UNIKLINIK
KÖLN

Neues und Bewährtes in der Behandlung der thrombotischen Mikroangiopathie

9. Brandenburger Nephrologie Kolleg
13.-14.06.2019
Potsdam, Resort Schwielowsee

Paul Brinkkötter, Klinik II für Innere Medizin

Offenlegung potentieller Interessenskonflikte

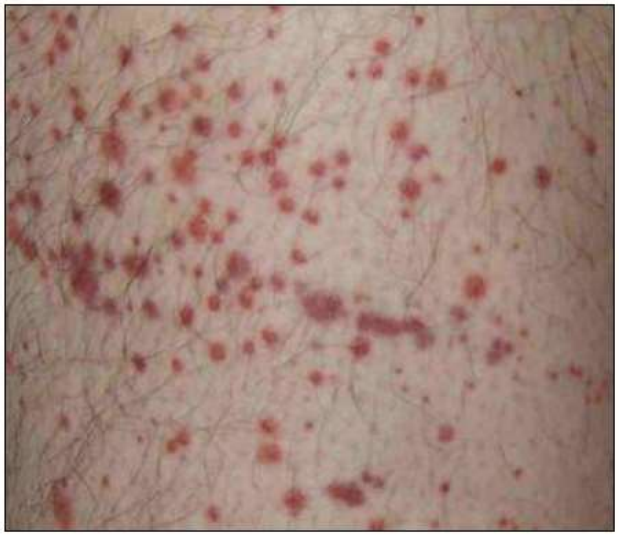
Vortragshonorare, Reisemittel, Advisory Boards:

Alexion, Astellas, Pfizer, Sanofi Genzyme

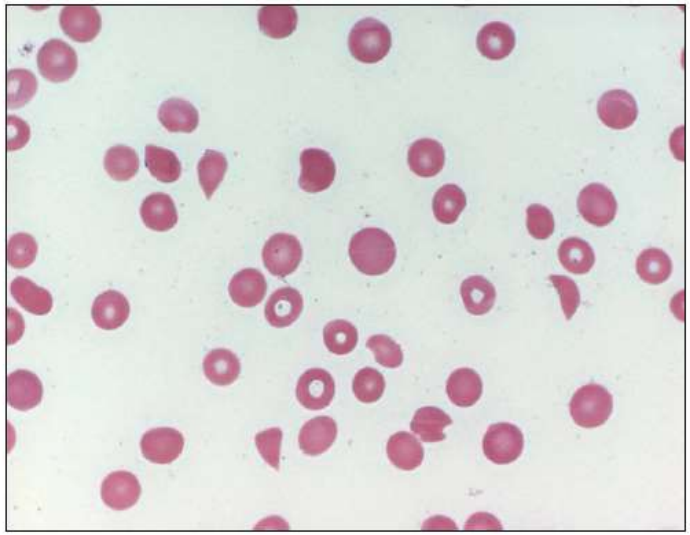
Thrombotische Mikroangiopathie (TMA)

Klassischer Symptomenkomplex

- Petechien
- Hämolytische Anämie
- Neurologische Auffälligkeiten
- Nierenversagen
- Fieber



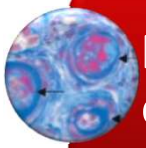
Petechien



Blutausstrich mit Fragmentozyten

Gasser et al. Schweiz Med Wochenschr 1955, Noris et al. JASN 2011
Fremenaux-Bacchi et al. CJASN 2013

Thrombotische Mikroangiopathie (TMA)



Histopathologisch: Fibrin und/oder Plättchenthromben in der Mikrozirkulation durch Endothelschaden

Klinische Trias

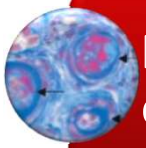
Coombs-negative, mechanische, mikroangiopathische hämolytische Anämie

- -LDH
- -Fragmentozyten
- -Indirektes Bilirubin
- -Haptoglobin

Thrombopenie

Endorganschaden

Thrombotische Mikroangiopathie (TMA)



Histopathologisch: Fibrin und/oder Plättchenthromben in der Mikrozirkulation durch Endothelschaden

