Thrombotisch thrombozytopenische Purpura – erworben & angeboren

INSELSPITAL
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UNIVERSITÄT BERN

Universitätsklinik für Hämatologie & Hämatologisches Zentrallabor

GTH INTENSIV-KURS
Hamburg, November 2022

Intressenkonflikte

Employment	-
Research Support	Baxter/Takeda (“hereditary TTP registry” www.ttpregistry.net)
Advisory boards	Takeda – rADAMTS13 Ablynx/Sanofi – Caplacizumab
Consultancy	CSL Behring, NovoNordisk, Roche; Federal Bureau of Public Health (FOPH)
Speakers bureau	CSL Behring, NovoNordisk, Roche,
Major stockholder	-
Other 1	Off-label use of anti-CD20, anti-CD38; Cablivi w/o PEX
2	Interprofessional Hemophilia Care EHCCC Inselspital (Bayer, CSL Behring, NovoNordisk, Octapharma, Sobi, Roche)

Alle Gelder & Honorare gehen an den Arbeitgeber, die INSEL Gruppe AG

Agenda

1. TTP – iTTP vs. hTTP/cTTP
   - ❖ Definition, Pathophysiologie und Klinik
   - ❖ ADAMTS13 Bestimmungsmethoden
     - ❖ Ausblick
2. iTTP Therapie – 3 Säulen
   - ❖ Therapeutischer Plasma-Austausch (TPE)
   - ❖ Immunsuppression
   - ❖ Hemmung Interaktion VWF – Plättchen
     - ❖Ausblicke
3. hTTP

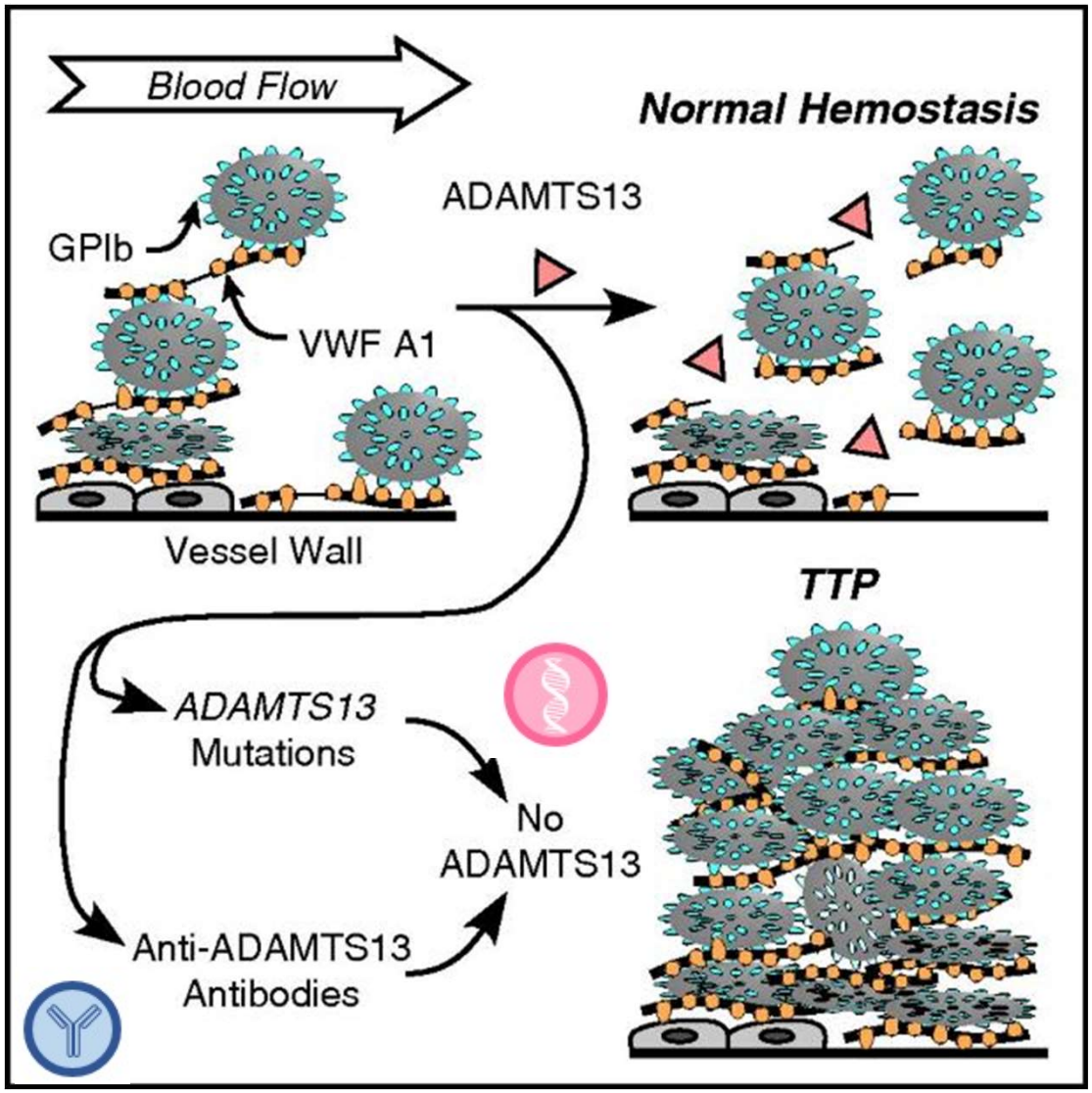
Pathophysiologie TTP

Von Willebrand Faktor (VWF)
- orange: VWF A1 Domain

Plättchen

GPIb = VWF Rezeptor auf Plättchen

ADAMTS13

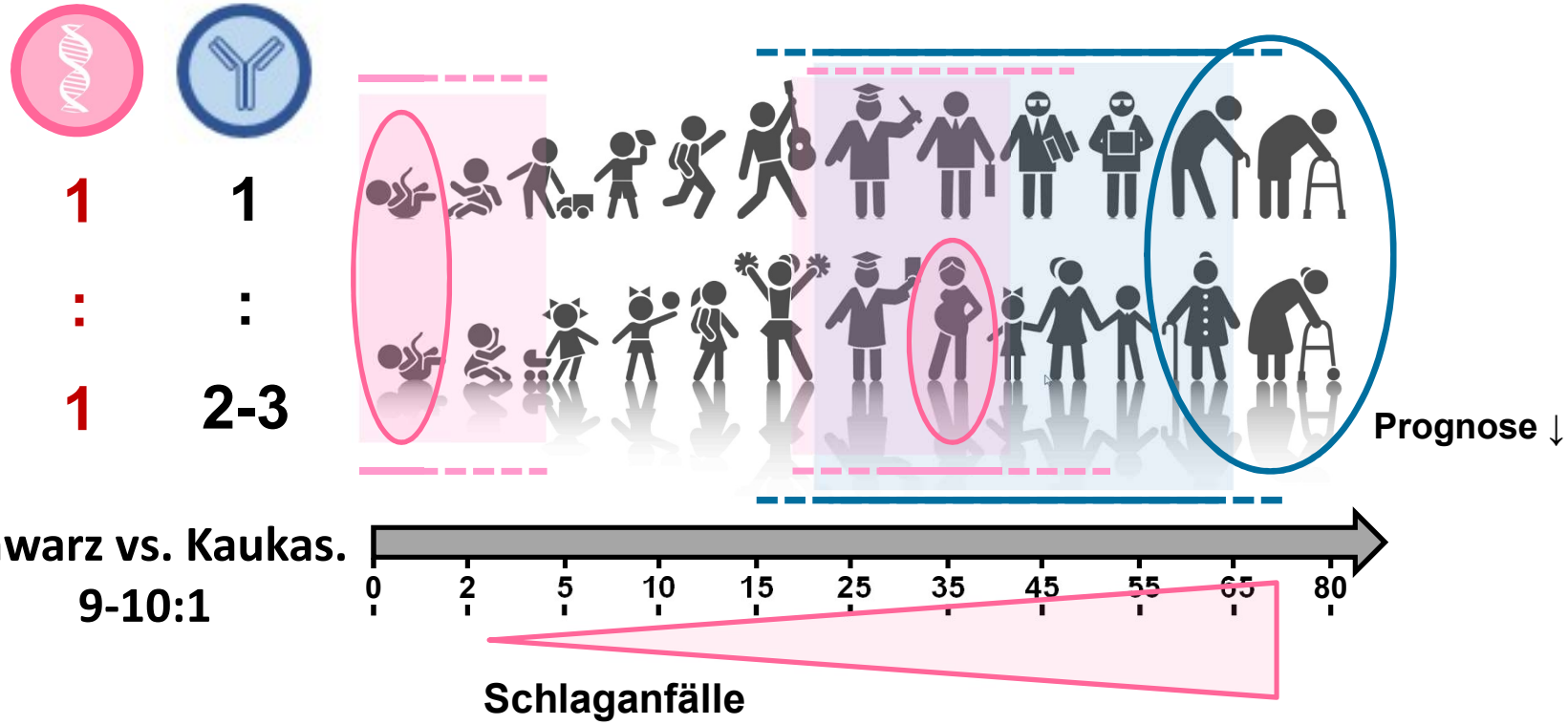


Sadler JE. Blood 2017;130:1811f

TTP Meilensteine

		Mortalität
1924	Moschcowitz – 1. TTP Fall in New York	100%
1947	**TTP** ≠ Idiopathische Thrombozytopenische Purpura	100%
1966	**TTP Pentade** (die 5 wichtigsten klinischen Symptome)	>90%
1977 & 1978	1. **Plasmaaustauschbehandlungen (TPE)** 1. **Plasmainfusionen (PI)**	~50%
1991	Canadian Apheresis Group Studie – TPE wird Standard	22%
1997	**ADAMTS13 <10%** bei akuter TTP; TPE **+ Steroide**	~10-15%
2001	ADAMTS13 Gen	
Ab 2003/4 2014	**Rituximab (Anti-CD20)** Rezidiv TTP → 1. Schub Prophylaktisch («präventiv»)	~5-10%
2019	**Caplacizumab**	<1-5%
2023 ??	**rADAMTS13 (TAK755/BAX930) (?)**	

Epidemiologie

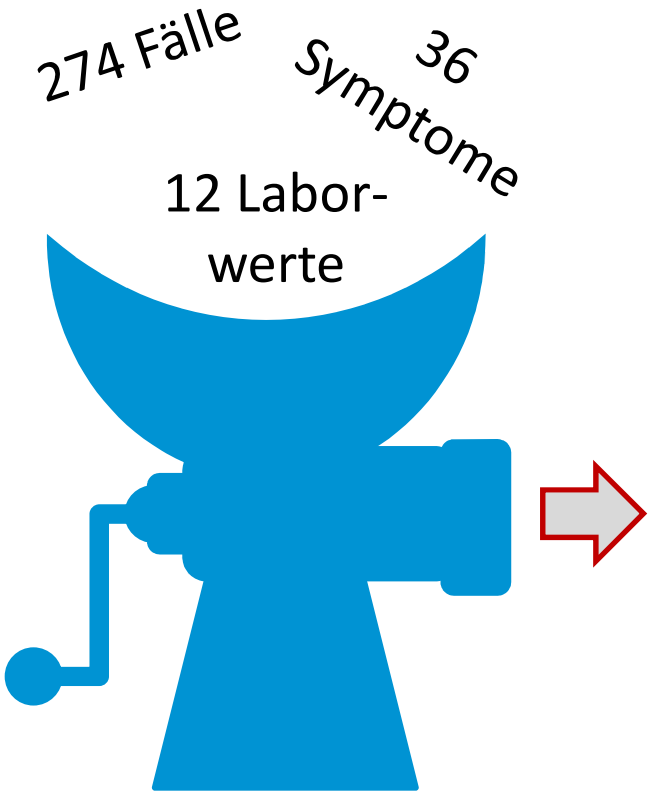


~2 Fälle/Million — INzidenz* — ~0.5-1 Fall/Million

~13-18 Fälle/Million — PräValenz

* Inzidenz = Neuerkrankungen; PräValenz = Vorkommen in der Bevölkerung.

Die “schwierige Diagnose”



	“MD”	Patient
Fieber	**98%**	20%
Purpura/Blutung		**44%**
Blässe/Anämie		17%
Neurologie		**60%**
Protein-/Hämaturie	**88%**	-

TTP PENTADE

Ikterus	42%	9%
AZ Verminderung*		**25%**
Übelkeit/Erbrechen		**24%**
Bauchschmerzen	13%	11%

Amorosi EL & Ultmann JE. Medicine 1966;45:139f

* Maiaise, Fatigue, Schwäche, etc.

