnancy, GA $18^{5/7}$ wks,
  - mild hypertension, mild edema, IUGR ~3weeks
  - GA $19^{0/7}$ weeks: 2nd IUFD; placenta with signs of chronic malperfusion & 50% infarction
- Lab: Platelets $37x10^9$/L; hemoglobin 85 g/L, MCV 89fl, schistocytes ++, LDH 1163 U/L; creatinine 88 μmol/L; liver enzymes normal; INR 1.2
  - Plasmic score 5/7 points

SYLVIA

- ADAMTS13 activity <5%, functional inhibitor & anti-ADAMTS13 antibodies negative
- *ADAMTS13* gene analysis:
  - IVS12, c.1436 -2 A → T (splice site mutation ?)
  - exon 25, c.3283 C → T, p.R1095W

…. Lost to follow-up with suspected hTTP diagnosis

- Jan 2021 (43.5y) – stroke w. left-sided hemiparesis
  - arrived in ER <6h –> stroke protocol with thrombolysis
  - followed by plasma infusions > full recovery
  - now prophylaxis w 600ml plasma (11ml/kg bw)/14dys

ACQUIRED (iTTP)

Immune-mediated TTP

- ADAMTS13 <10%,
- anti-ADAMTS13-Abs / functional inhibitor
- ADAMTS13 $t_{1/2}$ ↓
- spontaneous ADAMTS13 ↑ in remission
- Female: Male ratio ~2.5-3.5:1
- Additional auto-immune disorders (e.g. SLE)
- Incidence ca 2 cases / 1 million

HEREDITARY (hTTP/cTTP)

Upshaw-Schulman syndrome

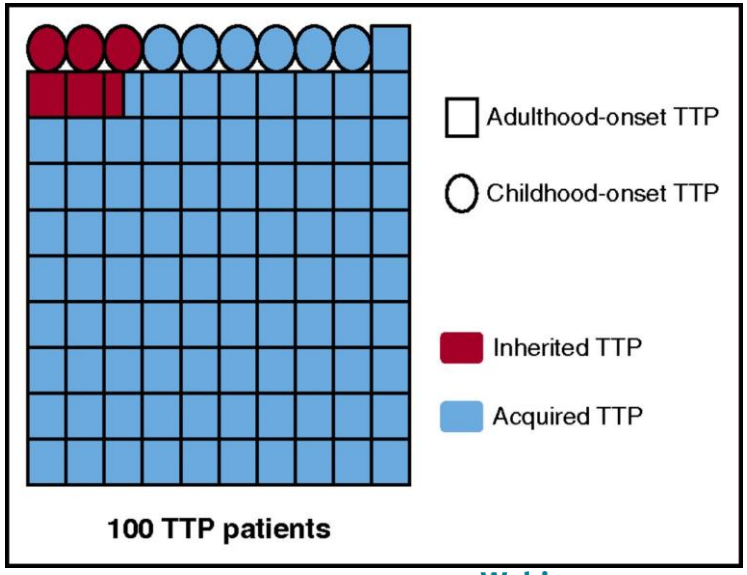
- ADAMTS13 <10%,
- no Inhibitor
- full recovery of plasma infused & $t_{1/2}$ 2-4days
- ≥2 *ADAMTS13* mutations
- Female: Male ratio ~1:1
- ADAMTS13 ~50% in "obligatory carriers"
- Prevalence estimates

Kremer Hovinga JA *et al*. Nat Rev Dis Primers. 2017;3:17020ff
Scully M et al. JTH 2017;15:312ff

Table 1. Main associated clinical contexts identified at the initial acute episode of TTP in reports involving more than 50 patients (both adults and children)

Series (year)	USS, %	Idiopathic, %	Infection* and HIV, %	Autoimmune disease, %	Cancer and/or organ/HSPC transplant, %	Pregnancy and postpartum, %	Other, %	Drugs, %
Scully et al (2008)[3] [N = 176]	5	77	<1 and 7	—	2	5†	4	<1
Kremer Hovinga et al (2010), Deford et al (2013)[6,8] [N = 60]	0	77	7	5	2 and 2	5	3	0
Lotta et al (2010)[4] [N = 136]	0	79	0	7	0	9	1	4
Fujimura et al (2010)[5] [N = 326]	12	60	0	14	2 and 0	1	4	7
Jang et al (2011)[7] [N = 66]	0	59	9	6	8 and 1	6	3	8
Blombery et al (2016)[9] [N = 57]	0	75	3 and 0	18	0	2	0	2
Coppo et al (2016)[10] [N = 772]	3	49	12 and 3	11	9 and 4	5	3	1

HIV, human immunodeficiency virus; HPSC, hematopoietic stem-cell; N, number of patients.
*Specific diagnosis made.
†Pregnancy and combined oral contraceptive pill.