Klinische Trias

Coombs-negative, mechanische, m… hä…

-L…

-Fragmentozyten

-Indirektes Bilirubin

-Haptoglobin

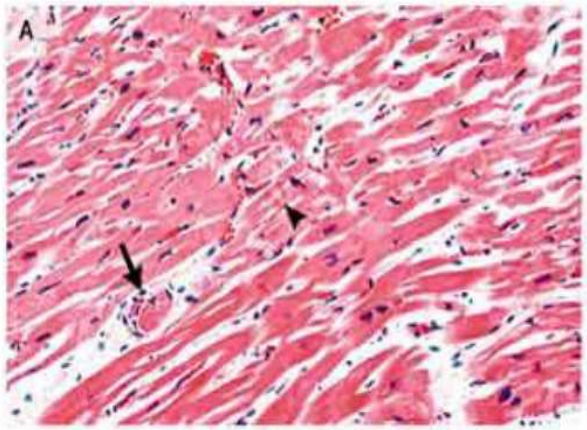
Thrombopenie

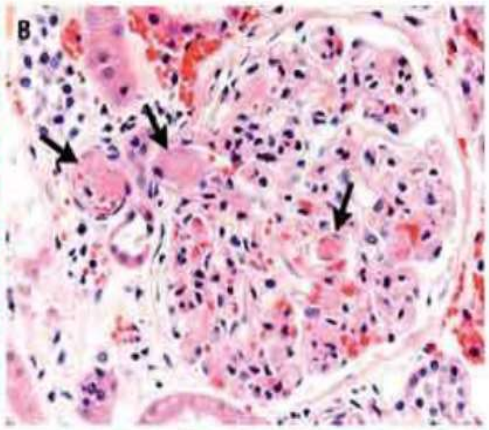
Endorganschaden

Komplette Trias liegt nur in ca. 75% der TMA Fälle vor

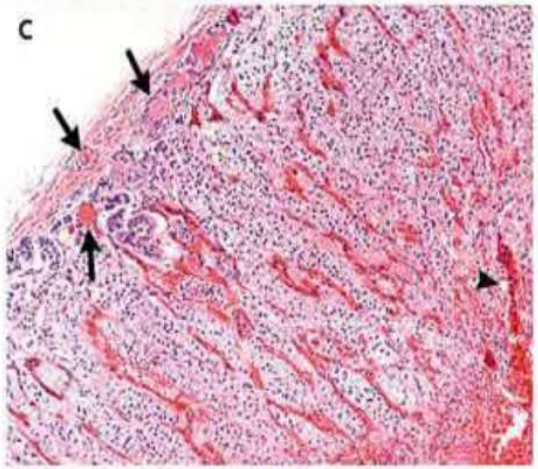
Mulitorganbeteiligung bei TMA

Herz:
intrakardiale
Mikrothromben