Schwierige Diagnose - heute

- 35j Mann, bisher gesund
- Seit 2 Tagen mit Bauch- und Kopfschmerzen, bierbrauner Urin
- Notfallmässige Vorstellung: Temp. 37.5°, Neurostatus o.B., keine Hämatome oder Petechien
- Labor
  - Hb 86g/L; Plättchen 6x10e9/L; zahlreiche Fragmentozyten
  - Bilirubin & LDH erhöht; Haptoglobin nicht messbar
  - Kreatinin 1mg/dl (88µmol)
  - HIV negativ
  - ❖ keine Info zum INR oder MCV

Bhandari S & Kumar R. NEJM 2019;380;16:e23

Schwierige Diagnose - heute

The NEW ENGLAND JOURNAL of MEDICINE

Bhandari S & Kumar R. NEJM 2019;380;16:e23

Pentade (1966): 3/5 Punkte
FRENCH Score: 2/2 Punkte
PLASMIC Score: 5 (+1-2)/7 Punkte

✓ ADAMTS13 <1%

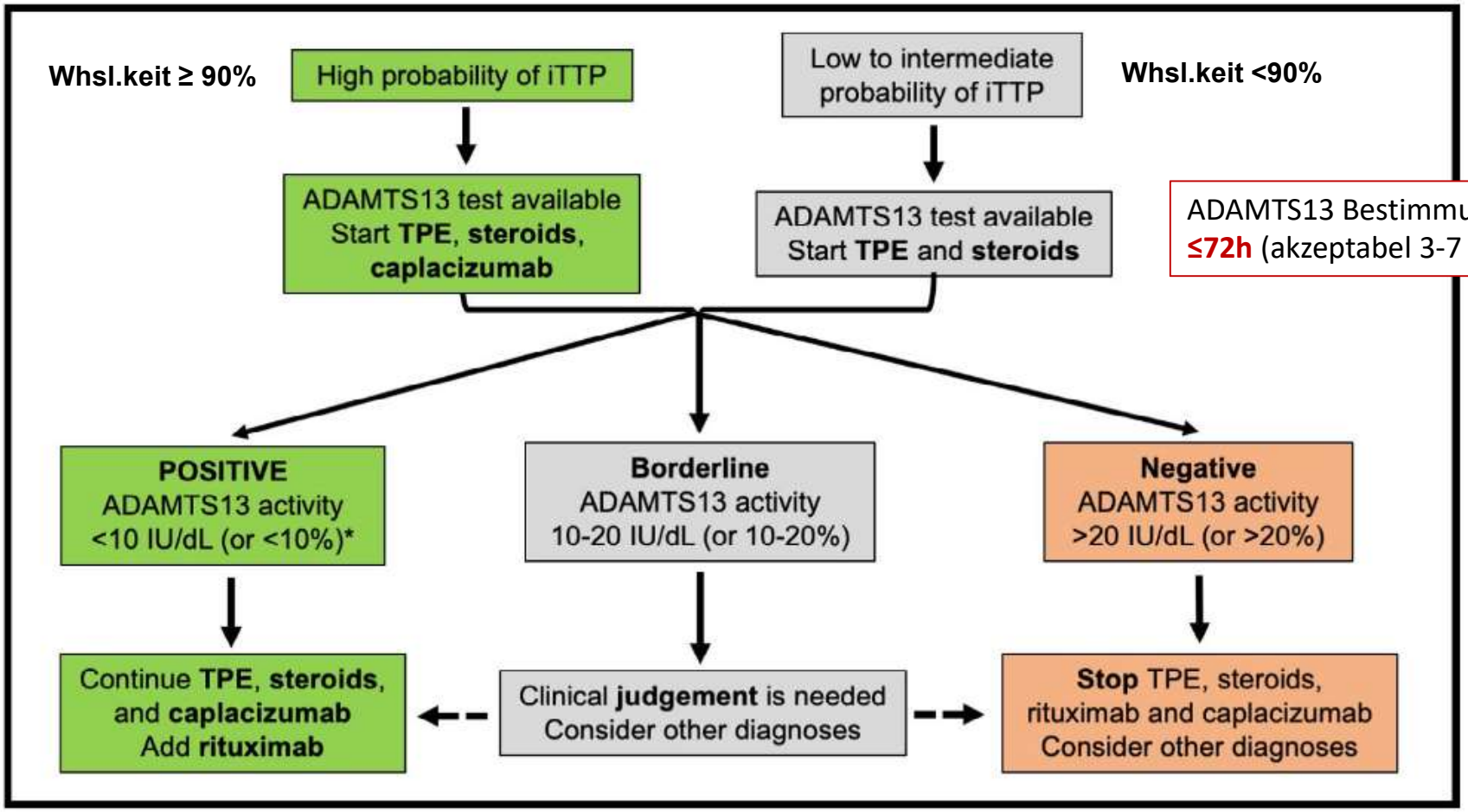
Zusätzliche Marker,
die auf eine TTP hinweisen:

✓ ↑ Troponin T (non-STEMI)
✓ ↑ Amylase, Lipase (Pankreatitis);
✓ etc.

Parameters	French Score	PLASMIC Score
Platelet count	<30 x 10^9/L (+1)	<30 x 10^9/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis Indirect bilirubin >2 mg/dL or reticulocyte count >2.5% or undetectable haptoglobin	[a]	+1
No active cancer in previous year	[a]	+1
No history of solid organ or SCT	[a]	+1
INR < 1.5	[a]	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2%	0-4: 0%-4%
	1: 70%	5: 5%-24%
	2: 94%	6-7: 62%-82%

Coppo P *et al.* PLoS One 2010;5:e10208f
Bendapudi PK *et al*. Lancet Haematol 2017;4:e157f
Zheng XL *et al*. JTH 2020;18:2486f

ISTH TTP Guidelines 2020



ADAMTS13 Bestimmung
≤72h (akzeptabel 3-7 Tage)

*Caplacizumab
nur wenn ADAMTS13 Bestimmung mgl.

Zheng XL *et al*. JTH 2020;18:2486 ff – ISTH Diagnosis Guideline 2020
Zheng XL *et al*. JTH 2021;19:1864 ff – Review

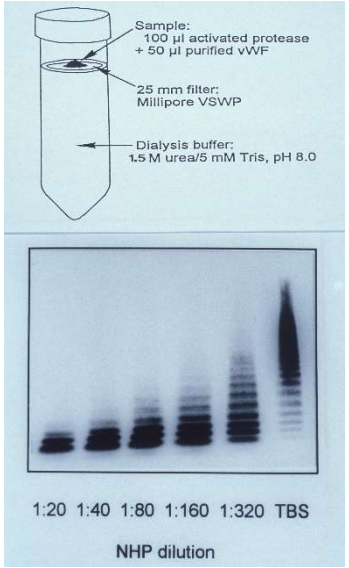
ADAMTS13 Assays – “Key points”

TAT*

1. und 2. Generationsteste:
Substrat: «full-length» VWF

3.5-4 Tage
- VWF-MM oder SDA-PAGE d. abgebauten VWF

1-2 Tage
- IRMA
- Residuelle VWF Funktion (CBA/Rco)
- WB d. gespaltenen VWF A1-A3 Fragment



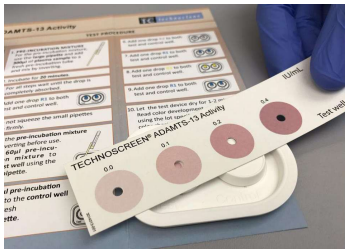
3. Generationsteste:
Substrate: VWF A2 Peptide

~1 Tage
- ELISA d. gespaltenen VWF73 (A2)
- SELDI-TOF VWF73

1-2 Std.
- **FRETS-VWF73** & VWF77 (in house & kommerziell: Technoclone; Immucor)
- ALEXA488VWF86 (in house & kommerziell: Sekisui)

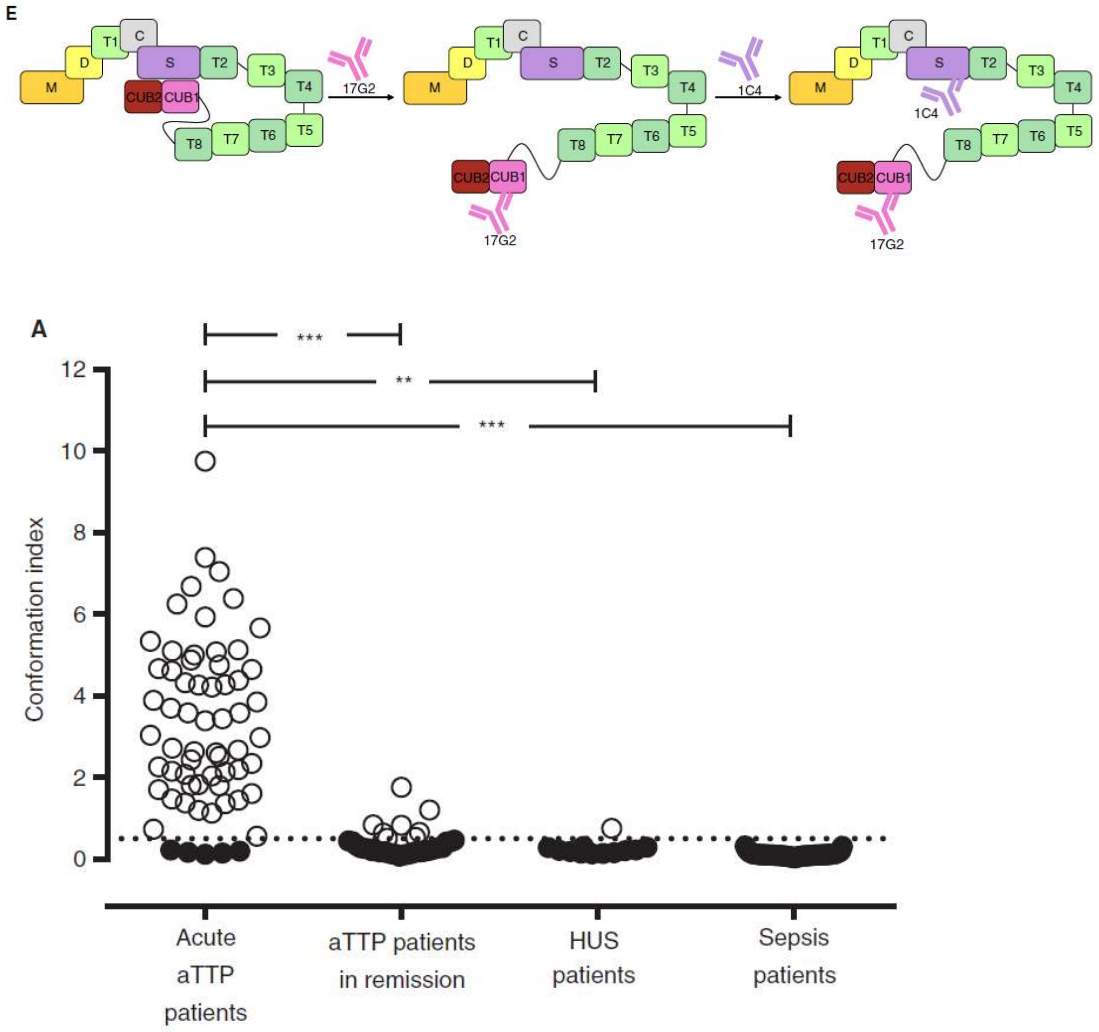
4. Generationsteste:

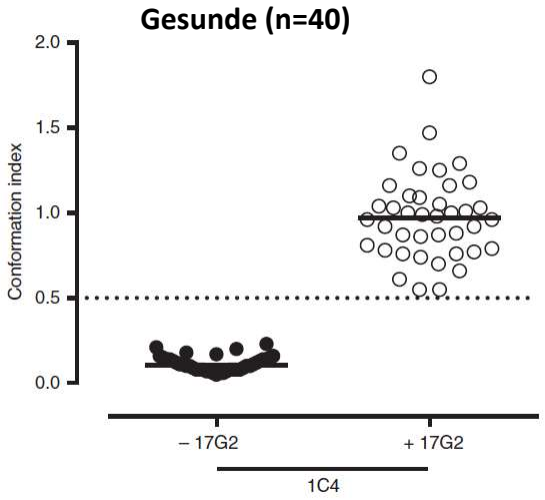
≤1 Std.
- «Schnellteste» (i.e. CLIA WERFEN HemosIL)
- POCT* (TECHNOSCREEN)



*POCT = Point of Care Test; TAT = Turn around time

ADAMTS13 Methoden – “Ausblick”

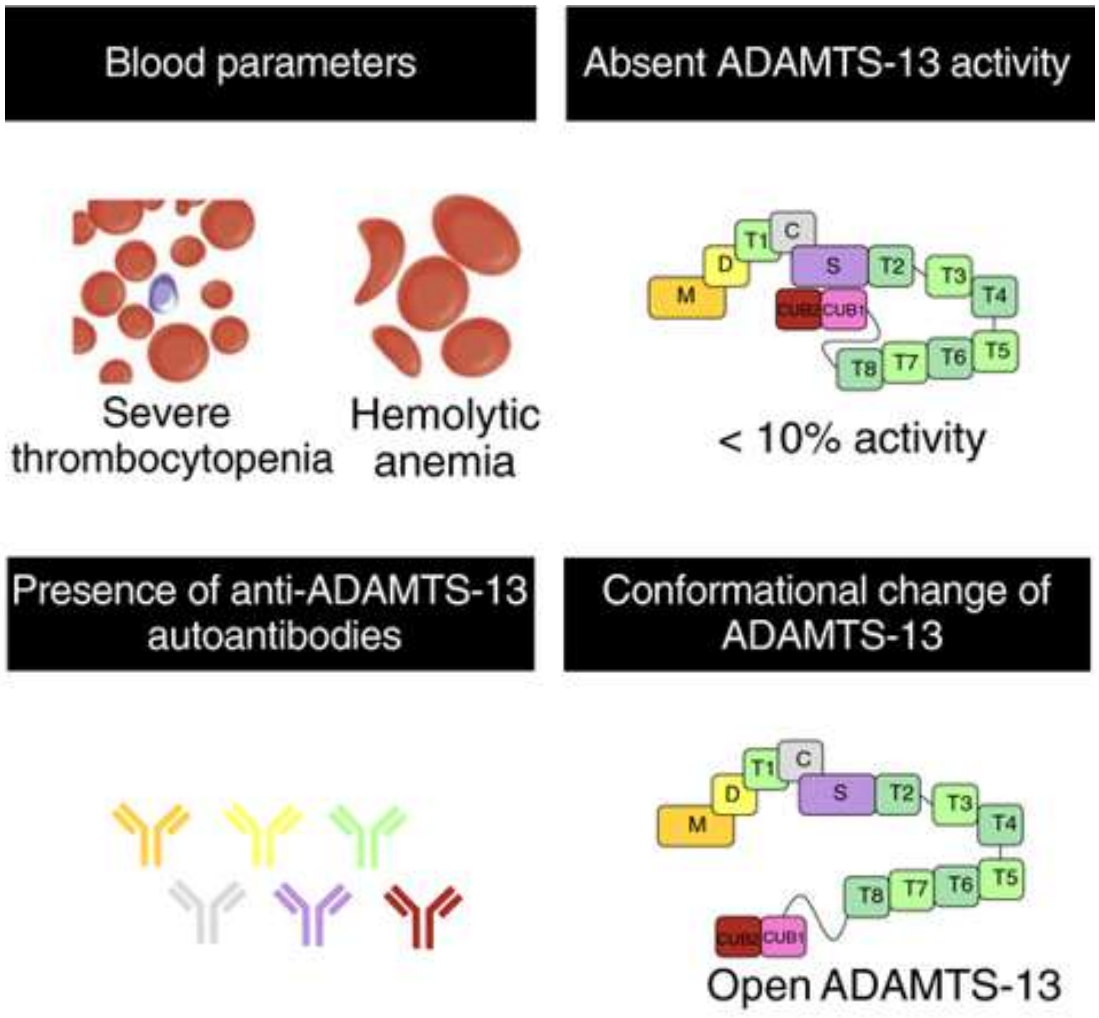




ADAMTS13 Antigen-Bestimmungsmethode: Offene vs. geschlossene ADAMTS13 Konformation