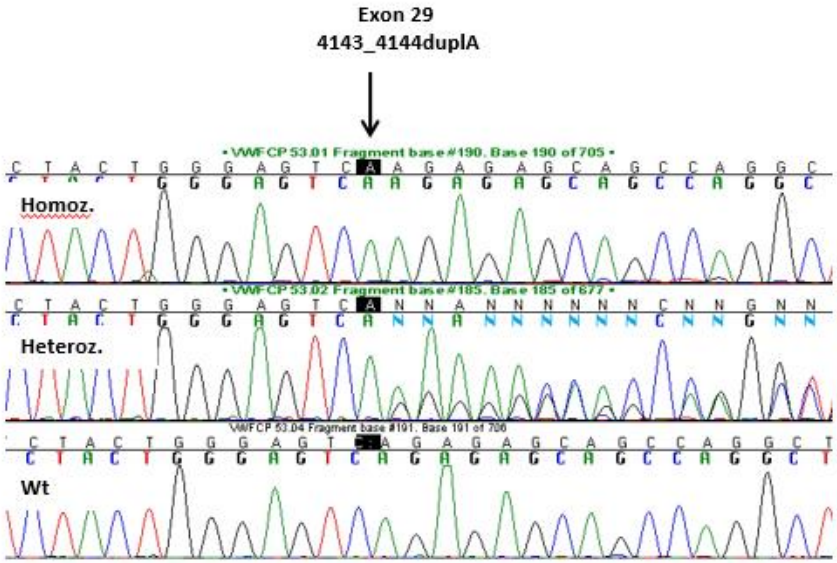
Joly BS *et al*. Blood 2017;129:2836ff

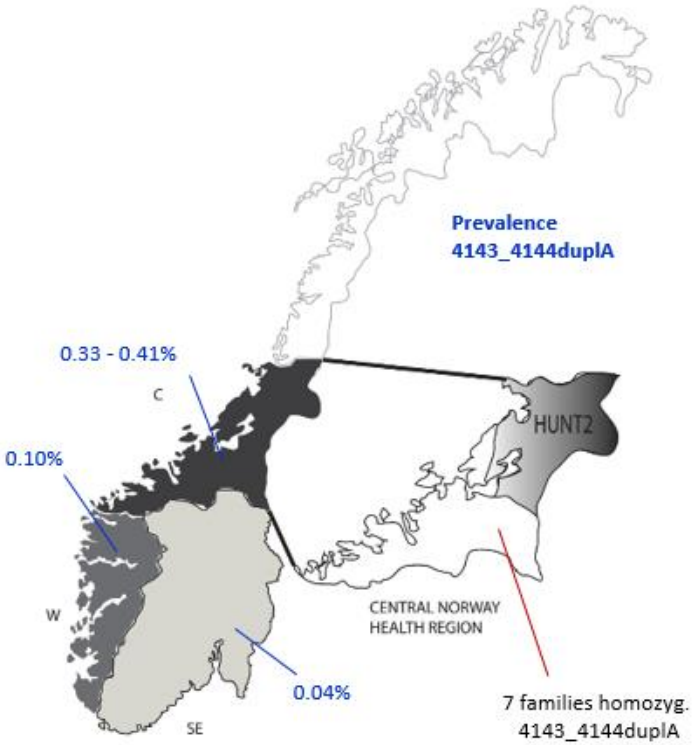
- Ultra-rare disease
  - Prevalence estimate ~0.5 – 2 cases / million

Hereditary TTP in Norway

18 USS families

- ABH BG BB in homozyg. 4143_4144duplA
- 11/18 families homozyg. 4143_4144duplA
  - 25/36 alleles 4143_4144duplA

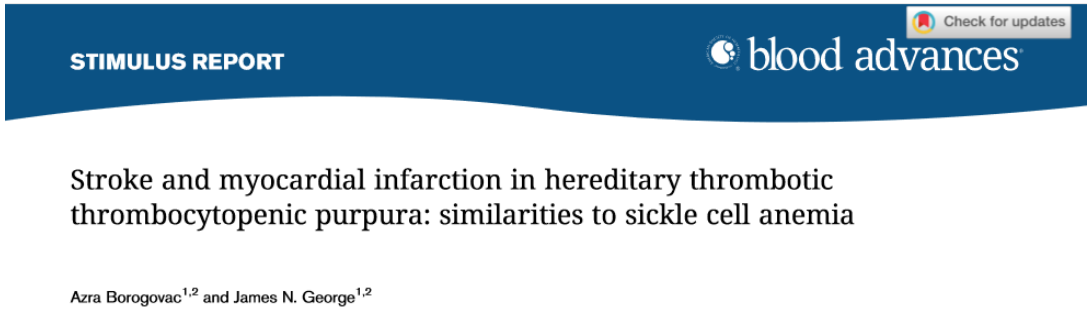




Von Krogh AS *et al*. JTH 2016;14:73f

- Ultra-rare disease
  - Prevalence estimate ~0.5 – 2 cases / million

Japan	65 cases / 130 Mio	→ 0.5 case / 1 million
Switzerland	9 cases / 8.4 Mio	→ 1 case / 1 million
Czech Republic	18 cases / 10.5 Mio	→ 2 cases / 1 million
Norway	21 cases / 4.5 Mio	→ 4.5 cases / 1 million

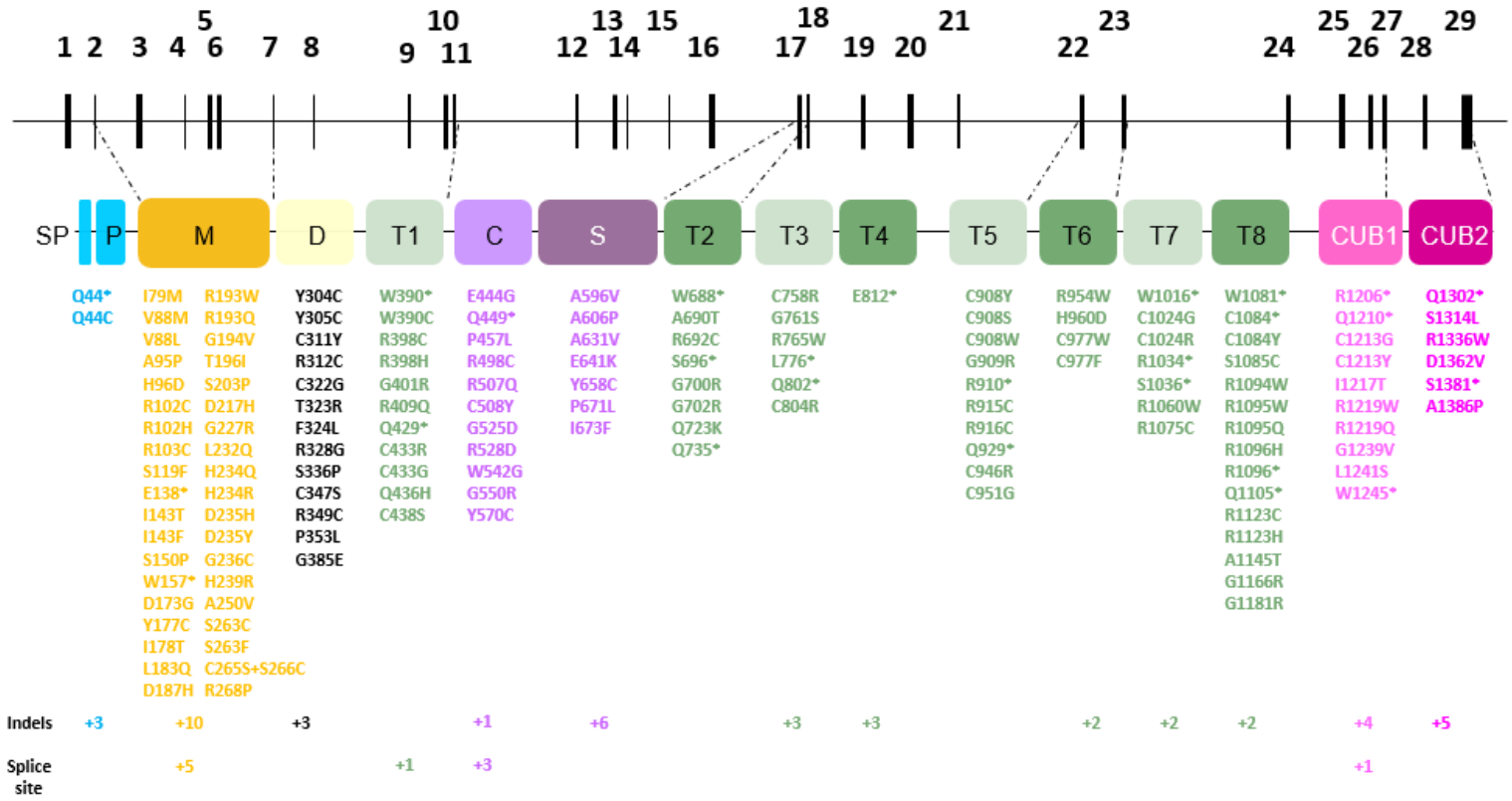


Blood Adv. 2019;3(23):3973ff
Review of published cases:
155 patients in 122 families