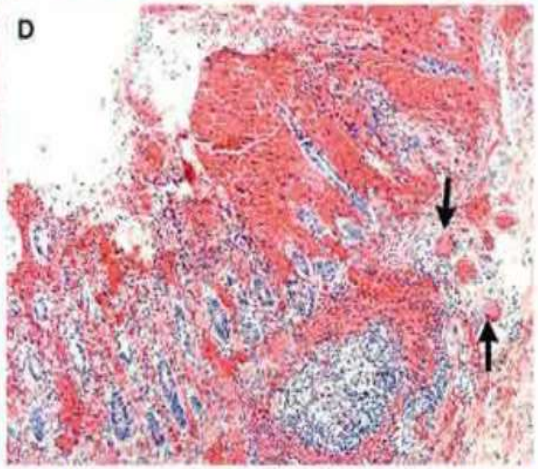




Niere:
Mikrothromben
in Arteriole
und Glomerulum



Nebenniere: Subkapsuläre Mikrothromben
und medulläre Hämorrhagie



Zökum: Submukosale Mikrothromben,
hämorrhagische Ulzerationen und Nekrosen

George J. N Engl J Med 2006

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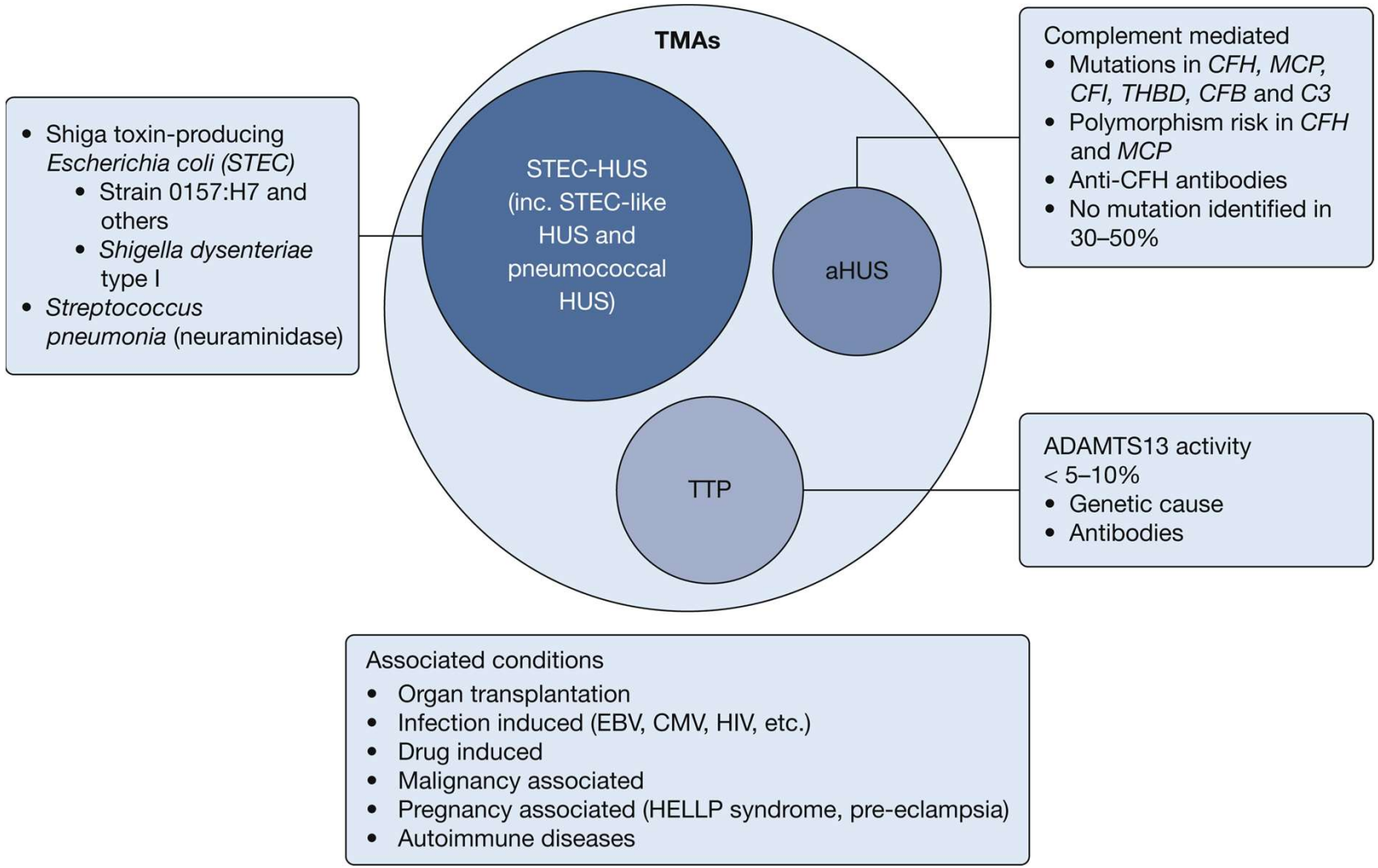
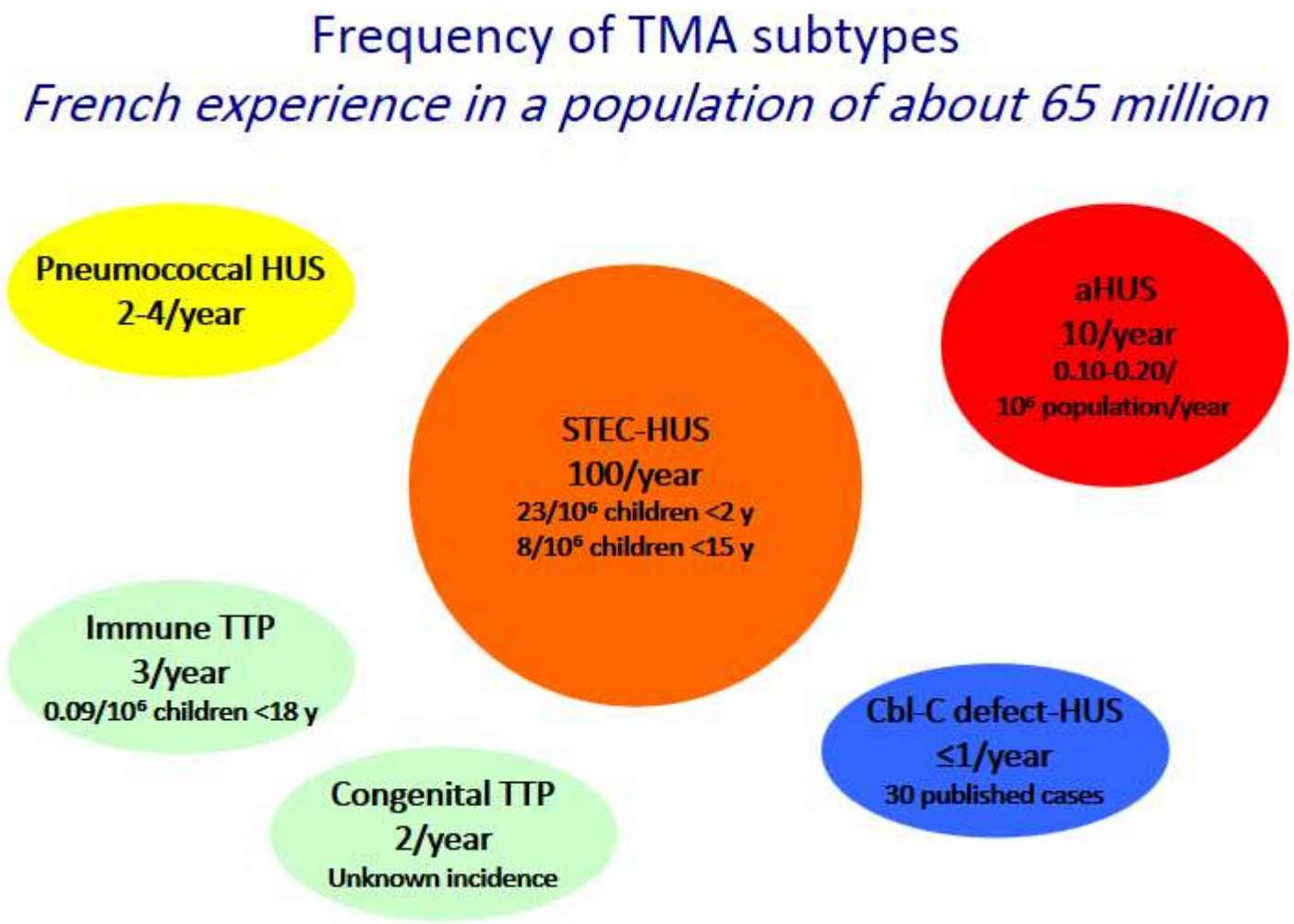
Differentialdiagnose TMA