Roose E *et al*. J Thromb Haemost 2018;16:378f

ADAMTS13 Methoden – “Ausblick”



iTTP =
4 Biomarker

- ✓ **Akut**
- ✓ **«Subclinical» iTTP**
- ○ **Drohendes Rezidiv (?)**

Roose E *et al*. J T H 2018;16:378f
Roose E *et al.* T & H 2018;118:1729f
Roose E *et al.* Blood 2020;136:353f
De Waele L *et al*. Blood Adv 2021;5:4480f

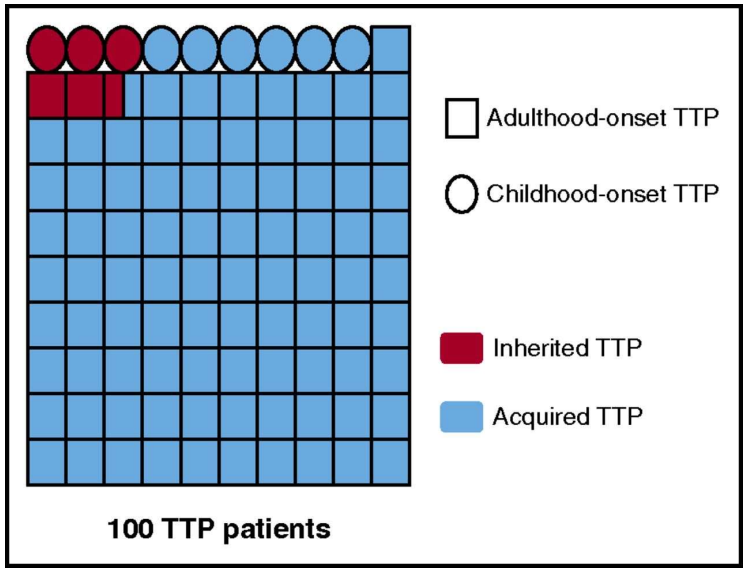
Roose E *et al*. J Thromb Haemost 2018;16:378f

ADAMTS13 <10% und klinischer Kontext

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

TTP Therapie: iTTP = 3 Säulen / hTTP

1	2	3
Ersatz von ADAMTS13	Immun-Suppression	“TARGET” on VWF
Plasma-Austausch (TPE)	Glukokortikoide	Caplacizumab
Plasma-Infusion	Anti-CD20 (rituximab, ofatumumab, obinutuzumab)	N-Acetylcystein
rADAMTS13	Bortezomib Cyclophosphamid Cyclosporin A	
	(Splenektomie)	
	Anti-CD38	

COMPARISON OF PLASMA EXCHANGE WITH PLASMA INFUSION IN THE TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

GAIL A. ROCK, PH.D., M.D., KENNETH H. SHUMAK, M.D., NOEL A. BUSKARD, M.D., VICTOR S. BLANCHETTE, M.D., JOHN G. KELTON, M.D., RAMA C. NAIR, PH.D., ROBERT A. SPASOFF, M.D., AND THE CANADIAN APHERESIS STUDY GROUP*

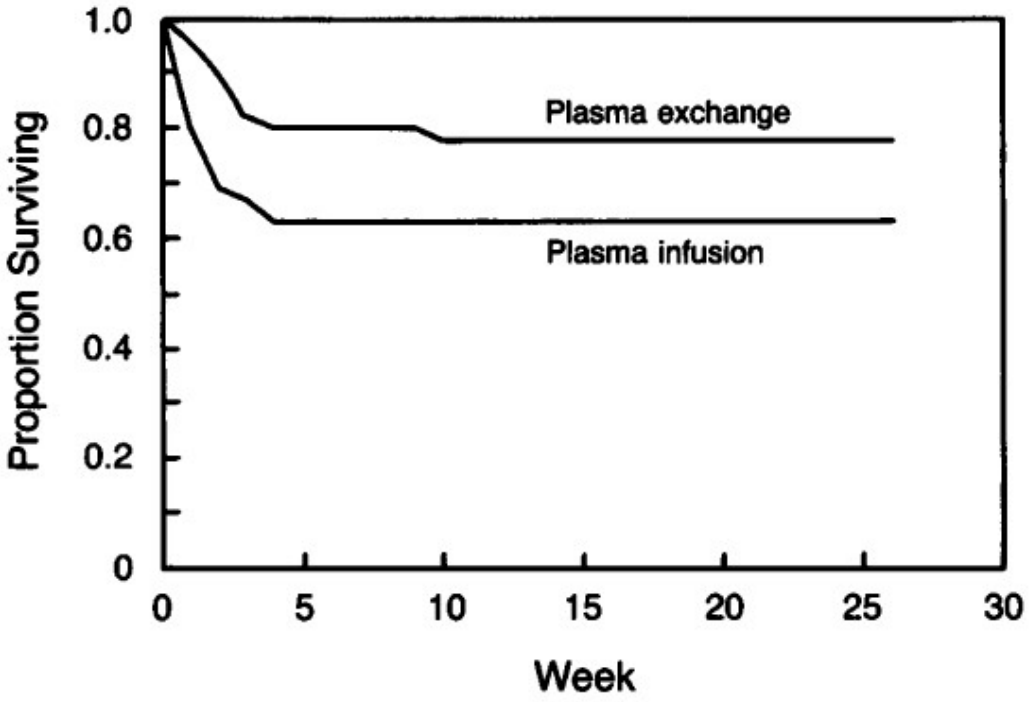


Figure 1. Survival of Patients with Thrombotic Thrombocytopenic Purpura.

Ansprechrate (Überleben)
TPE 78%

«Heute»:
TPE &
Steroide ~90%

p=0.036

Rock GA *et al*. NEJM 1991; 325:393ff

II. Rituximab

iTTP (ATS13 <10%) PEX kein Rituximab - Rezidivrate

- nach 1J = 24 %
- nach 7J = 41 %

Kremer Hovinga JA & Vesely SK *et al*. Blood 2010; 115:1500ff

Table 1
Reports involving 10 or more patients treated with rituximab in the acute phase of autoimmune TTP.

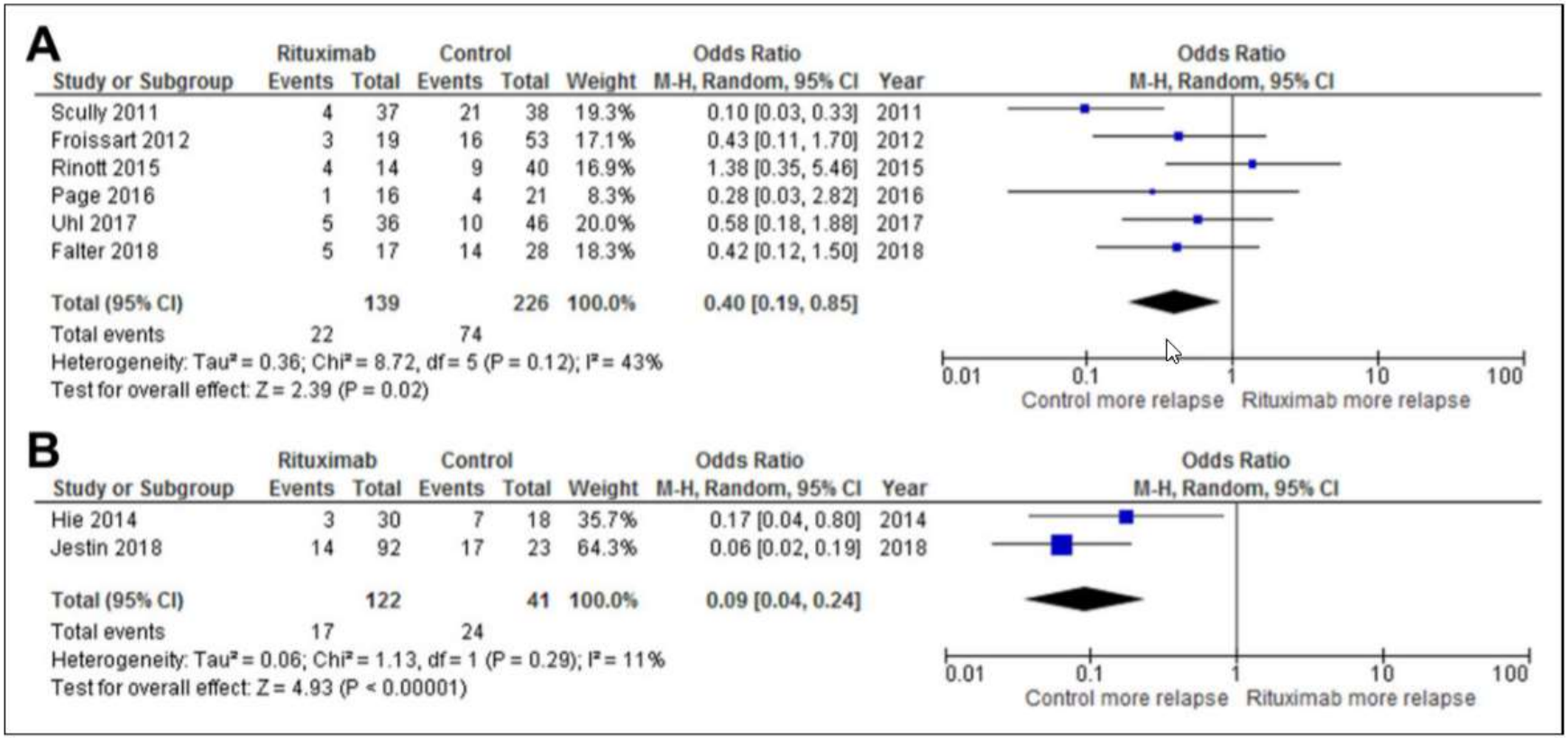
Series (year)	N	Age (yr) median (range)	% F	% R	Number of rituximab infusions, median (range)	CR (%)	Days to CR median (range)
Scully et al. (2007) [9]	25	43 (17–67)	76	44	4 (2–8)	100	11
Jasti et al. (2008) [5]	12	43 (19–59)	83	8	(1–13)	83	18 (14–41)
Ling et al. (2009) [6]	13	42 (23–71)	69	54	NA	92	NA
de la Rubia et al. (2010) [7]	24	(24–72)	71	42	4 (1–8)	87.5	14 (7–35)
Scully et al. (2011) [12]	40	42 (21–76)	65	15	4 (2–8)	82.5	12
Froissart et al. (2012) [10]	22	36.8 ± 11	67	14	4	82	12 ± 6.7
Page et al. (2016) [8]	16	41 (20–79)	75	0	4 (1–4)	100	21 (5–76)[a]
Benhamou et al. (2016) [11]	24	39.3 (30–47)	75	12.5	2 (14 patients) or 3 (10 patients)	95	14 (IQR, 12–22)[a]

Series (year)	Clinical relapse (%)	Time to relapse median (range)	Clinical RFS[b] median (range)	Serious adverse events
Scully et al. (2007) [9]	0	/	10 (1–33)	1 fatal pneumonia, 1 morbilliform rash
Jasti et al. (2008) [5]	8	23 months	48.5 (1–79)	1 VZV transverse myelitis and encephalitis
Ling et al. (2009) [6]	0	/	24 (13–84)	0
de la Rubia et al. (2010) [7]	12.5	29 months (7–29)	30 (7.5–64)	0
Scully et al. (2011) [12]	10	27 months (17–31)	≥ 12	0
Froissart et al. (2012) [10]	14	24 months (20–36)	33 ± 17.4	0
Page et al. (2016) [8]	12.5[c]	2.5 and 9.9 years	–	0
Benhamou et al. (2016) [11]	5[d]	/	–	0

N: number of patients, F: female, R: relapsing patients, CR: complete remission, NA: data not available, yr: year.
[a] Days from first to last TPE. IQR: interquartile range.
[b] Provided in months. RFS: relapse-free survival, VZV: varicella zoster virus.
[c] Two relapses.
[d] One relapse.

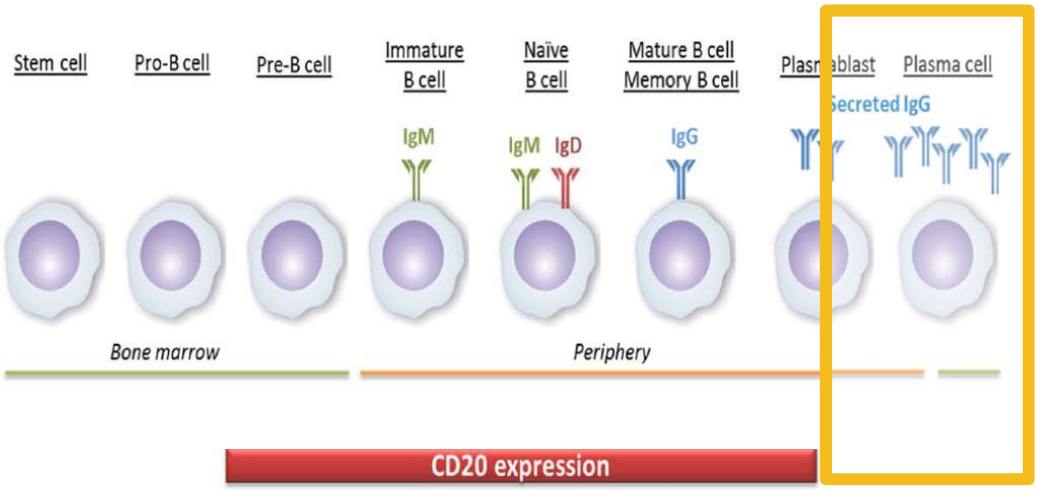
Coppo P *et al*. Transfus Apher Sci. 2017;56:52-56

II. Rituximab

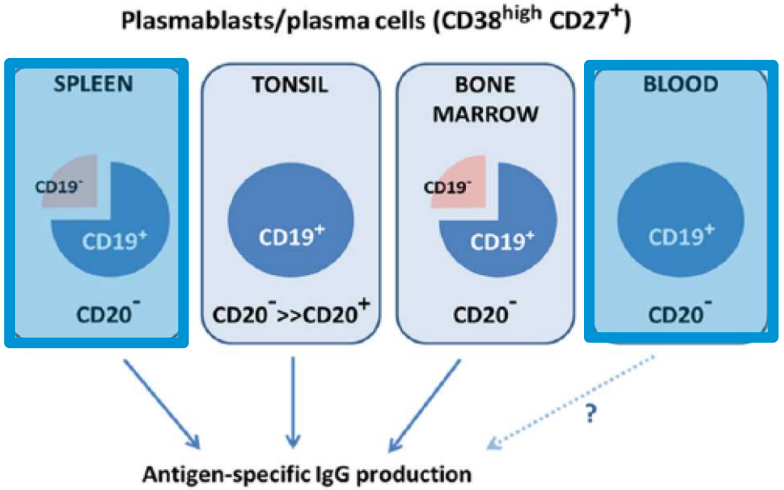


A – akute Episoden
B – präventiv

II. “Langfristiges Problem” αCD20 Therapie



ANTI-CD20=
Rituximab, Ofatumumab, Obinutuzumab



=> Anti-ADAMTS13 spezif. PB/PC

- Splenektomie ?