➢ Many patients known to us, have not been published or enrolled in registries

***ADAMTS13* Chr. 9q34** – 37 kb; cDNA 4.1 kb

ADAMTS13 **1427 AA** – MW ~150kD; in gel MW 180-190kD (glycosylation)



Kremer Hovinga JA *et al*;
JTH 2018:16:618-29

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Thrombotic Microangiopathies
EuroBloodNet Topic on Focus

Presentation of an international registry for the ultra-rare disease congenital thrombotic thrombocytopenic purpura

Hereditary thrombotic thrombocytopenic purpura registry

Patient recruitment from 2006 to 2017

123 Patients with congenital thrombotic thrombocytopenic purpura

Median age	Years
• at enrollment	26.1 (range 0.1-75.0)
• at clinical diagnosis	16.7 (range 0-69.8)
• at reported overt disease onset	4.5 (range 0-69.8)

ADAMTS13 parameters	Results
ADAMTS13 activity values	Identified in 121/123 patients, all values <10%
Functional inhibitors	Negative in all reported cases
Anti-ADAMTS13 antibodies	Positive in 12/103 patients analyzed
Molecular analysis of the ADAMTS13 gene	98 different ADAMTS13 mutations were identified

- The most frequent mutation observed was **ADAMTS13 c.4143_4144dupA** in exon 29, present on 60/246 alleles
- 19 of the 98 mutations have not been reported before

van Dorland HA *et al*.
Haematologica 2019;104:2107ff

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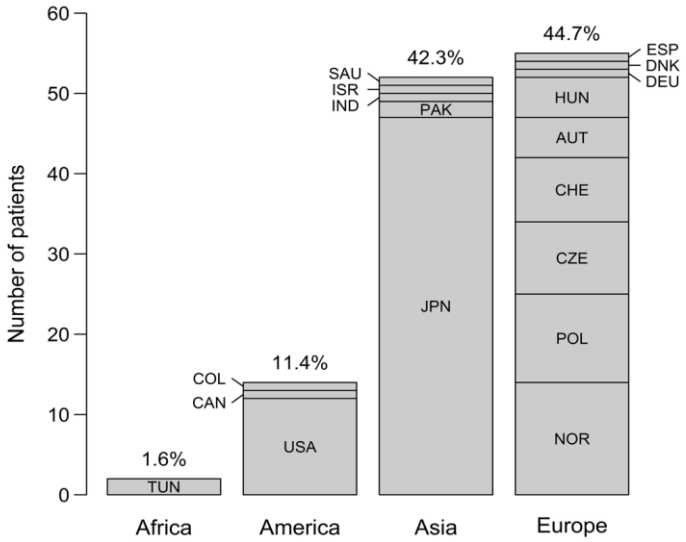
Characteristic	All patients (N=123)
Median age at enrollment (n=118)†	26.1 [0.1, 15.1, 37.2, 75.0]
Median age at overt disease onset (n=111)	4.52 [0.00, 0.01, 20.1, 69.8]
Median age at clinical diagnosis (n=122)	16.7 [0.00, 4.00, 28.6, 69.8]
Gender (F/M)	62/61
Ethnicity (self-reported)	
Caucasian	65 (53%)
Hispanic	3 (2.4%)
Asian	52 (42%)
Other	3 (2.4%)
ADAMTS13 activity (≤10%)	121/121
ADAMTS13 functional inhibitor (+)	0/114
Anti-ADAMTS13 antibodies (+)§	12/103
Consanguinity of parents	14/104
Homozygous genotypes	47/123
Compound heterozygous genotypes	76/123

TODAY:
145 confirmed patients
> 50 family members



van Dorland HA *et al*.
Haematologica 2019;104:2107ff

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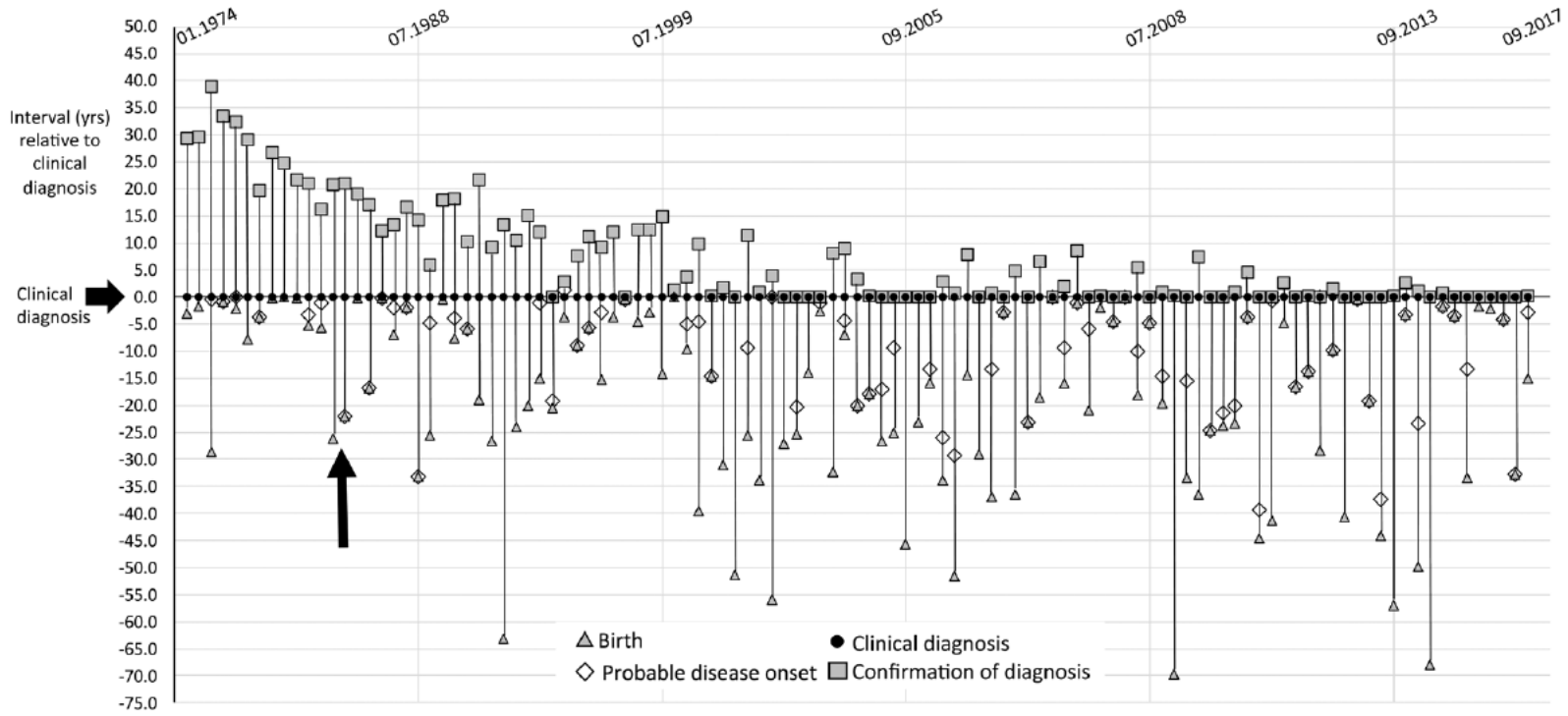