Azoulay et al, Chest 2017

Thrombotische Mikroangiopathie (TMA)



Licht C / Loirat C unpublished

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Fallvorstellung

43 Jahre (weiblich)

Initial HWI, antibiotische Therapie,
aktuell: ubiquitäre Petechien

> Vorstellung beim Hausarzt
> Thrombozytopenie

VE: Melanom 2009
(operative Exzision)

> Vorstellung in ZNA UKK

Fallvorstellung

43 Jahre (weiblich)

Initial HWI, antibiotische Therapie, aktuell: ubiquitäre Petechien

> Vorstellung beim Hausarzt
> Thrombozytopenie

VE: Melanom 2009
(operative Exzision)

> Vorstellung in ZNA UKK

46 Jahre (männlich)

Seit 5 Tagen zunehmende Schwäche, temporäre Visusminderung, Sklerenikterus / Petechien

> Vorstellung bei Notfallambulanz
> Zeichen einer Hämolyse

VE: Spondylitis Ankylosans

> Verlegung in UKK

Fallvorstellung

43 Jahre (weiblich)

Z.n. HWI, ubiquitäre Petechien

Labor bei Aufnahme UKK:

- Kreatinin:	0,71 mg/dl
- LDH:	852 U/l
- Haptoglobin:	<0,2 g/l
- Hb:	8,4 g/dl
- Fragmentozyten	76/1000 Ery
- Thrombozyten	8.000