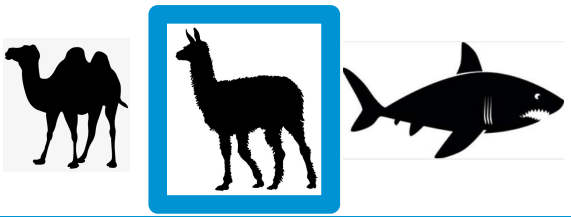
Kremer Hovinga JA, *et al*. Haematologica 2004;89:320f
Kappers-Kluinne MC, *et al*. B J H 2005;130:768f
Schaller M, *et al*. Blood 2014;124:3469f

- Anti-CD38 ?

Van den Berg J, *et al*. Blood Adv 2022; 6:993f

Nach Forsthuber TG *et al. Ther Adv Neurol Disord* 2018;11:1f

III. Caplacizumab



Phase 2 RCT f. Pat. mit erworbener TTP (n=75)

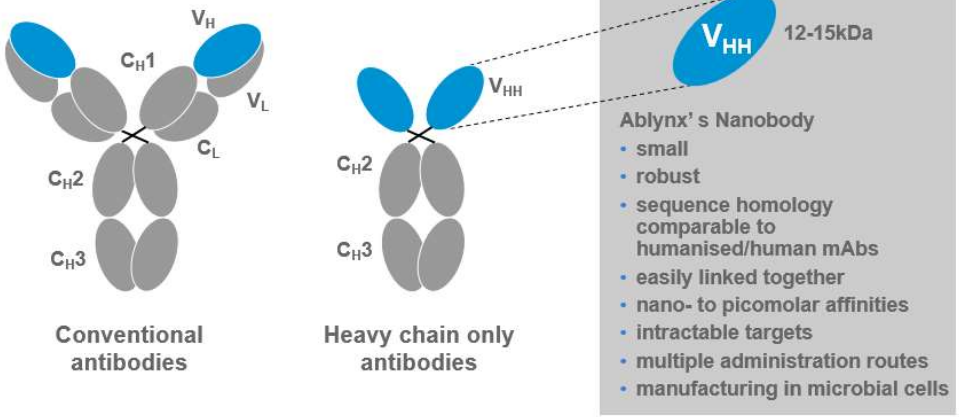
TITAN Studie

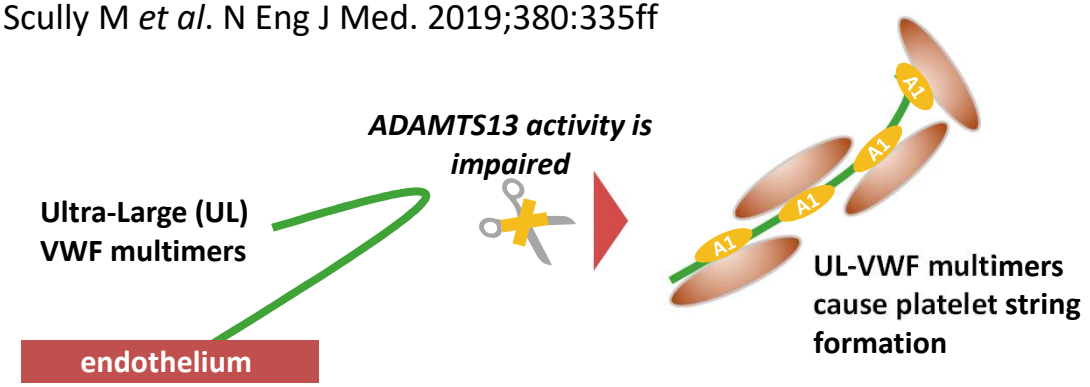
Peyvandi F *et al*. N Engl J Med 2016; 374:511ff

Phase 3 RCT f. Pat. mit erworbener TTP (n=145)

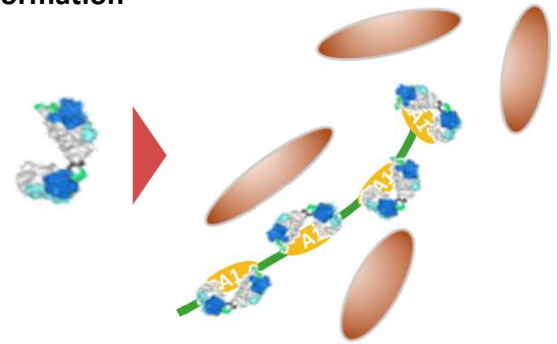
HERCULES Studie

Scully M *et al*. N Eng J Med. 2019;380:335ff





Caplacizumab binds to VWF A1 domain and inhibits platelet string formation



Caplacizumab blockiert die Bindung von Thrombozyten an den VWF - sofortiger Effekt auf die Mikrothrombenbildung

III. Caplacizumab – TITAN & HERCULES

Efficacy end points	Caplacizumab (n = 108)	Placebo (n = 112)	P
Proportion of participants with ≥1 of the events below while receiving blinded study drug treatment	14 (13.0)	53 (47.3)	<.001
TTP-related death	0 (0.0)	4 (3.6)	
Major thromboembolic event*	8 (7.4)	14 (12.5)	
TTP exacerbation	6 (5.6)	39 (34.8)	
TTP recurrences†			
TTP exacerbation during blinded treatment period	6 (5.6)	39 (34.8)	<.001
TTP relapses during treatment-free follow-up period	14 (13.0)	0 (0.0)	n/s
TTP exacerbation or relapse during overall study	19 (17.6)	39 (34.8)	.0040
Refractory to treatment‡	0 (0.0)	8 (7.1)	<.01
Mortality rate			
During the blinded treatment periods	0 (0.0)	4 (3.6)	.0477
During the overall study period	1 (0.9)§	5 (4.5)§	n/s

Weitere „2nd“ Endpunkte:
↓ 38% TPE Sitzungen
↓ 41% Plasmavolumen
↓ 65% Intensiv Tage
↓ 31% Spital Tage

Peyvandi F *et al*. Blood Adv 2021;5:2137f - Integrated data

III. Caplacizumab – Nebenwirkungen

Preferred term	Overall			
	Caplacizumab (n = 106)		Placebo (n = 110)	
	n (%)	No. of events	n (%)	No. of events
At least 1 TEAE	102 (96.2)	790	105 (95.5)	897
At least 1 serious TEAE	31 (29.2)	44	54 (49.1)	72
Any bleeding TEAE excluding TTP*	62 (58.5)	157	47 (42.7)	94
Any serious bleeding TEAE excluding TTP	12 (11.3)	15	2 (1.8)	2
Epistaxis	4 (3.8)	4	0	0
Subarachnoid hemorrhage	2 (1.9)	2	0	0
Gingival bleeding	1 (0.9)	1	0	0
Gastric ulcer hemorrhage	1 (0.9)	1	0	0
Hematemesis	1 (0.9)	1	0	0
Upper gastrointestinal hemorrhage	1 (0.9)	1	0	0
Retinal hemorrhage	1 (0.9)	1	0	0
Metrorrhagia	1 (0.9)	2	0	0
Mennorrhagia	1 (0.9)	1	0	0
Hemorrhagic ovarian cyst	1 (0.9)	1	0	0
Cerebral hemorrhage	0	0	1 (0.9)	1
Hemorrhagic transformation Stroke	0	0	1 (0.9)	1

Participants may have had more than 1 adverse event (AE) per preferred term. An individual was counted only once if he or she experienced 1 or more AE.
*A bleeding TEAE was defined as a Standardized MedDRA Query bleeding TEAE (excluding TTP events), with an onset date on or after the first dose of study medication.

Unerwünschte Arzneimittelwirkung 1

~ VWD Typ 2M –

v.a. muco-kutane Blutungen

i.R. mild-moderat; selten schwer

Unerwünschte Arzneimittelwirkung 2

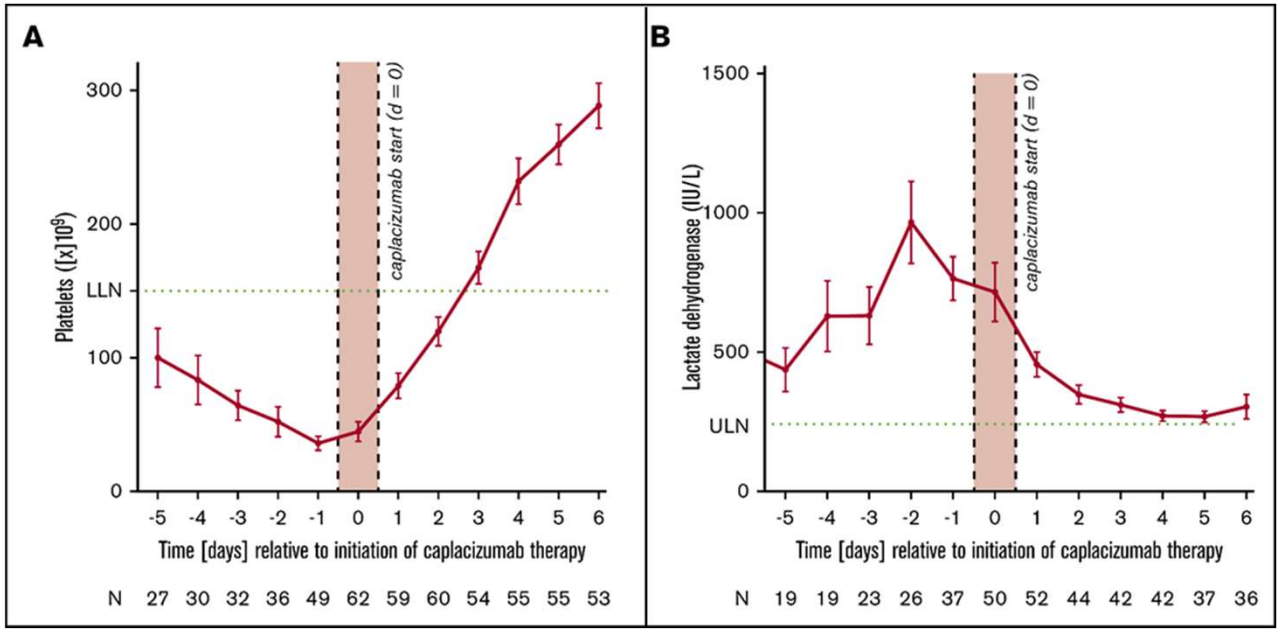
Peyvandi F *et al.* Blood Adv 2021;5:2137f - Integrated data

Kaufeld J *et al*. Ann Hematol 2021;100:3051f

III. Caplacizumab – REAL WORLD D

29 Zentren in Deutschland – **60 Pat.** (06/2018 – 12/2019)

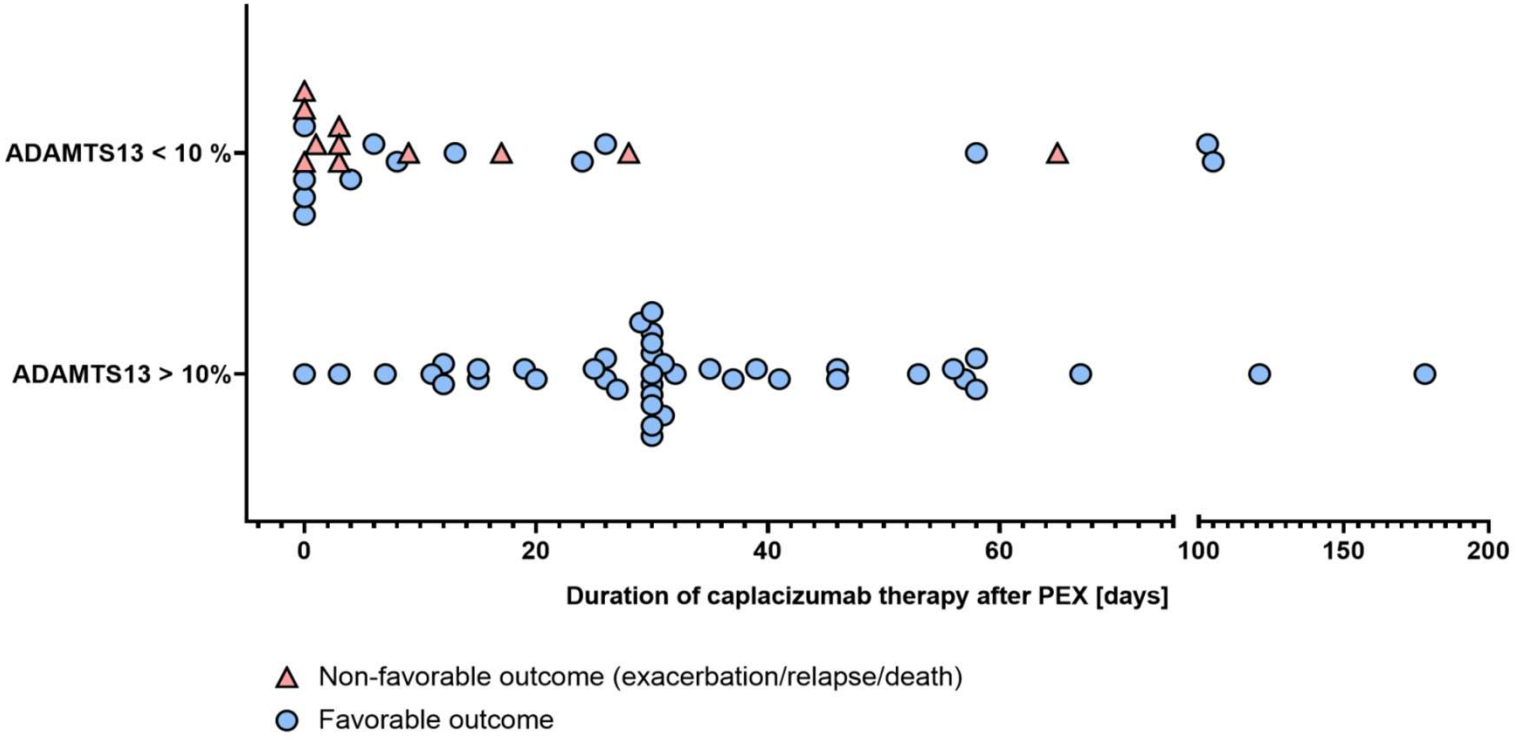
- 46/60 (76.7%) erster iTTP Schub
- 8/60 (13.3%) analog HERCULES, 52/60 «freies» Protokoll.
- Caplacizumab: 35/60 «Front-Line»; 25/60 «Rescue»