Vertical arrow: Patient example

– disease onset in neonatal period, clinical diagnosis of hTTP 22 years later

– confirmation of hTTP by ADAMTS13 testing 21years after clinical diagnosis

van Dorland HA *et al*.
Haematologica 2019;104:2107ff

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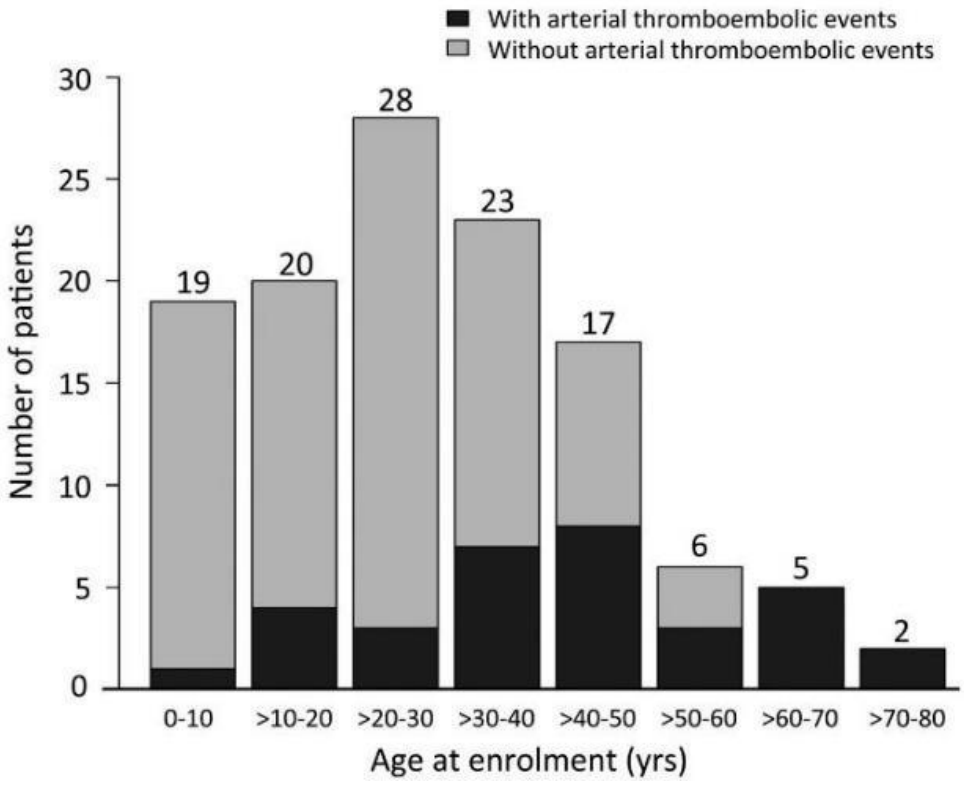
Table 2. Reported concomitant diseases and disorders in congenital thrombotic thrombocytopenic purpura patients up to enrollment.

Type of disease/disorder	All patients (N=120)
Arterial thromboembolic diseases†	33 (28%)
Myocardial infarction	5 (4.2%)
Transient ischemic attack	12 (10%)
Stroke	25 (21%)
Other	6 (5.0%)
Other neurological disorders†	27 (22%)
Epileptic seizure	6 (5.0%)
Headache	5 (4.2%)
Various other	20 (17%)
Renal insufficiency†	30 (25%)
Hemodialysis	12 (10%)
Kidney transplant	3 (2.5%)
Jaundice (hemolysis or liver disease)	59 (49%)
Hyperbilirubinemia in neonatal period††	30 (25%)
Anemia	
Iron deficiency	8 (6.7%)
Renal anemia	8 (6.7%)
Other diseases	
Cancer	2 (1.7%)
Autoimmune disorders	4 (3.3%)



van Dorland HA *et al*.
Haematologica 2019;104:2107ff

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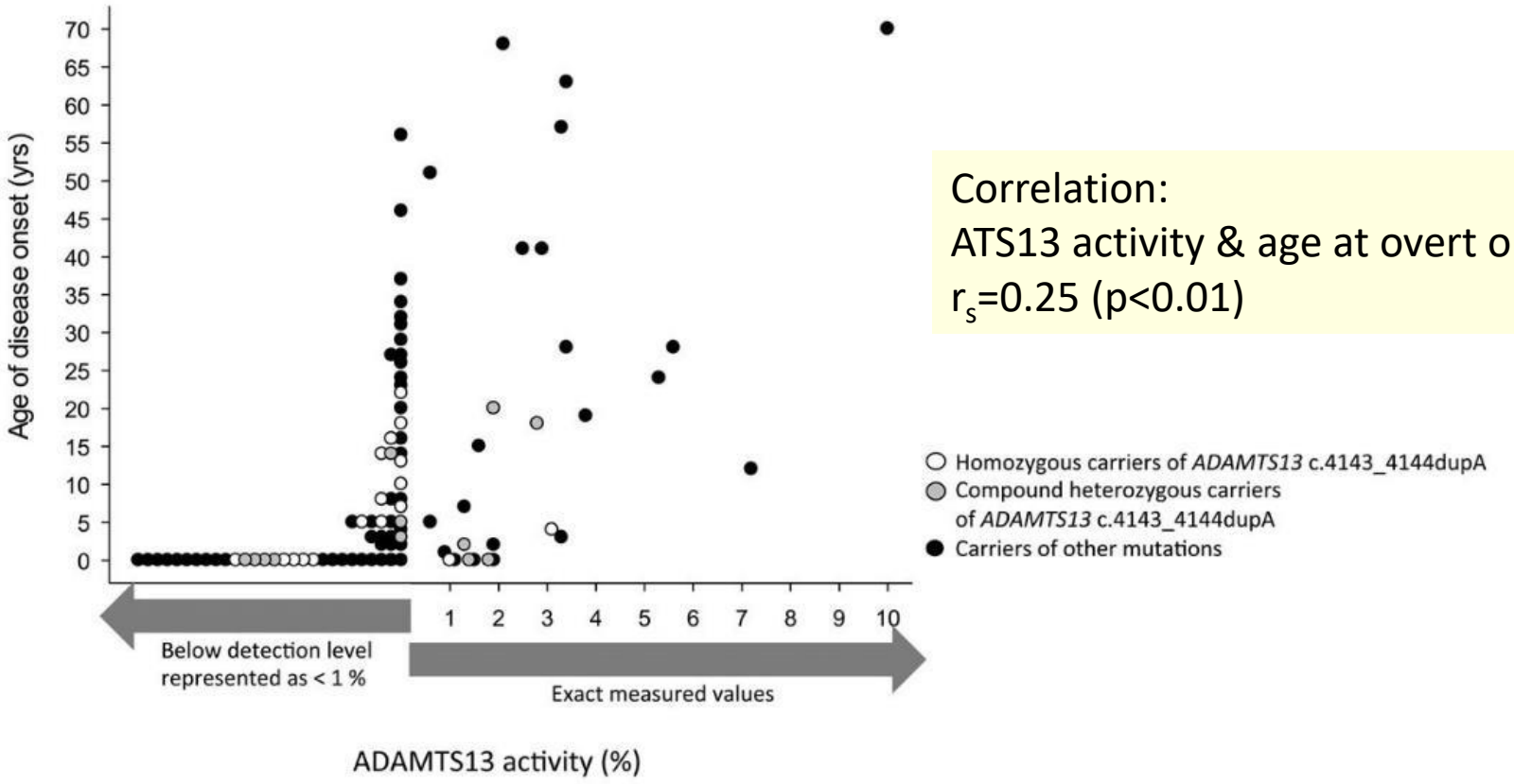
Diagnosis and arterial events in reported hTTP cases