TMA

46 Jahre (männlich)

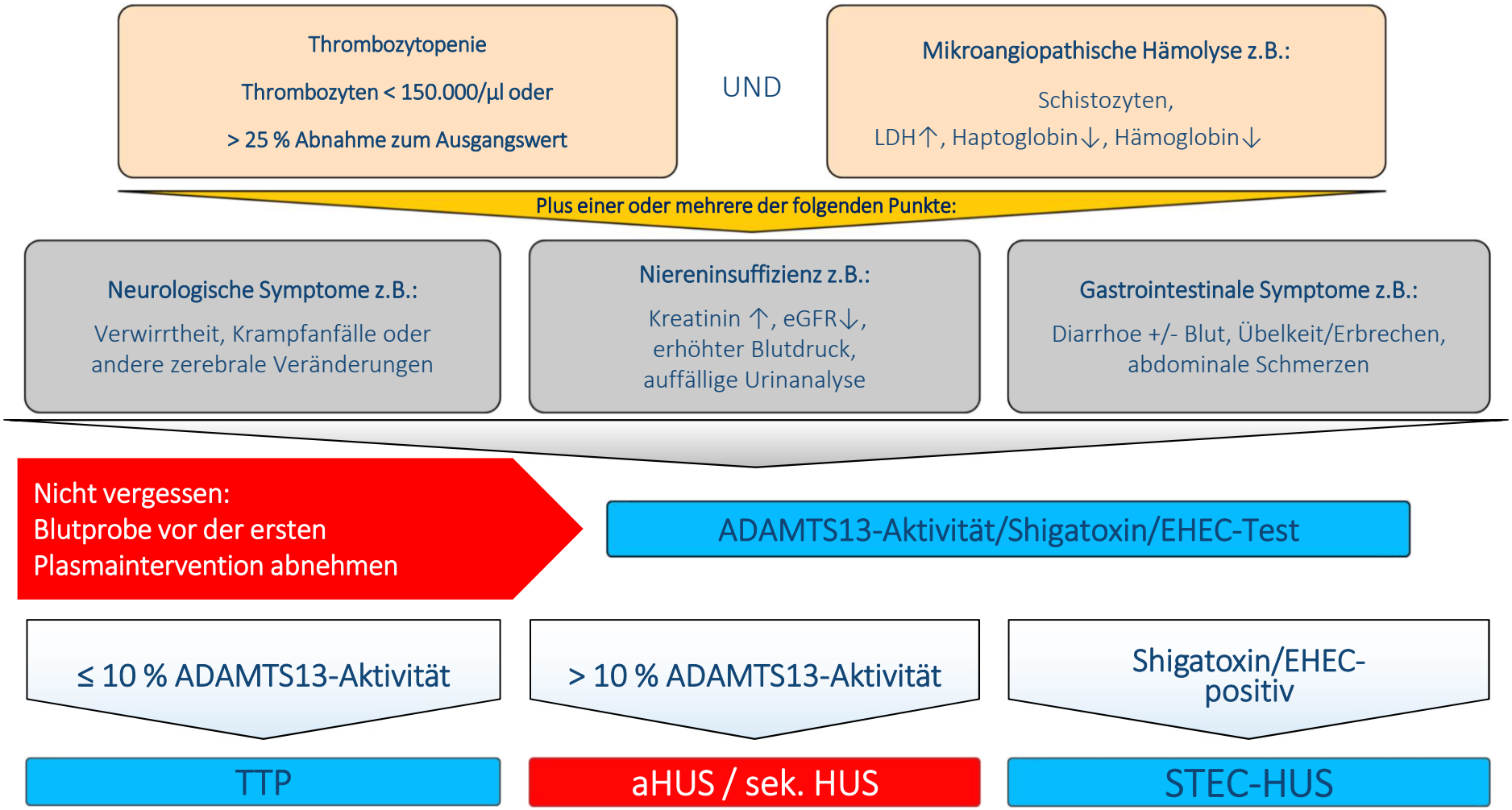
Schwäche, Ikterus / Petechien

Labor bei Aufnahme UKK:

- Kreatinin:	5,31 mg/dl
- LDH:	1677 U/l
- Haptoglobin:	<0,2 g/l
- Hb:	9,3 g/dl
- Fragmentozyten	6/1000 Ery
- Thrombozyten	3.000

TMA

Differentialdiagnose TMA



modifiziert nach Campistol JM, et al. Nefrologia 2015;35:421-47.

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Fallvorstellung

43 Jahre (weiblich)

Z.n. HWI, ubiquitäre Petechien

Labor bei Aufnahme UKK:

- Kreatinin: 0,71 mg/dl
- Thrombozyten: 8.000
- C3 1,2 g/l
- C4 0,19 g/l

ADAMTS13 Akt.: 8 %

Stuhl (Shigatoxin) negativ

ANA 1:320 (unspezif.)

46 Jahre (männlich)

Schwäche, Ikterus / Petechien

Labor bei Aufnahme UKK:

- Kreatinin: 5,31 mg/dl
- Thrombozyten: 5.000
- C3 1,5 g/l
- C4 0,3 g/l

ADAMTS13 Akt.: < 0,3%

Stuhl (Shigatoxin) negativ

ANA: 1:1.000 (unspezif.)