Caplacizumab
Median ab Tag 3

Plättchen >150G/L
Median am Tag 3
nach Start Capla

III. Caplacizumab – REAL WORLD D

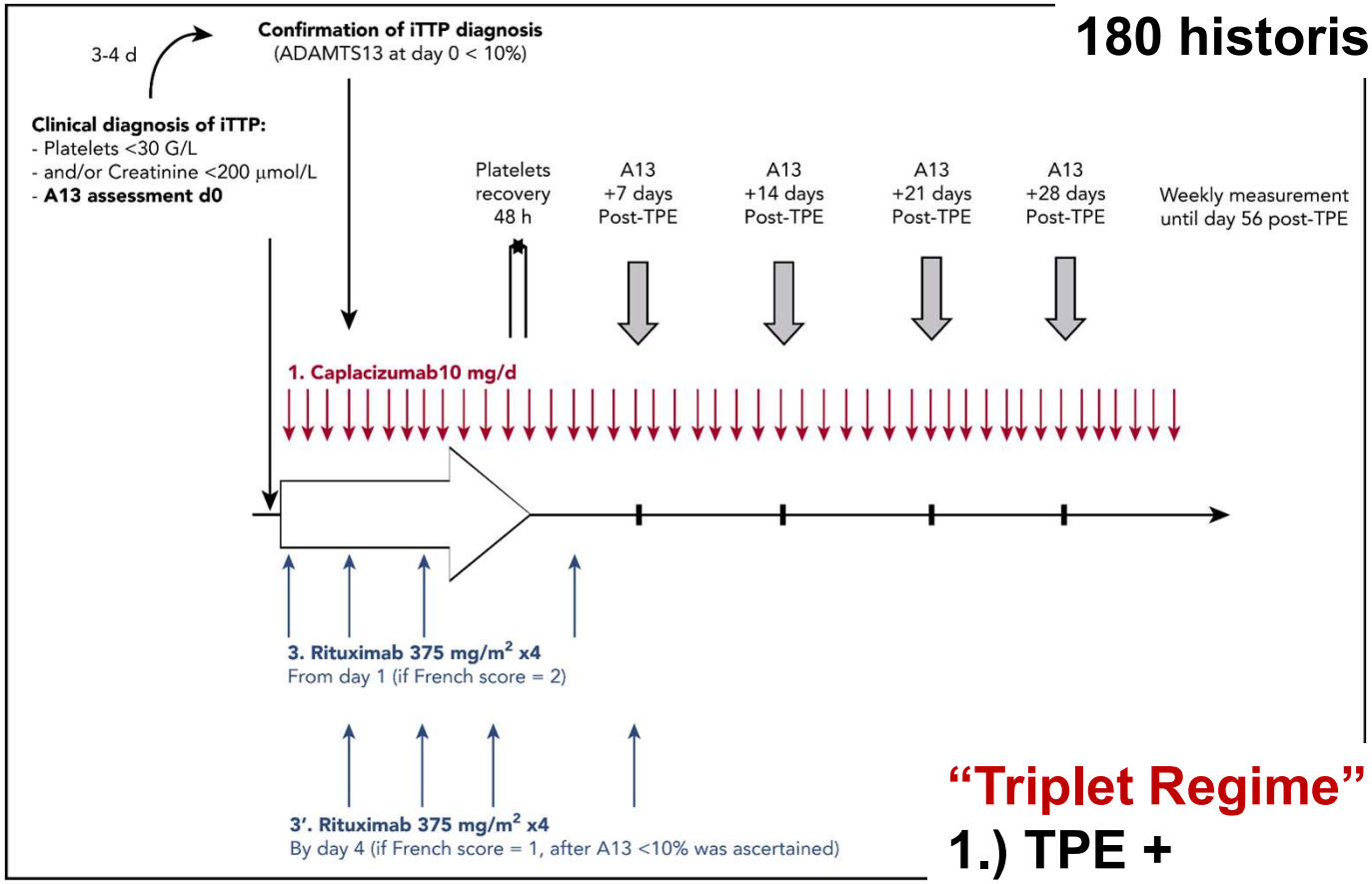


ADAMTS13 zum Zeitpunkt Stopp Caplacizumab:

- <10% : 11/34 Pat. mit Rezidiv/Exazerbation; 91% innerhalb der erste 28 Tage
- >10% : **KEIN REZIDIV** / keine Exazerbation

Völker LA *et al.* Blood Adv 2020;4:3093f

III. Caplacizumab – REAL WORLD F



90 Patienten
180 historische Kontrollen

“Triplet Regime”
1.) TPE +
2.) Capla (TPE + 30 Tage;…) +
3.) Rituximab

Coppo P, *et al.* Blood 2021;137:733f

III. Caplacizumab – REAL WORLD F

Outcome	Triplet regimen (N = 90)	Historical cohort (N = 180)	P
Primary outcome			
Composite of death and refractoriness			
All patients	2 (2.2%)	22 (12.2%)*	.01
According to French Severity score			
0-2	2 (2.8%)	15 (8.3%)	<.01
3-4	0	7 (33%)	
Secondary outcomes			
Death	1 (1.1%)	12 (6.7%)	.06
Refractoriness	1 (1.1%)	16 (18%)†	.01
Exacerbations	3 (3.4%)	70 (44%)	<.01
Time to durable platelet count recovery	5 (4-6)	12 (6-17)	<.01
Number of daily TPE until remission	5 (4-7)	10 (6-16)	<.01
Volume of plasma (L) until remission	24.2 (18.3-30.2)	44.4 (26.3-74.3)	<.01
Time to ADAMTS13 activity > 20% (days)	28 (14-42)	48 (24-83)	<.01
Length of hospitalization (days)	13 (9-19)	22 (15-30)	.01
Thromboembolic events	11 (12%)	20 (11.1%)	.79

Data are given as median (25th-75th percentile) for quantitative variables and as n (%) for qualitative variables. Patients at high risk of early death of iTTP were defined by a French severity score ≥ 3 (cerebral involvement: yes = 1/no = 0, LDH: >10×ULN = 1/≤10×ULN = 0, age: >60 y = 2/>40 and ≤60 y = 1/≤40 y = 0).[12]

*Includes 10 refractory patients who survived (only 1 event per patient was considered).

†Includes 6 deaths.

Coppo P *et al.* Blood 2021;137:733f

III. Caplacizumab – REAL WORLD F

Adverse event	Number of adverse events	Description
Major bleeding	2	One with hemorrhagic shock with lower digestive bleeding One with abundant menorrhagia with a decrease in hemoglobin level of 2.5 g/dL
Clinically relevant nonmajor bleeding	11	Three with macroscopic gastrointestinal hemorrhage Seven with epistaxis One with subcutaneous hematoma larger than 25 cm^2
Non–clinically relevant nonmajor bleeding	17	Nine with ecchymosis or small hematoma Six with gingival bleedings Two with catheter site hemorrhage
Inflammatory reaction	6	Inflammatory swelling at the injection site, especially at the end of the treatment course
Thrombocytosis	19	Platelet count ($\times 10^3/mm^3$) >450-600: 11 cases >600-900: 7 cases >900: 1 case

> hat überlebt; Capla vorübergehend pausiert – symptomat. Therapie (leider keine Details)

Kein Patient erhielt ein
- **VWF Konzentrat oder eine**
- **andere hämostatische Therapie**

Coppo P *et al.* Blood 2021;137:733f

Wohin geht die Reise?

iTTP Therapie ohne TPE (I. Säule)

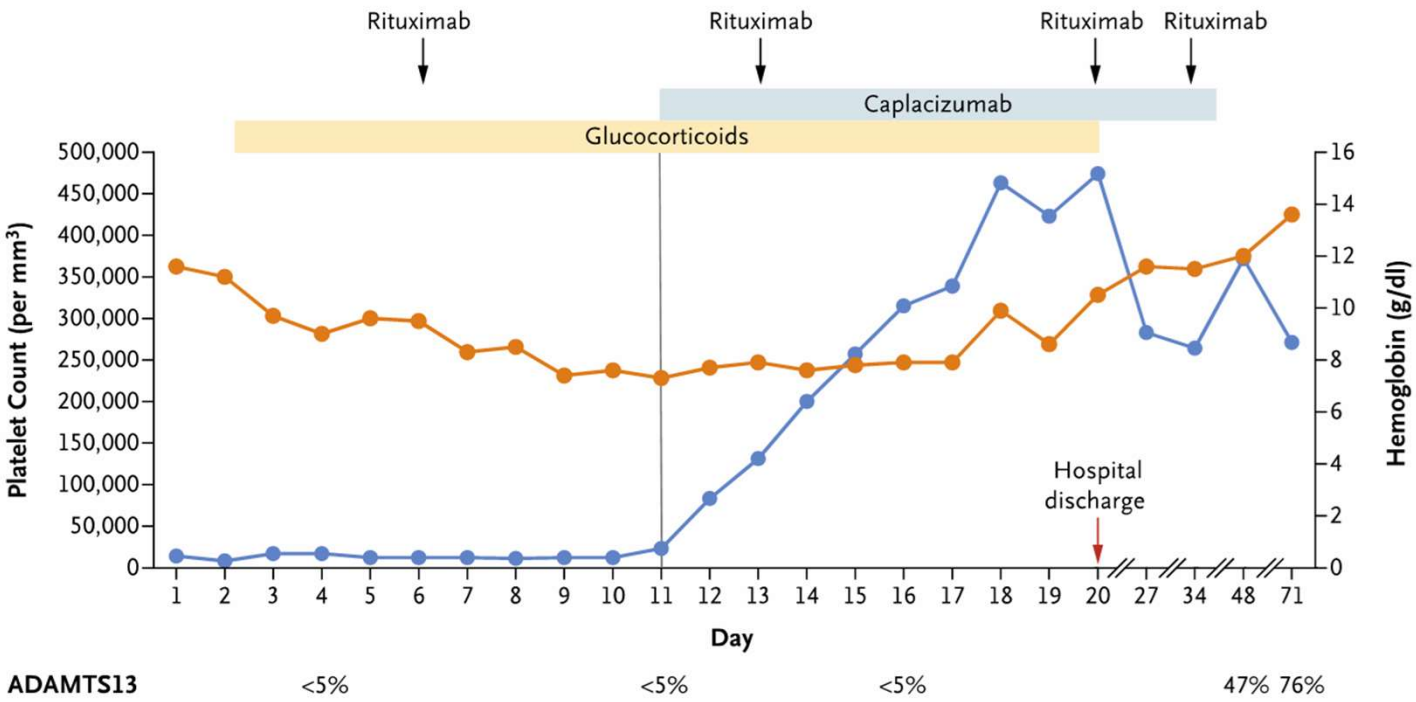
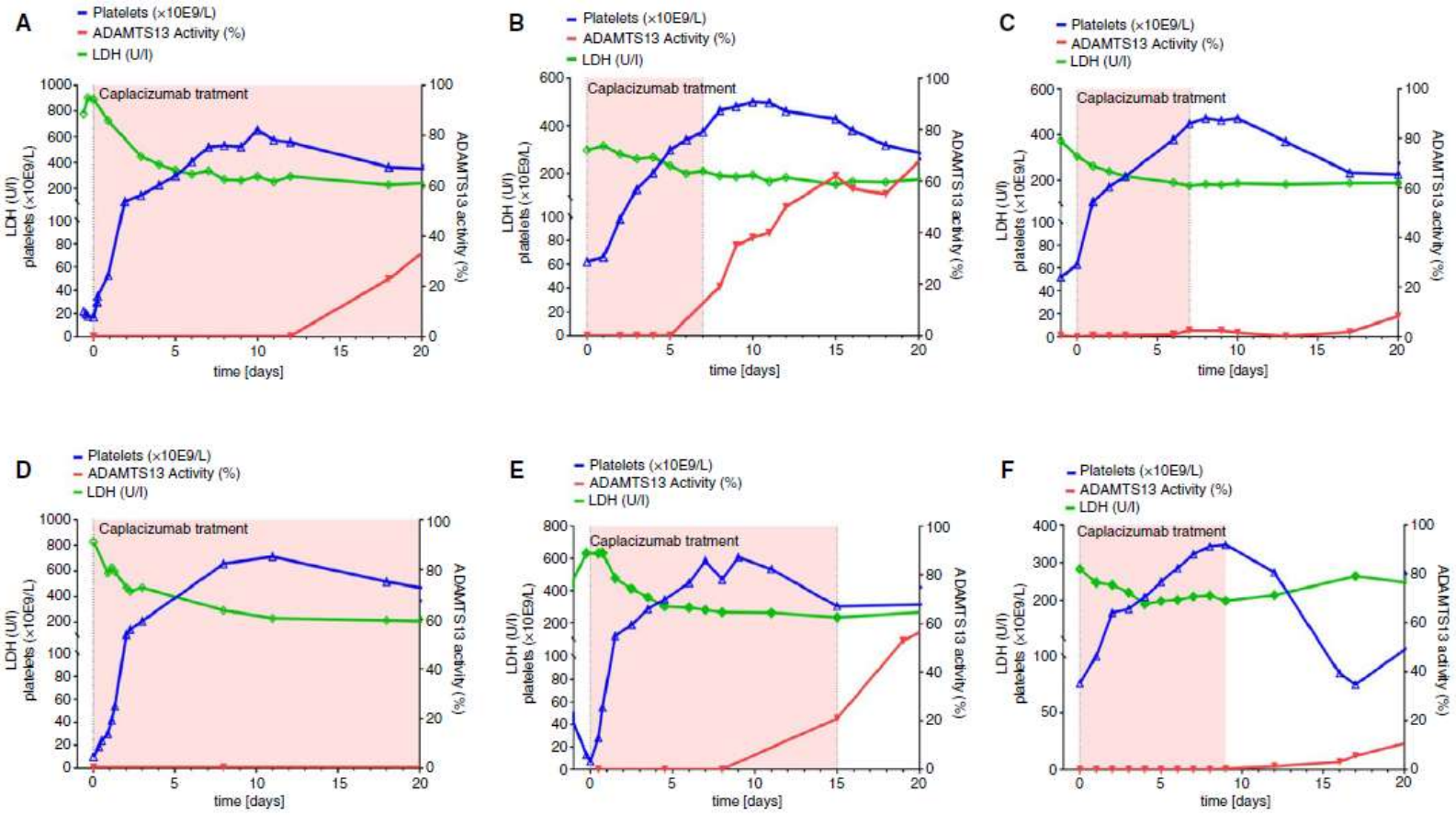


Figure 1. Acquired Thrombotic Thrombocytopenic Purpura (TTP) in a Jehovah's Witness Patient Treated with Caplacizumab.