	UK registry 2019 [1]	International registry 2019 [2]	Review of hTTP cases 2019 [3]
Patients (females, %)	73 (51; 79%)	123 (62;52%)	155 (89; 57%)
Age at diagnosis median (range)	24 y (newborn - 71 y)	17 y (newborn - 70 y)	15 y (newborn - 77 y)
First symptoms median (range)	18 y (newborn - 67 y)	5 y (newborn - 70 y)	11 months (newborn - 63 y)
TIA/stroke (n; %)	**18 (25%)**	**37 (31%)**	**40 (26%) 19 y (1 d - 77 y)**
Myocardial infarction	0 (0)	5 (4%)	5 (3%)
Death	5 (7%)	5 (4%)	13 (8%) 23 y (newborn - 79 y)

1.) Alwan F et al. Blood 2019;133:1644f
2.) van Dorland HA *et al*. Haematologica 2019;104:2107f
3.) Bogorovic & George. Blood Adv 2019;3;3973f

Residual ADAMTS13 activity and disease onset



Correlation:
ATS13 activity & age at overt onset:
r_s=0.25 ($p<0.01$)

van Dorland HA *et al*.
Haematologica 2019;104:2107ff

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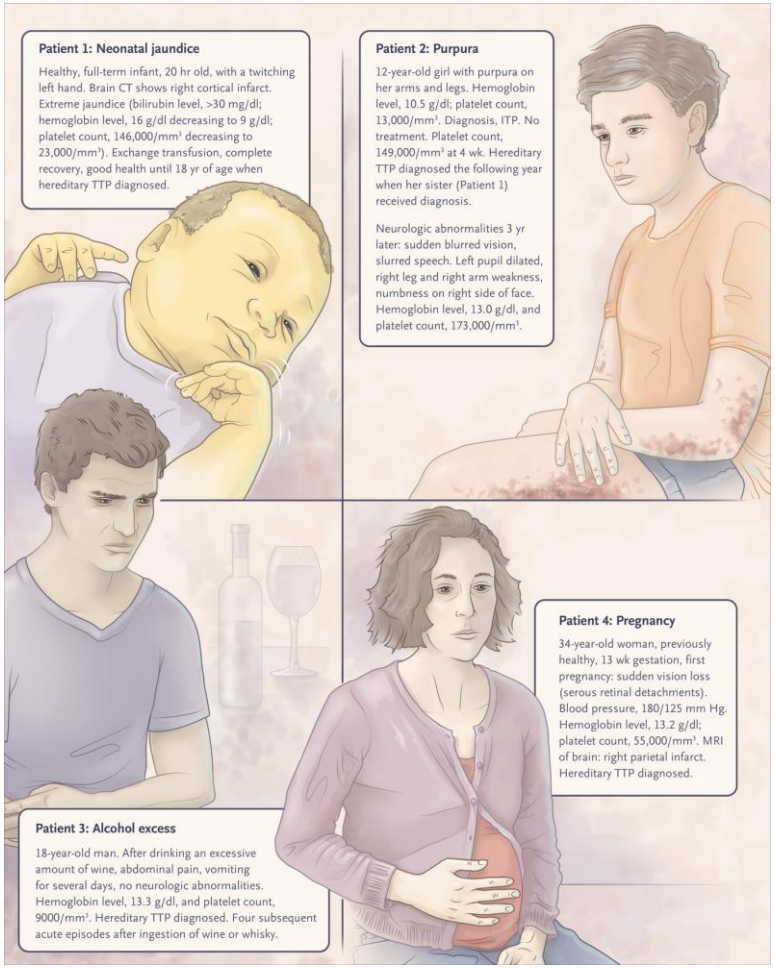
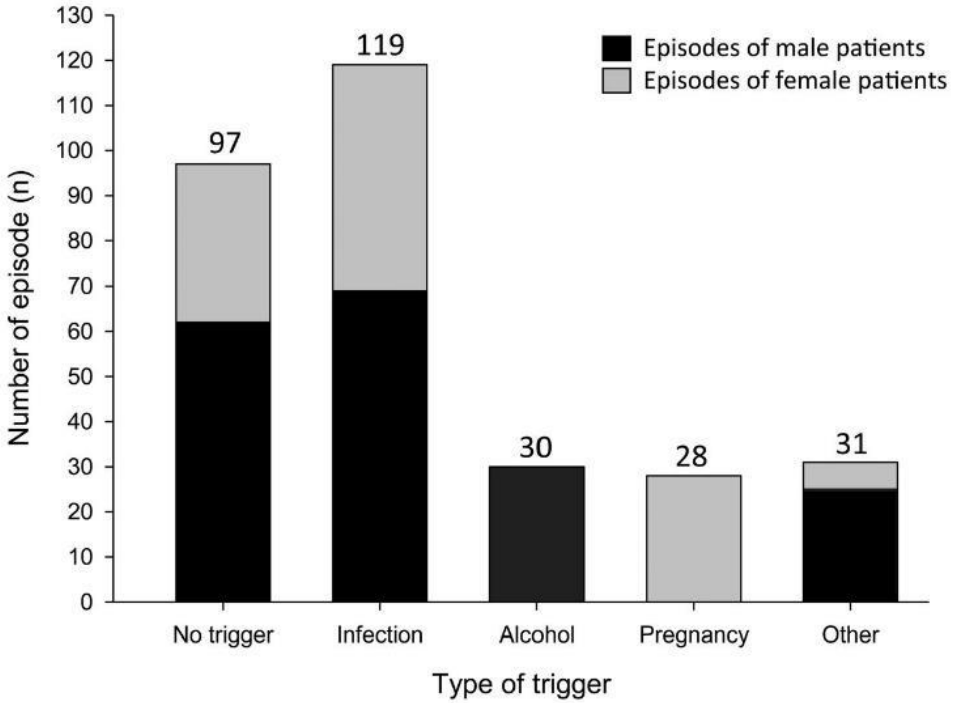
Circumstances of / risk periods for hTTP episodes