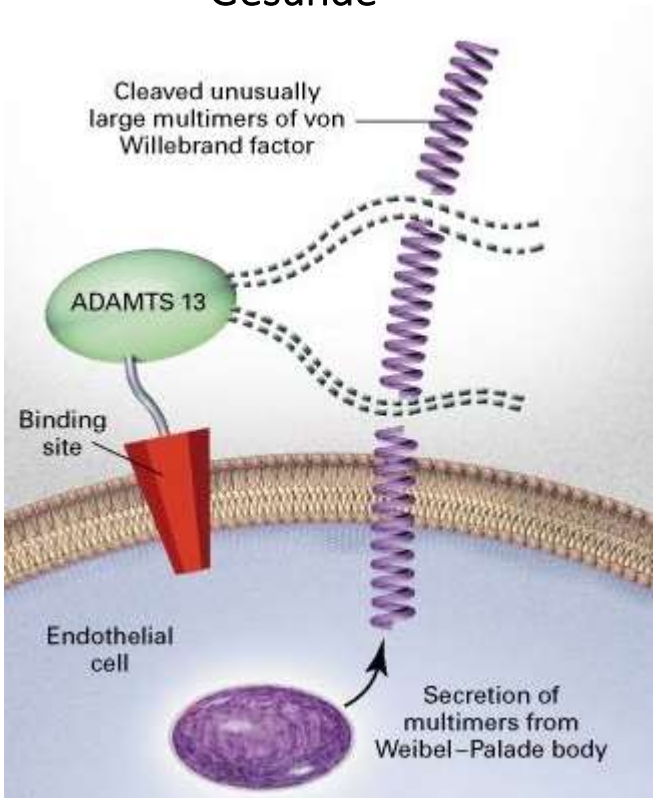
aTTP

Pathophysiologie der thrombotisch-thrombozytopenen Purpura (TTP)

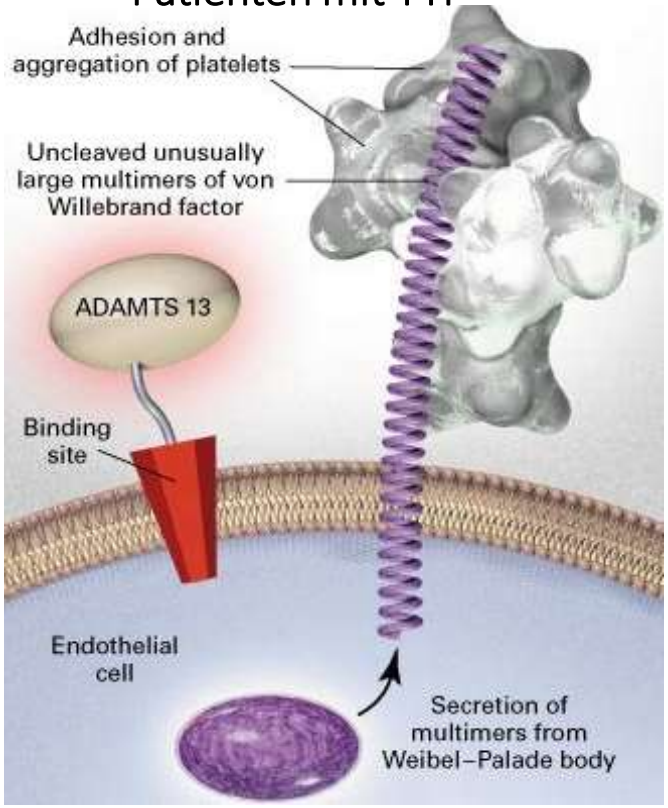
Schwerer ADAMTS13-Mangel: vWF und Thrombozyten

*"**A** **D**isintegrin **A**nd **M**etalloproteinase with **T**hrombo**S**pondin-1-like domains"*

Gesunde



Patienten mit TTP



vWF, von-Willebrand-Faktor

Moake JL. N Engl J Med 2002

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aTTP: Stellenwert der Nierenfunktion / Thrombozyten - PLASMIC score -

Variables	Points*
Platelet count <30 x 109 per L	1
Hemolysis variable†	1
No active cancer	1
No history of solid-organ or stem-cell transplant	1
MCV <90 fL	1
INR <1.5	1
Creatinine <2.0 mg/dL	1
INR: International normalized ratio. MCV: Mean corpuscular volume. †Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL.	

Score	Risk Category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Bendapudi et al. Lancet Hematology 2017, Williams LA et al. Am J Clin Pathol February 2016

Fallvorstellung

Score	Risk Category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Plasmic Score 6

43 Jahre (weiblich)

Z.n. HWI, ubiquitäre Petechien

Labor bei Aufnahme UKK:

- Kreatinin: 0,71 mg/dl
- LDH: 852 U/l
- Haptoglobin: <0,2 g/l
- Hb: 8,4 g/dl
- Fragmentozyten 76/1000 Ery
- Thrombozyten 8.000
- C3 1,2 g/l
- C4 0,19 g/l

ADAMTS13 Akt.: 8 %

Stuhl (Shigatoxin) negativ

ANA 1:320 (unspezif.)