Shown is the clinical course of an initial episode of TTP in a 63-year-old woman who presented with spontaneous purpura and who declined to undergo plasma exchange because of religious prohibition. Data are presented from hospital admission (day 1) until the most recent follow-up at 51 days after hospital discharge and 31 days after caplacizumab was discontinued on day 40.

Chander DP *et al.* N Engl J Med. 2019;381:92f

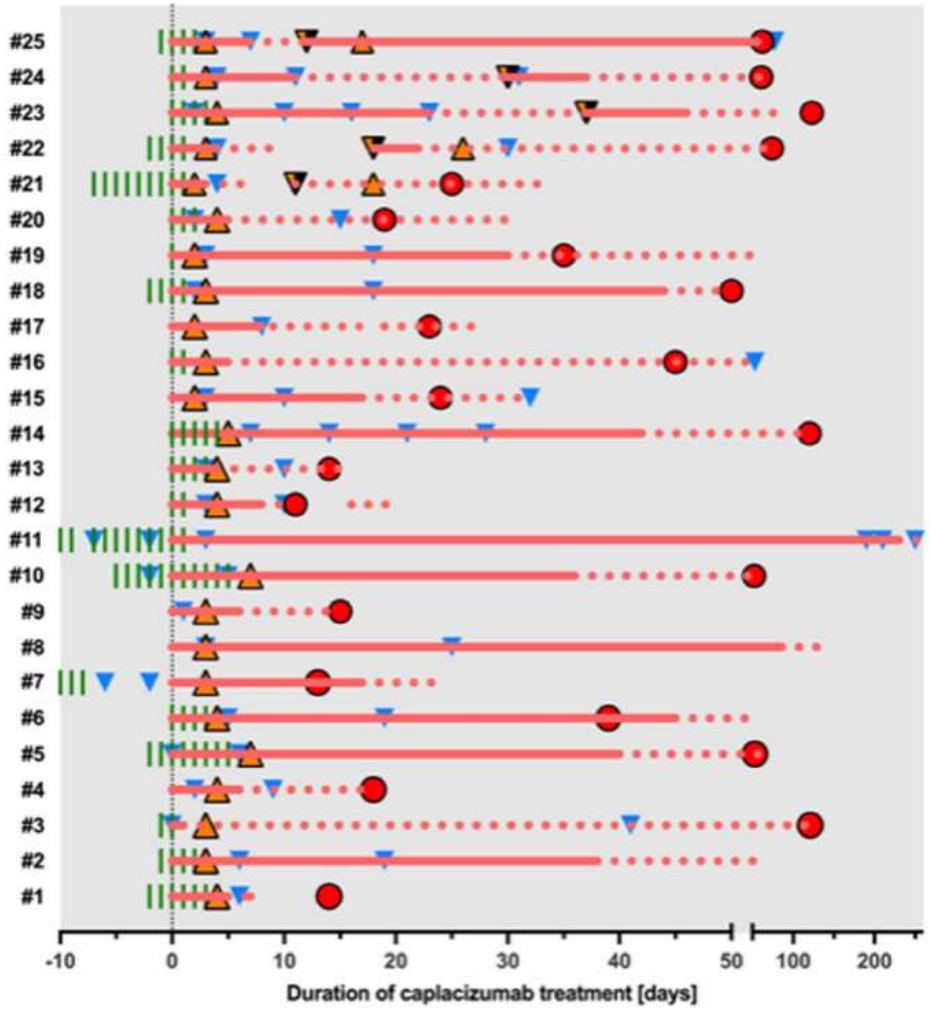
iTTP Therapie ohne TPE

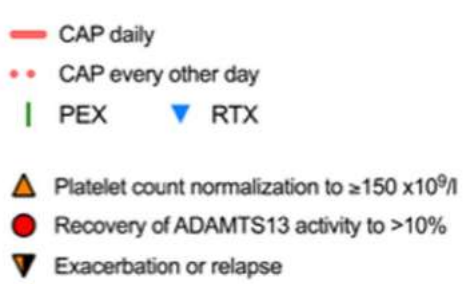


Abgebildet sind 6 von 7 behandelte Pat.; Th neben Caplacizumab: Steroide in 7/7
Rituximab in 4/7

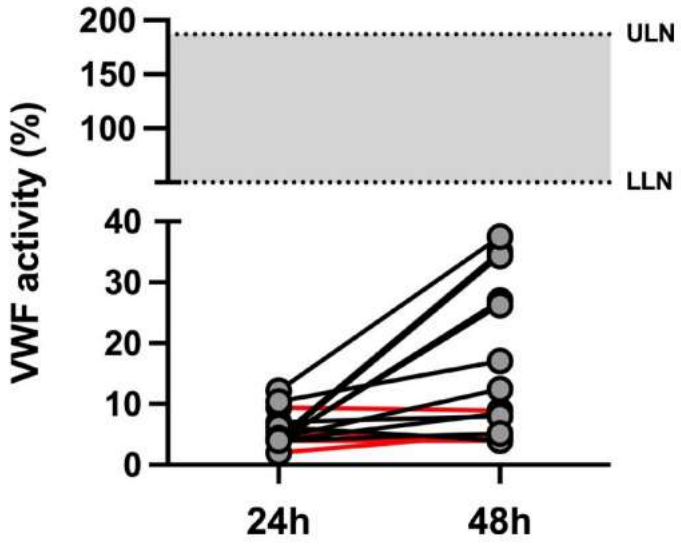
Völker LA *et al*. JTH 2020;18:3061f

Wohin geht die Reise? Capla q1 > q2





25 Pat., retrospektiv

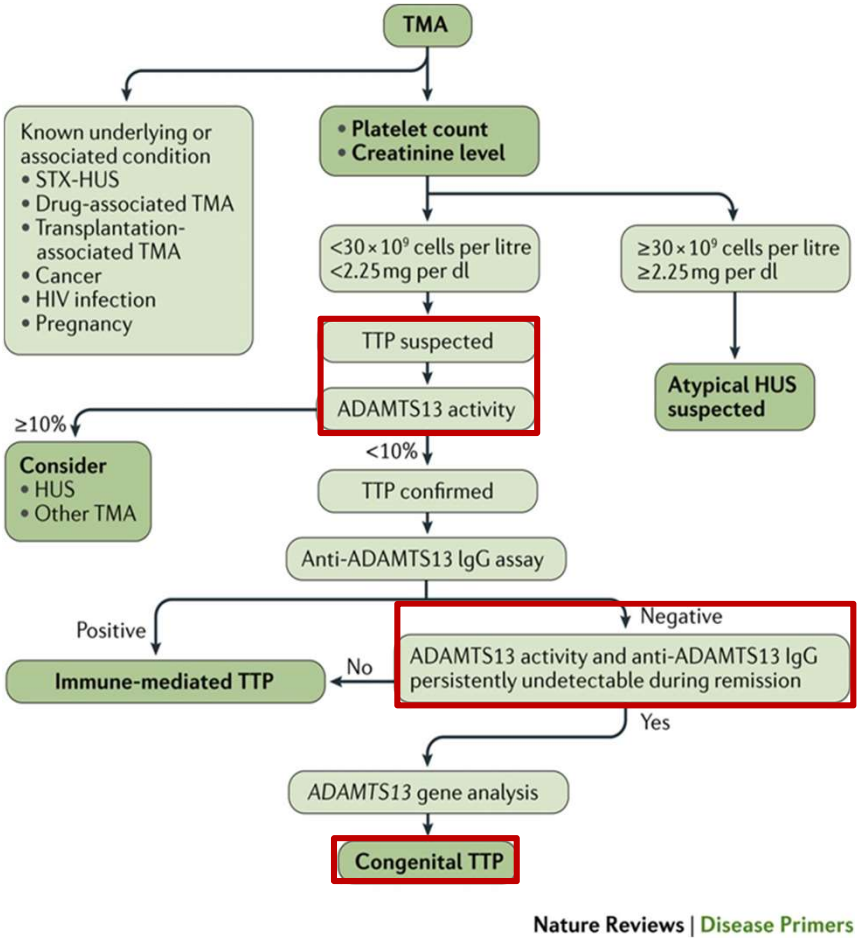


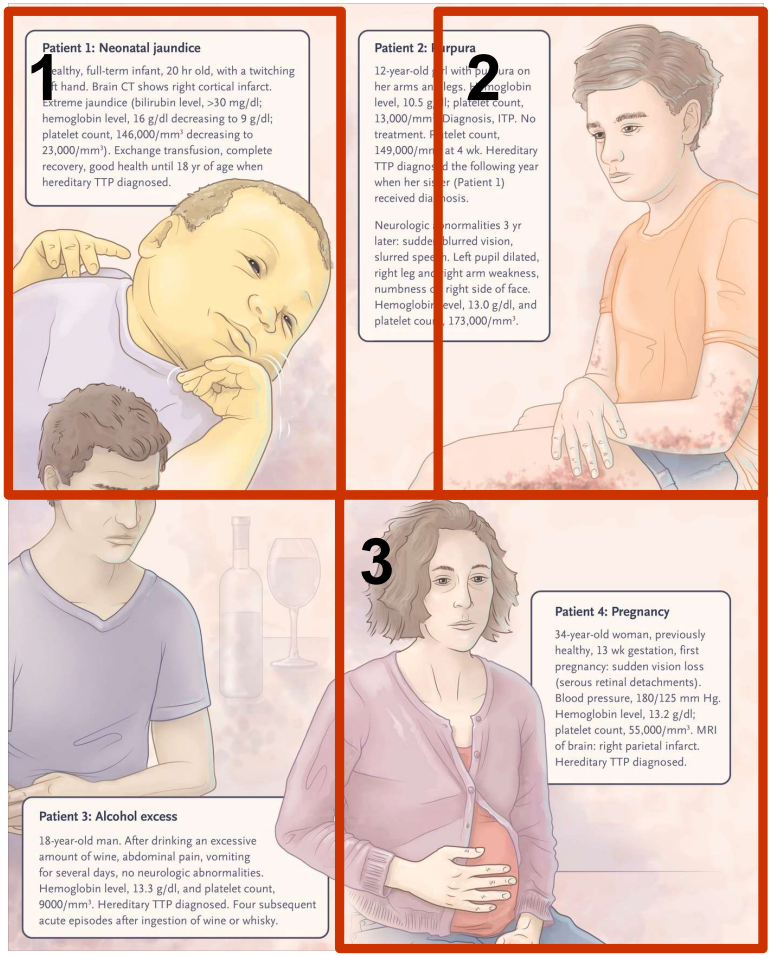
Kühne L *et al.* J Thromb Haemost 2022;20:951f

Fazit für die Klinik

- "Triplet Therapie" (TPE + Capla$^{ab\ Tag1}$ + Ritux^{Tag1-3}) = neuer TTP-Therapie Standard
  - Möglichst früher Einsatz von Caplacizumab
  - Rituximab Start in den ersten 3 Tagen
    - Capla Start bevor, Rituximab wenn ADAMTS13 Resultat da ist
- ADAMTS13 (& VWF?) für Therapie-Monitoring(=off-label)
  - sobald ADAMTS13 stabil >20% - Capla Stopp
  - Capla-Gabe nach "Akutphase" q2 (?)
- iTTP Therapie mit Capla & Immunsuppression ohne TPE => Phase III Studie (MAYARI) gestartet