Kremer Hovinga JA & George JN. N Engl J Med 2019;381:1653-62

van Dorland HA *et al*. Haematologica 2019;104:2107ff

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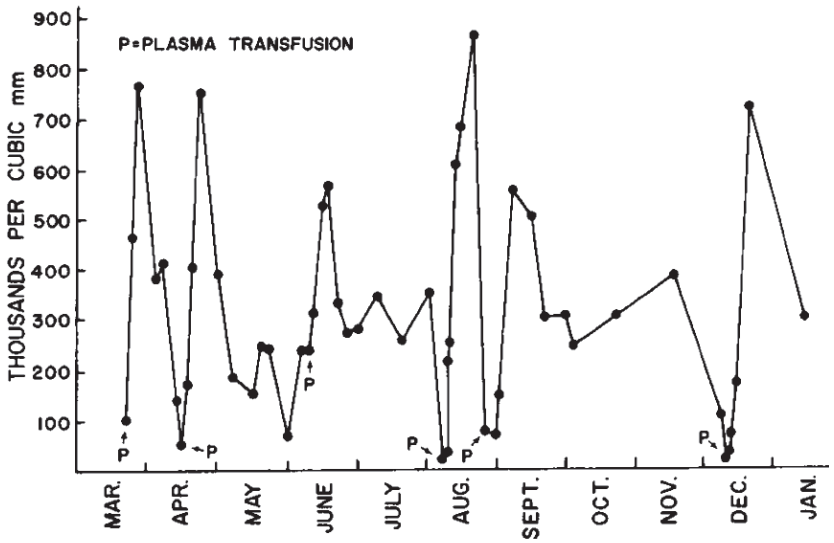
Upshaw's case

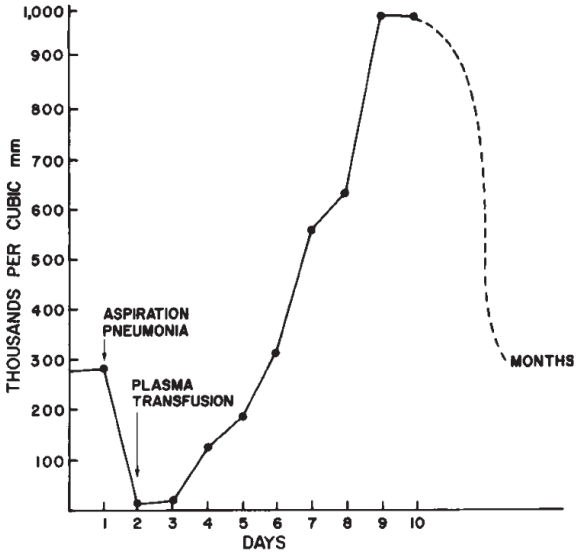
- 29y female; w. lobster hand; moved to US from Germany; there she had been diagnosed with ITP
- 0-12y: 6-10 episodes/y w. acute onset high fever; petechial rash; clinically diagnosed infection; laboratory: severe thrombocytopenia & anemia; schistocytes on blood smear
- After 12y: 3-4 episodes/y;
  between 1966-1977 total of 32 acute episodes documented
  - 5/32 spontaneous
  - 18/32 precipitating infection
  - 9/32 other precipitating factors (surgery; pregnancy;..)

Upshaw. NEJM 1978;298:1350f

Upshaw's case

- Splenectomy (aged 2y) and steroids – without effect;
- Plasma containing blood products:





Upshaw. NEJM 1978;298:1350f

Plenary Paper

blood

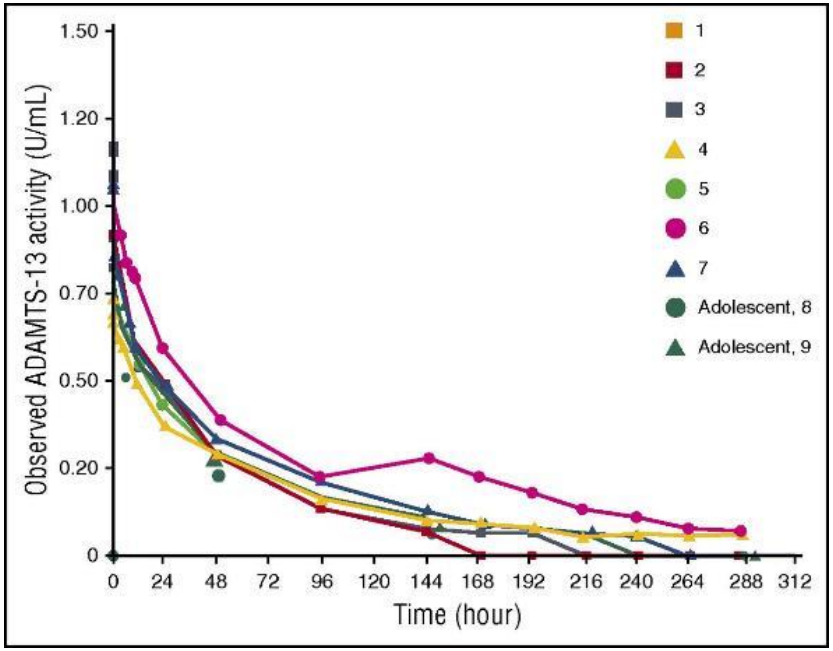
CLINICAL TRIALS AND OBSERVATIONS

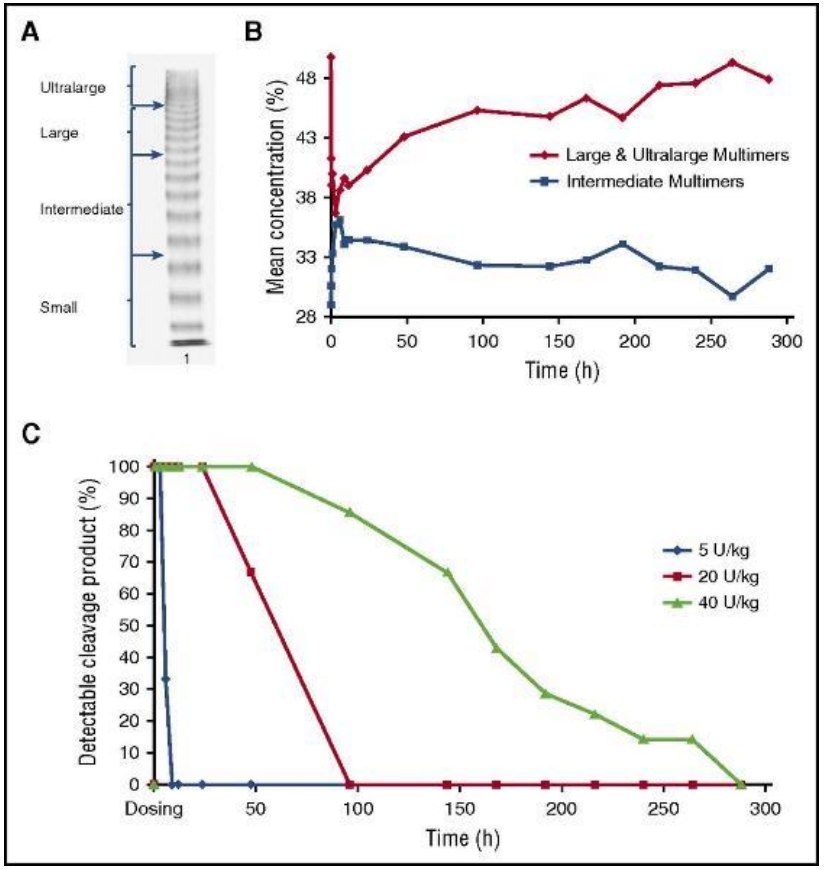
Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura

Marie Scully,[1] Paul Knöbl,[2] Karim Kentouche,[3] Lawrence Rice,[4] Jerzy Windyga,[5] Reinhard Schneppenheim,[6] Johanna A. Kremer Hovinga,[7] Michiko Kajiwara,[8] Yoshihiro Fujimura,[9] Caterina Maggiore,[10] Jennifer Doralt,[11] Christopher Hibbard,[12] Leah Martell,[12] and Bruce Ewenstein[12]

[1]Department of Haematology and Cardiometabolic BRC, University College London Hospitals/University College London, London, United Kingdom; [2]Division of Hematology and Hemostasis, Department of Medicine 1, Medical University of Vienna, Austria; [3]Jena University Hospital, Jena, Germany; [4]Department of Medicine, Houston Methodist Hospital, Weill Cornell Medical College, Houston, TX; [5]Department Disorders of Hemostasis and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [6]Department of Pediatric Hematology and Oncology, Universitaetsklinikum Hamburg-Eppendorf, Hamburg, Germany; [7]Inselspital, University Hospital Bern, Bern, Switzerland; [8]Tokyo Medical and Dental University Hospital Faculty of Medicine, Tokyo, Japan; [9]Nara Medical University, Nara, Japan; [10]Quintiles, Milan, Italy; [11]Shire, Vienna, Austria; and [12]Shire, Cambridge, MA

Blood 2017;130:2055-2063





rADAMTS13 terminal $t_{1/2}$ 59.2h (= 2.5 days) [1]

pdADAMTS13 2.1 – 3.3 days [2]
pdADAMTS13 2.1 – 3.5 days [3]

1.) Scully M *et al.* Blood 2017;130:2055f
2.) Furlan M *et al*. Thromb Haemost. 1999;81:8f
3.) Kovarova P *et al*. J Clin Apher 2019;34:13f

	UK registry 2019 [1]	International registry 2019 [2]
Patients (females, %)	73 (51; 79%)	123 (62;52%)
Age at diagnosis median (range)	24 y (newborn - 71 y)	17 y (newborn - 70 y)
Regular prophylactic plasma therapy (Children / Adults)	**67% (94% / 61%)**	**71%**
On Demand	12%	29%
Never had plasma therapy	21%	-
Treatment interval, median (range)	-	14 dy (2-21 dy)
Functional ADAMTS13 inhibitor	Not reported	0/114 tested
Anti-ADAMTS13 antibodies	Not reported	12/103 tested

1.) Alwan F et al. Blood 2019;133:1644f
2.) van Dorland HA *et al*. Haematologica 2019;104:2107f

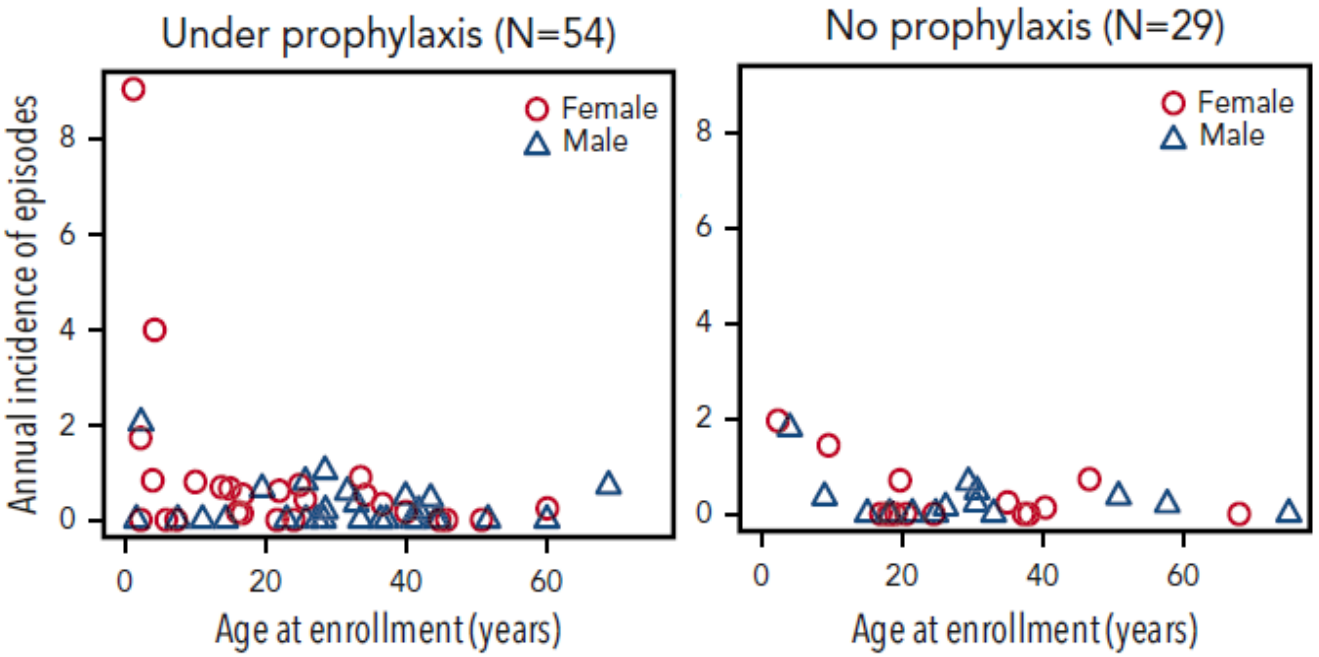
International hTTP Registry – Prospective follow-up

Characteristic	All patients		No TTP episodes during follow-up		Acute TTP episodes during follow-up		P*
	N	n (%) or median [min, lq, uq, max]	N	n (%) or median [min, lq, uq, max]	N	n (%) or median [min, lq, uq, max]	
Sex	87		44		43		.13
Male		46 (53%)		27 (61%)		19 (44%)	
Female		41 (47%)		17 (39%)		24 (56%)	
Consanguinity of parents	67	9 (13%)	32	6 (19%)	35	3 (8.6%)	.29
Family member is confirmed patient	87	13 (15%)	44	5 (11%)	43	8 (19%)	.38
Age, y, at							
Overt disease onset	77	4.6 [0.0, 0.0, 19, 70]	35	4.7 [0.0, 0.0, 20, 70]	42	3.6 [0.0, 0.0, 19, 68]	.80
Clinical diagnosis	85	18 [0.0, 4.2, 29, 70]	42	20 [0.0, 9.4, 33, 70]	43	15 [0.0, 3.5, 28, 68]	.12
Enrollment	87	26 [1.2, 16, 40, 75]	44	27 [1.7, 18, 44, 75]	43	26 [1.2, 14, 37, 69]	.33
The last follow-up	87	32 [2.1, 21, 46, 79]	44	31 [5.2, 22, 48, 79]	43	32 [2.1, 21, 42, 73]	.51
Treatment							
Prophylactic plasma infusions	83	47 (57%)	40	24 (60%)	43	23 (53%)	.66
Antiaggregation/anticoagulation	79	21 (27%)	37	12 (32%)	42	9 (21%)	.31
Antihypertensive medication	79	25 (32%)	37	14 (38%)	42	11 (26%)	.33