Fallvorstellung

Score	Risk Category	Risk of severe ADAMTS13 deficiency (≤ 10%)
0-4	Low	4.3%
5-6	Intermediate	56.8%
7	High	96.2%

Plasmic Score 5

46 Jahre (männlich)

Schwäche, Ikterus / Petechien

Labor bei Aufnahme UKK:

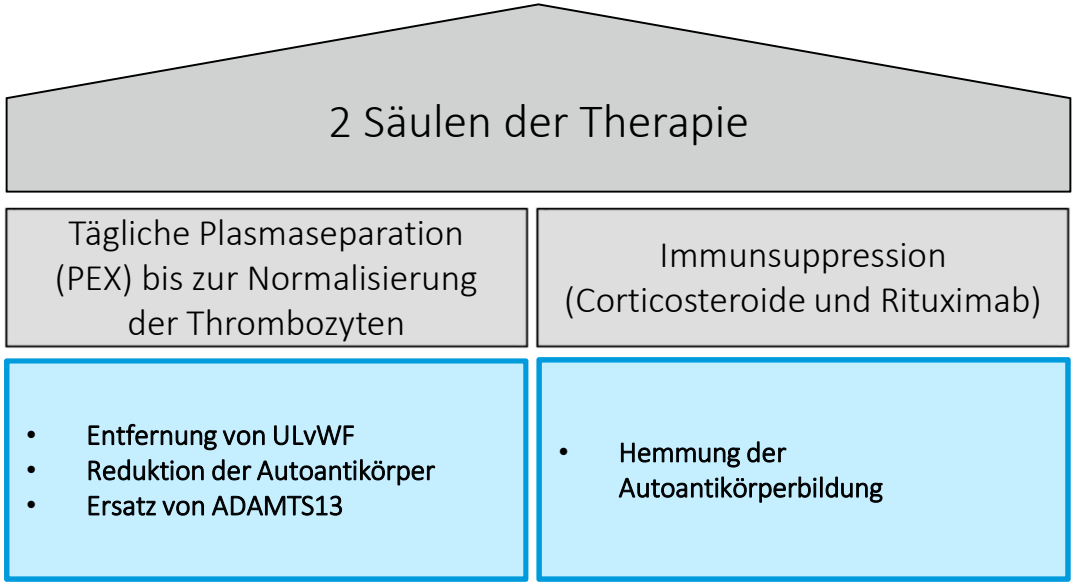
- Kreatinin: 5,31 mg/dl
- LDH: 1677 U/l
- Haptoglobin: <0,2 g/l
- Hb: 9,3 g/dl
- Fragmentozyten 6/1000 Ery
- Thrombozyten 3.000
- C3 1,5 g/l
- C4 0,3 g/l

ADAMTS13 Akt.: < 0,3%

Stuhl (Shigatoxin) negativ

ANA: 1:1.000 (unspezif.)

aTTP – Therapieoptionen



PEX: Plasmaseparation
ULvWF: Ultra-large von Willebrand Factor
ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13

nach Scully M et al. Br J Haematol. 2012; 158(3): 323-35.