Hereditäre (congenitale) TTP

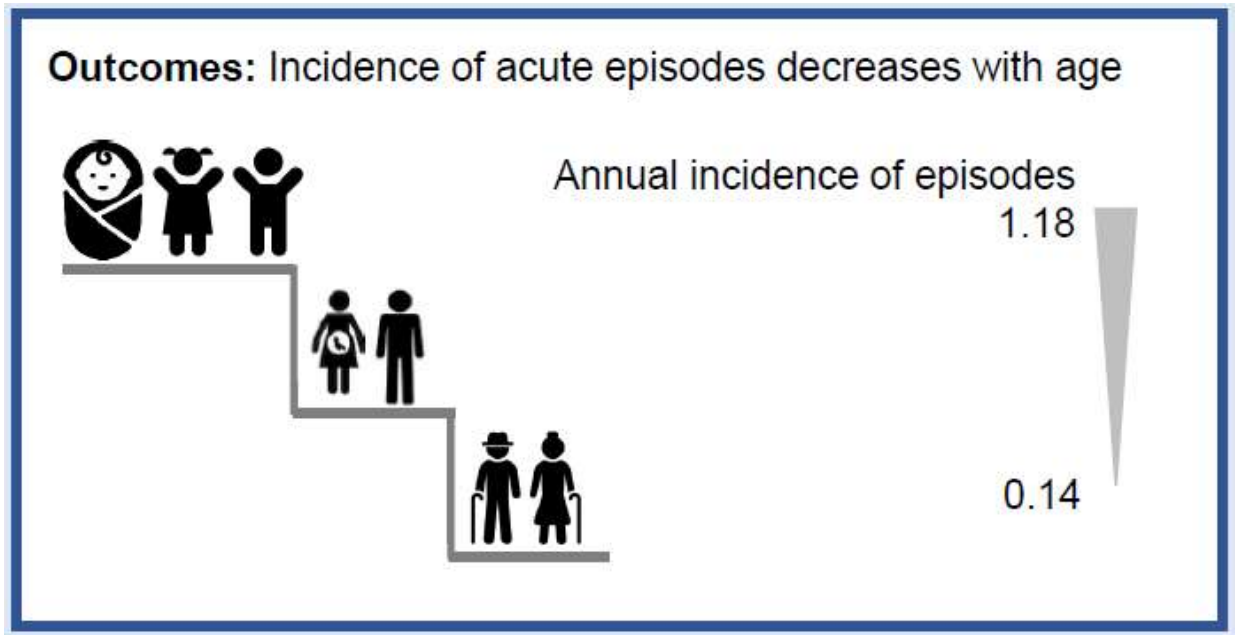


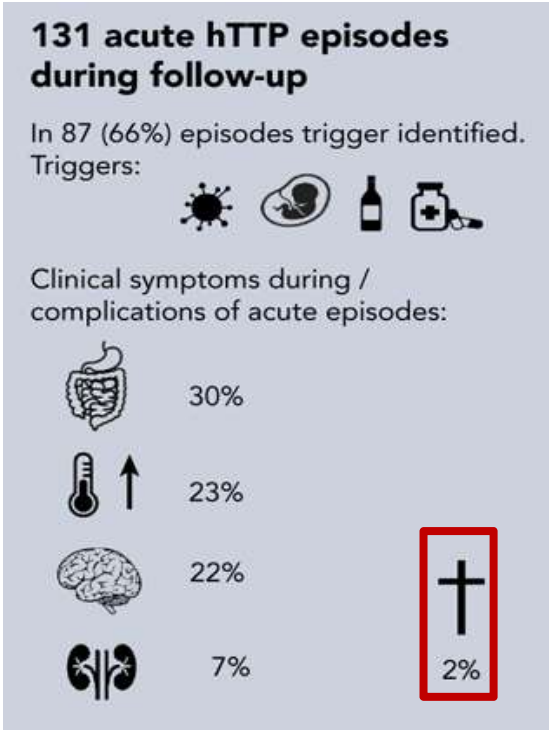


Kremer Hovinga JA *et al*. Nat Rev Dis Primers. 2017;3:17020

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

hTTP – Inzidenz akute Episoden





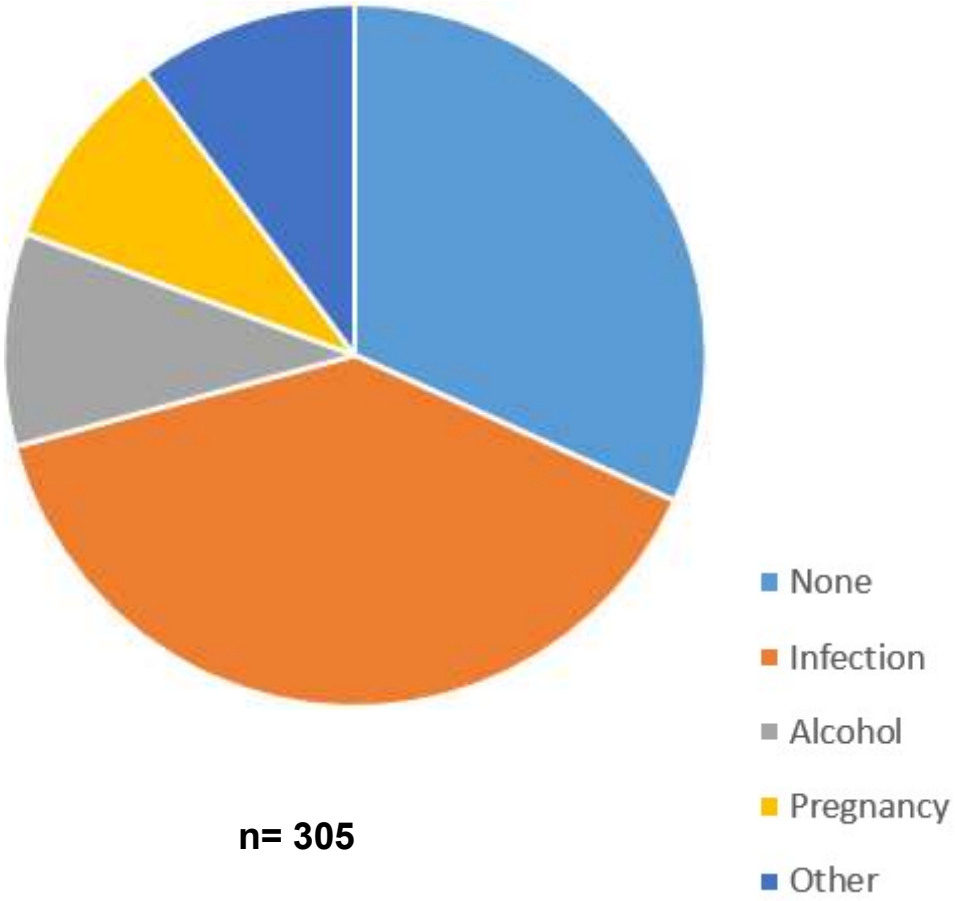
Grösster Benefit – und grösste Bürde – einer Plasma-Prophylaxe bei Kindern und in der Schwangerschaft

> rADAMTS13 …..

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

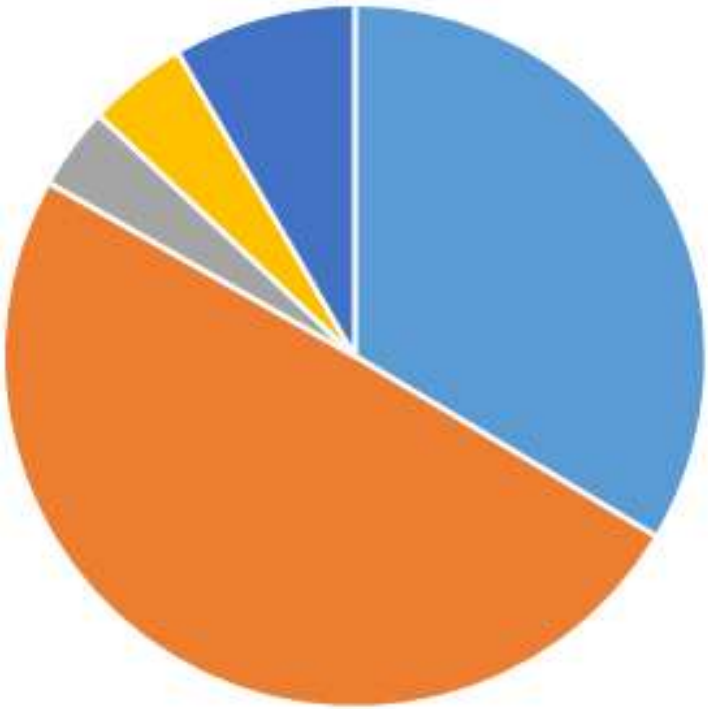
hTTP – Trigger akuter Episoden

Retrospektive Dokumentation



n= 305

Prospektive Beobachtung



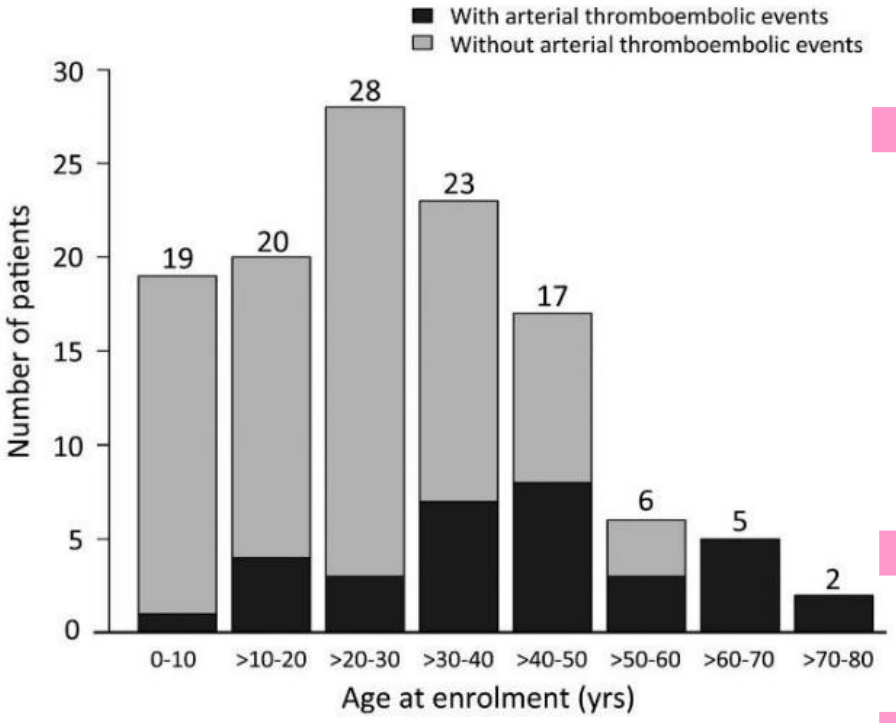
n= 131

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

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

Hereditäre TTP - Morbidität

International Hereditary TTP Registry (www.ttpregistry.net)



Treatment		
Prophylactic plasma infusions	83	47 (57%)
Antiaggregation/anticoagulation	79	21 (27%)
Antihypertensive medication	79	25 (32%)
Comorbidities at enrollment		
Arterial thrombotic disease	83	30 (36%)
Myocardial infarction	83	4 (4.8%)
Transient ischemic attack	83	13 (16%)
Stroke	83	22 (27%)
Other	83	4 (4.8%)
Neurologic disorders	83	18 (22%)
Epileptic seizure	83	6 (7.2%)
Headache	83	3 (3.6%)
Other neurologic disease	83	12 (14%)
Venous thrombotic disease	83	3 (3.6%)
Renal insufficiency	83	26 (31%)
Pathologic renal parameters	83	17 (20%)
On dialysis	83	8 (10%)
Kidney transplantation	83	2 (2.4%)
Neonatal hyperbilirubinemia	83	36 (43%)

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

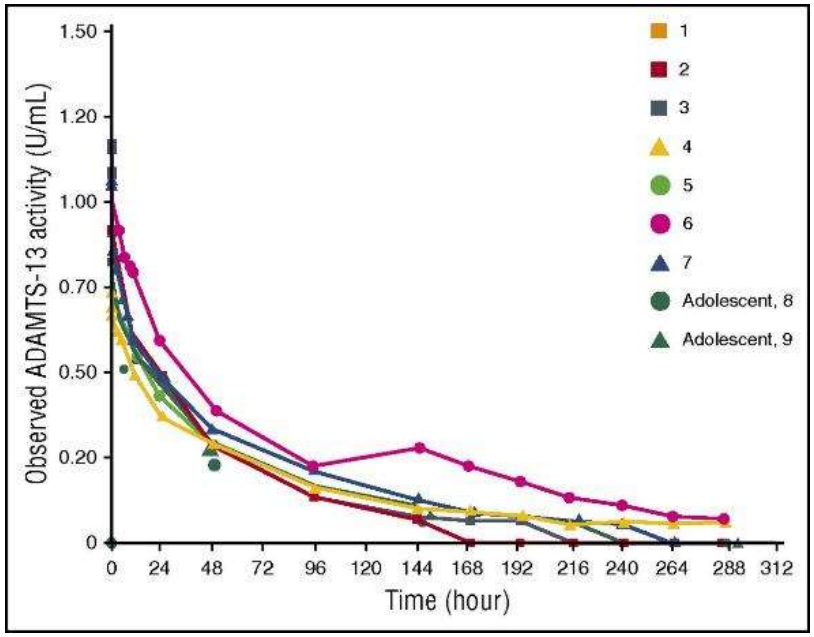
Tarasco E *et al*. Blood 2021;137:3563f

Hereditäre TTP – Behandlung

	UK Register[1]	Internat. Register[2]
Patienten (weiblich, %)	73 (51; 79%)	123 (62;52%)
Alter bei Diagnose; Median (Streubreite)	24 J (Geburt - 71 J)	17 J (Geburt - 70 J)
Plasmaprophylaxe (Kinder / Erwachsene)	**67% (94% / 61%)**	**71%**
Plasma on demand (Episodisch)	12%	29%
Noch keine Plasmatherapie	21%	-
Plasamprophylaxe Intervall, Median (Streubreite)	-	14 Tage (2-21 Tage)
Funkt. ADAMTS13 inhibitor	Ohne Angabe	0/114 Getestete
Anti-ADAMTS13 Antikörper	Ohne Angabe	12/103 Getestete