Tarasco E *et al*.
Blood 2021;137:3563f

International hTTP Registry – Prospective follow-up

- Prospective episodes & prophylaxis (n=87 hTTP patients)



131 acute hTTP episodes during follow-up

In 87 (66%) episodes trigger identified.
Triggers:

Clinical symptoms during / complications of acute episodes:

30%

23%

22%

7%

2%

Tarasco E *et al*.
Blood 2021;137:3563f

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International hTTP Registry – Prospective follow-up

Table 3. Incidence of documented acute episodes during follow-up according to sex, age at enrollment, and prophylactic plasma treatment

Variable	Patients with follow-up	Patients with any episode	Total prospective episodes	Total person-years	Annual incidence rate (95% CI)
Overall	87	43	131	371	0.35 (0.29-0.42)
Male sex	46	19	43	194	0.22 (0.16-0.30)
Female sex	41	24	88	177	0.50 (0.40-0.61)
Age at enrollment, y					
<10	15	9	51	43	1.18 (0.88-1.55)
10-20	16	8	27	78	0.35 (0.23-0.50)
20-30	18	8	21	75	0.28 (0.17-0.43)
30-40	15	9	17	65	0.26 (0.15-0.42)
>40	23	9	15	110	0.14 (0.08-0.23)
Prophylaxis*					
Yes	61	31	91	254	0.36 (0.29-0.44)
No	40	17	40	97	0.41 (0.30-0.56)

*For 4 patients with 21 person-years and 0 episodes, data on prophylaxis were not available; 18 patients had follow-up time with and without prophylaxis (5 with episodes).

Tarasco E *et al*.
Blood 2021;137:3563f

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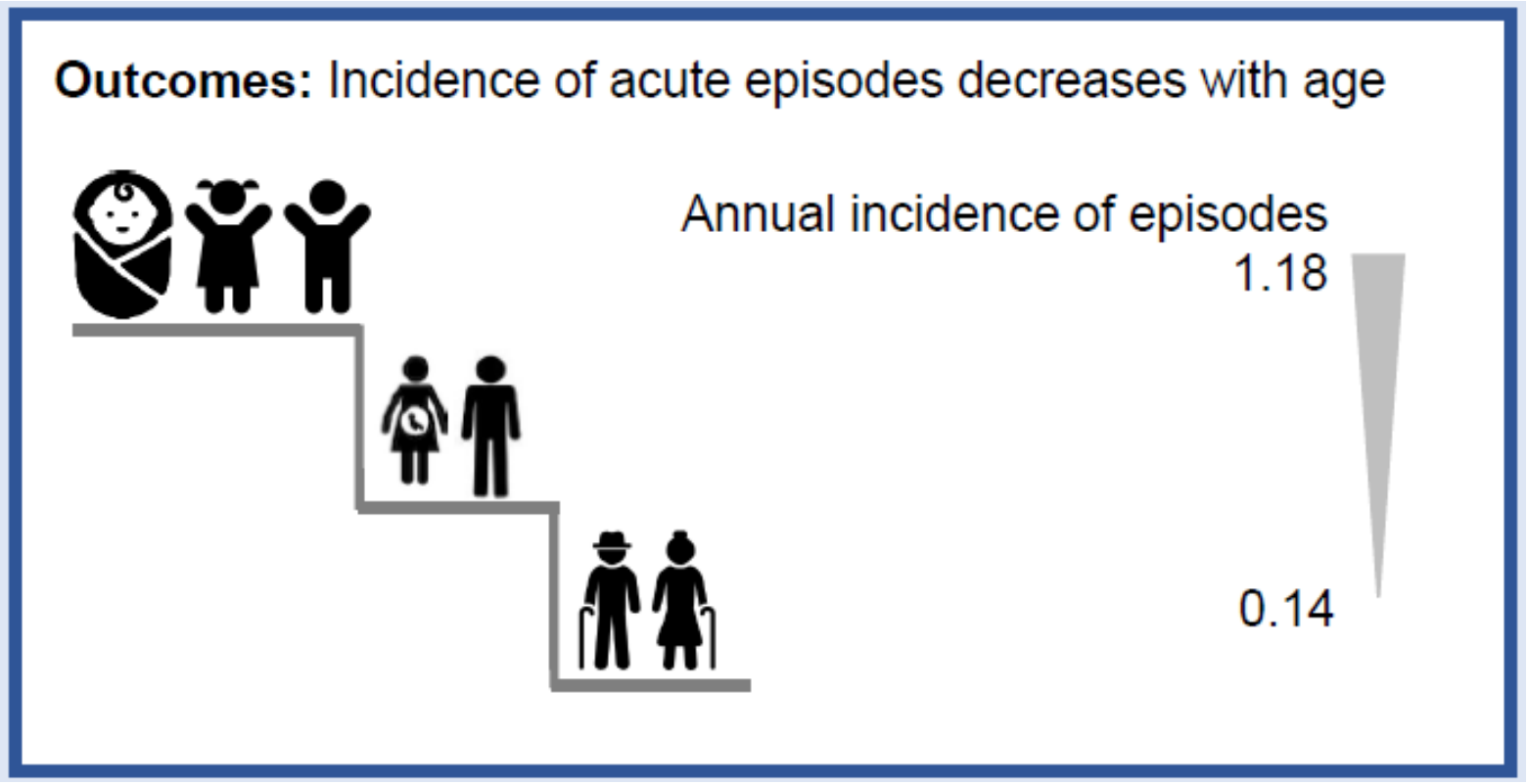
- hTTP is rare and likely underreported
- Episodes despite plasma prophylaxis
  - Situations of increased risk: Neonatal period, pregnancy
  - Prevention of acute episodes vs. of long-term sequels
  - Incidence of episodes in children > adults
- Inhibitor formation following exposure to plasma-derived ADAMTS13 seems low
- Residual ADAMTS13 activity only partially explains phenotype/severity
  (age at first disease manifestation; number of episodes; etc.)
  - Additional, so far unknown disease modifiers likely
- Phase 3 trial on rADAMTS13 under way – First data at ISTH / ASH ?

Highest benefit from prophylactic treatment



Tarasco E *et al*.
Blood 2021;137:3563f

The Hereditary TTP Registry Acknowledgement: Team Bern and International

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