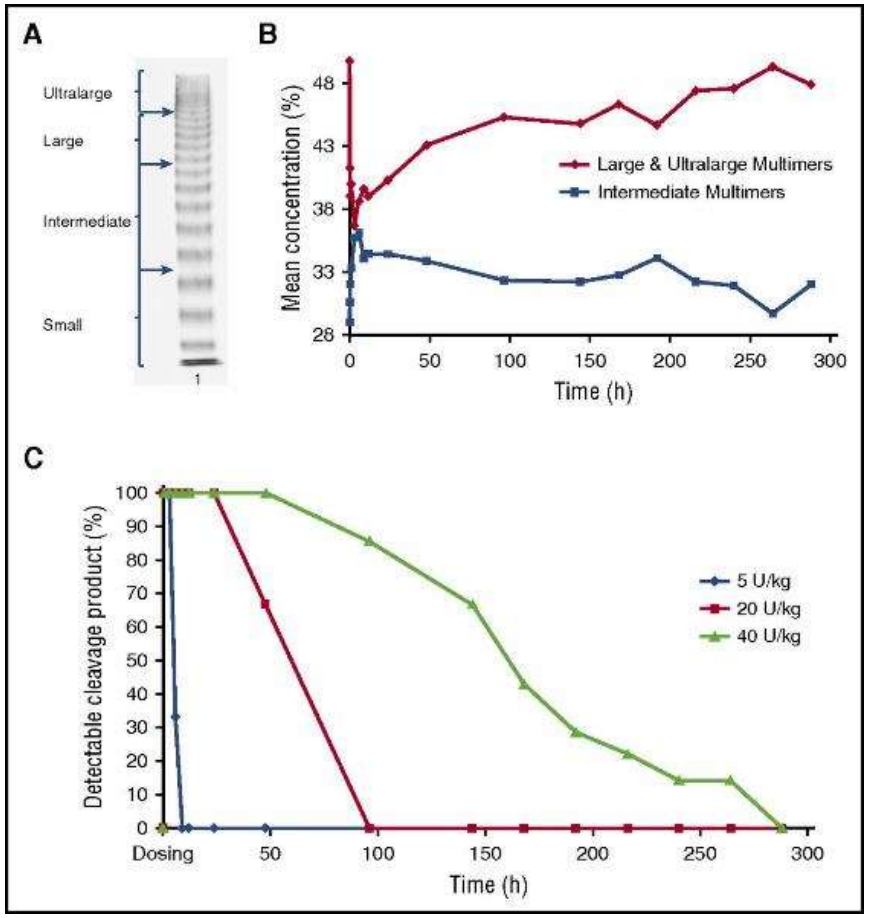
1. Alwan F et al. Blood 2019;133:1644f | 2. van Dorland HA *et al*. Haematologica 2019;104:2107f

Hereditäre TTP – Behandlung



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

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

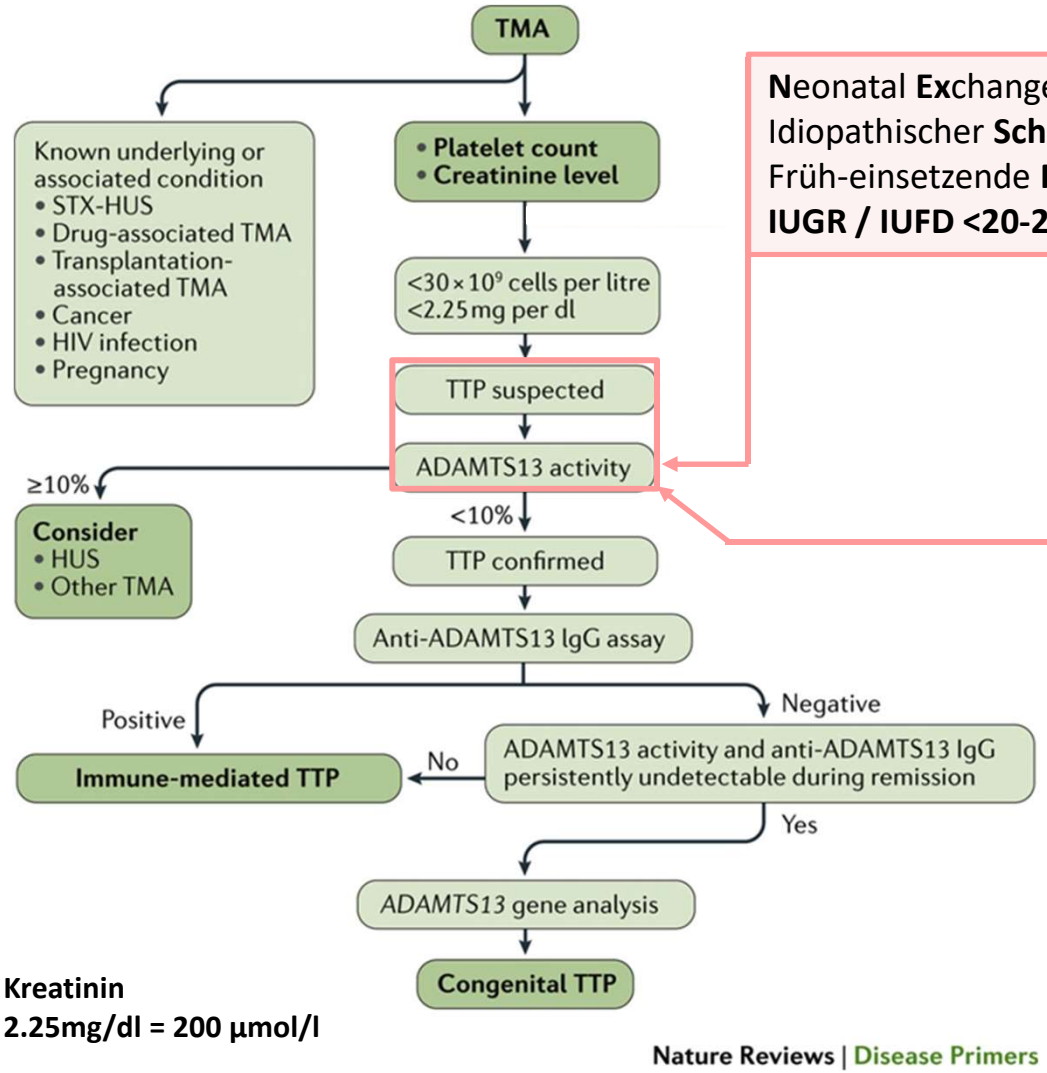


1. Scully M *et al.* Blood 2017;130:2055f | 2. Furlan M *et al*. T & H 1999;81:8f | 3. Kovarova P *et al*. J Clin Apher 2019;34:13f

TAKE HOME MESSAGES - TTP

1. selten; Morbidität & Mortalität > rasche Diagnose;
2. Diagnost. Algorythmen (PLASMIC, “French score”) = 1. Einschätzung, aber ADAMTS13 Bestimmung nötig
3. ADAMTS13 <10%
   a. Beweisst eine TTP
   b. Erworben (immune-vermittelt) vs. angeboren; und iTTP ≠ hTTP
   c. Biomarker f. Therapie-Entscheide (z.B. Rituximab-Prophylaxe, Caplacizumab Stopp, etc).

TAKE HOME – An hTTP denken!!



Kreatinin
2.25mg/dl = 200 µmol/l

Neonatal **Ex**change **T**ransfusion
Idiopathischer **Schlaganfall <20 J** (<50J ?)
Früh-einsetzende **Präeklampsie 2. Trimenon**, oft <20-26 Wo.
IUGR / IUFD <20-26 Wo

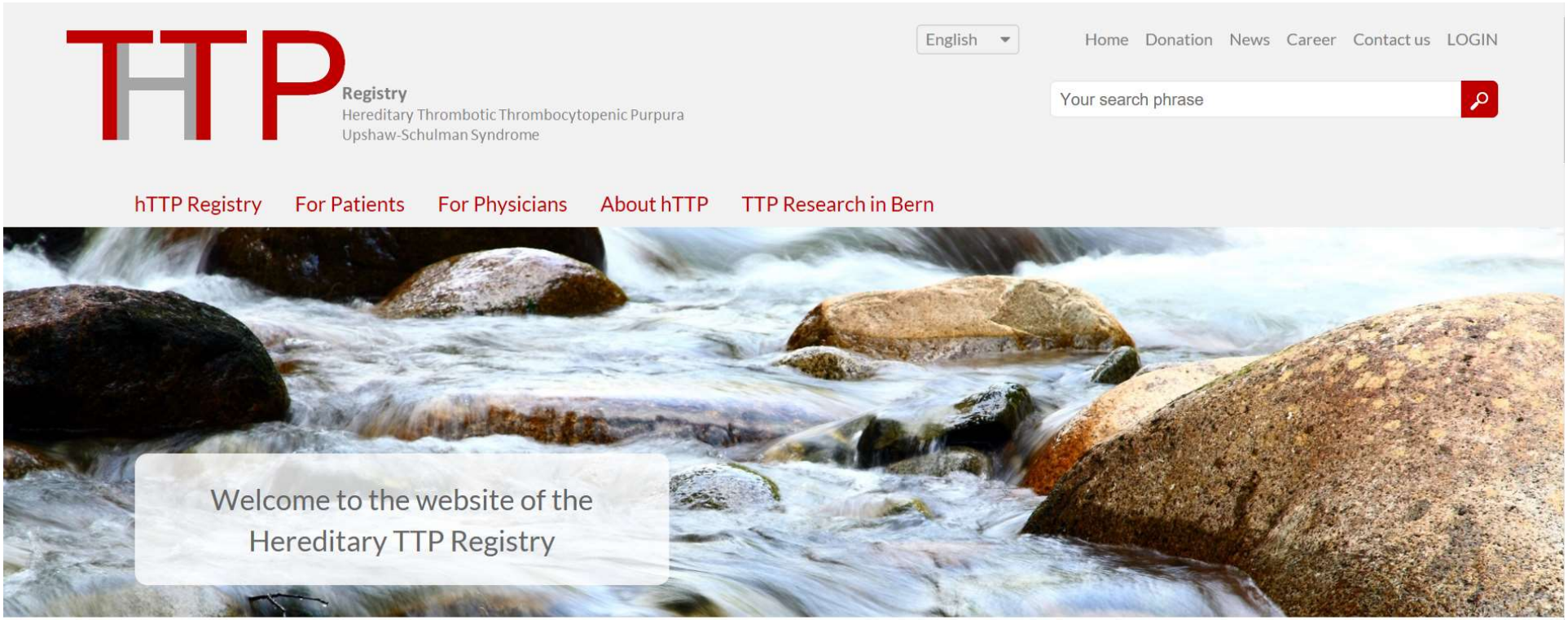
Milde Thrombozytopenie
+ Schlaganfall / TIA, oder
+ Akute Niereninsiffizienz
(mit Nausea und Erbrechen)

ADAMTS13 Teste sind verfügbar !

rADAMTS13: in Entwicklung
- Early Access Program kommt (2023?)
- Compassionate Use (auf Anfrage)

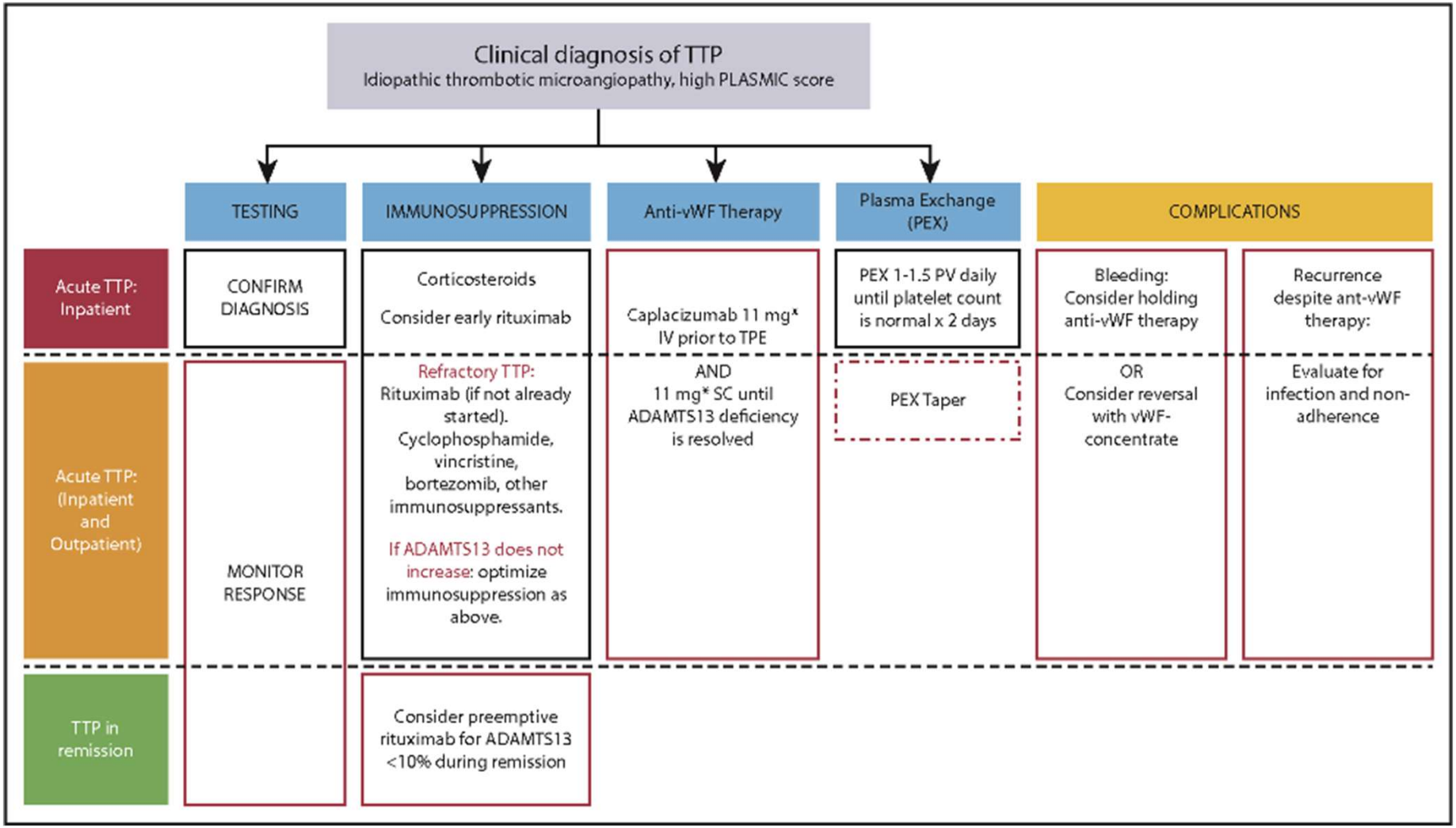
Kremer Hovinga JA *et al*. Nat Rev Dis Primers. 2017 Apr 6;3:17020

International Hereditary TTP Registry (www.ttpregistry.net)



KONTAKT: support@ttpregistry.net **oder**
erika.tarasco@insel.ch
johanna.Kremer@insel.ch

TTP Management - Zusammenfassung



*tägliche Dosis gem. Zulassung: FDA: 11mg iv/sc
EMA/SwissMedic: 10mg iv/sc

Mazepa MA *et al*. Blood 2019;134:415f