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aTTP – Therapieoptionen

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*

Rock GA et al. N Engl J Med 1991;325:393-397

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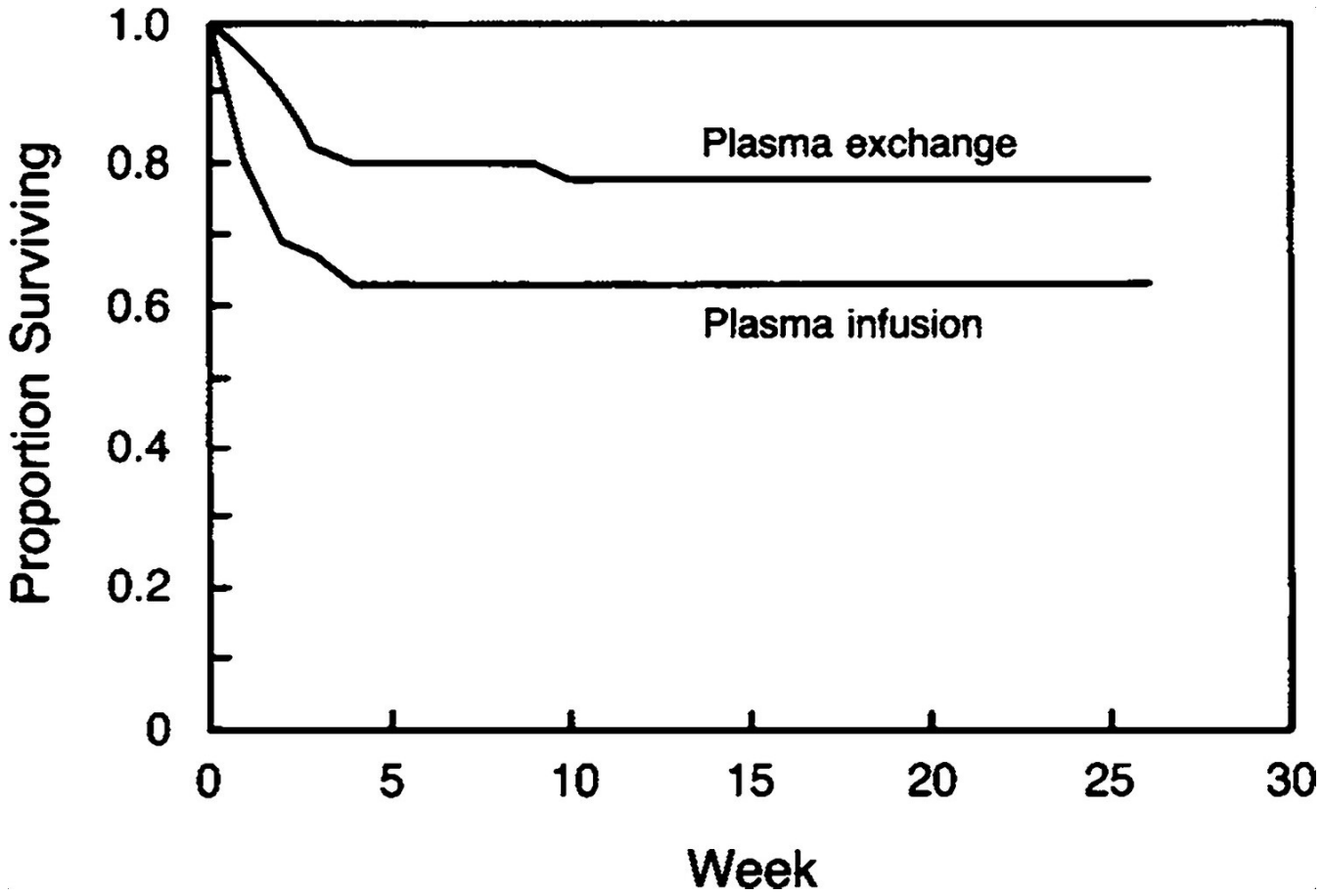
aTTP – Therapieoptionen



Rock GA et al. N Engl J Med 1991;325:393-397

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aTTP – Therapieoptionen

398 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 8, 1991

IMPROVED SURVIVAL IN THROMBOTIC THROMBOCYTOPENIC PURPURA–HEMOLYTIC UREMIC SYNDROME

Clinical Experience in 108 Patients

WILLIAM R. BELL, M.D., HAYDEN G. BRAINE, M.D., PAUL M. NESS, M.D., AND THOMAS S. KICKLER, M.D.

Abstract *Background and Methods.* Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, central nervous system abnormalities, and renal dysfunction. In early reports the mortality approached 100 percent. A treatment protocol was introduced in 1979 for patients admitted to Johns Hopkins Hospital with the diagnosis of TTP-HUS. Treatment regimens included 200 mg of prednisone a day, for patients with minimal symptoms and no central nervous system symptoms, and prednisone plus plasma exchange, for patients with rapid clinical deterioration who did not improve after 48 hours of prednisone alone and for patients presenting with central nervous system symptoms and rapidly declining hematocrit values and platelet counts.

Results. A total of 108 patients were treated, and 91 percent survived. Prednisone alone was judged to be effective in 30 patients with mild TTP-HUS (2 relapses and 2 deaths). Plasma exchange plus prednisone was given to 78 patients with complicated TTP-HUS, resulting in 67 relapses and 8 deaths. Relapses occurred in 22 of 36 patients given maintenance plasma infusions. Neither splenectomy nor treatment with aspirin and dipyridamole was effective in those with a poor response to plasma exchange. None of the 71 patients tested had positive cultures for O157:H7 *Escherichia coli*. Nine percent of the patients were pregnant, and none gave birth to infants with TTP-HUS.

Conclusions. Effective treatment with 91 percent survival is available for patients with TTP-HUS. (N Engl J Med 1991; 325:398-403.)

Bell WR et al. N Engl J Med 1991;325:398-403

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aTTP – Therapieoptionen

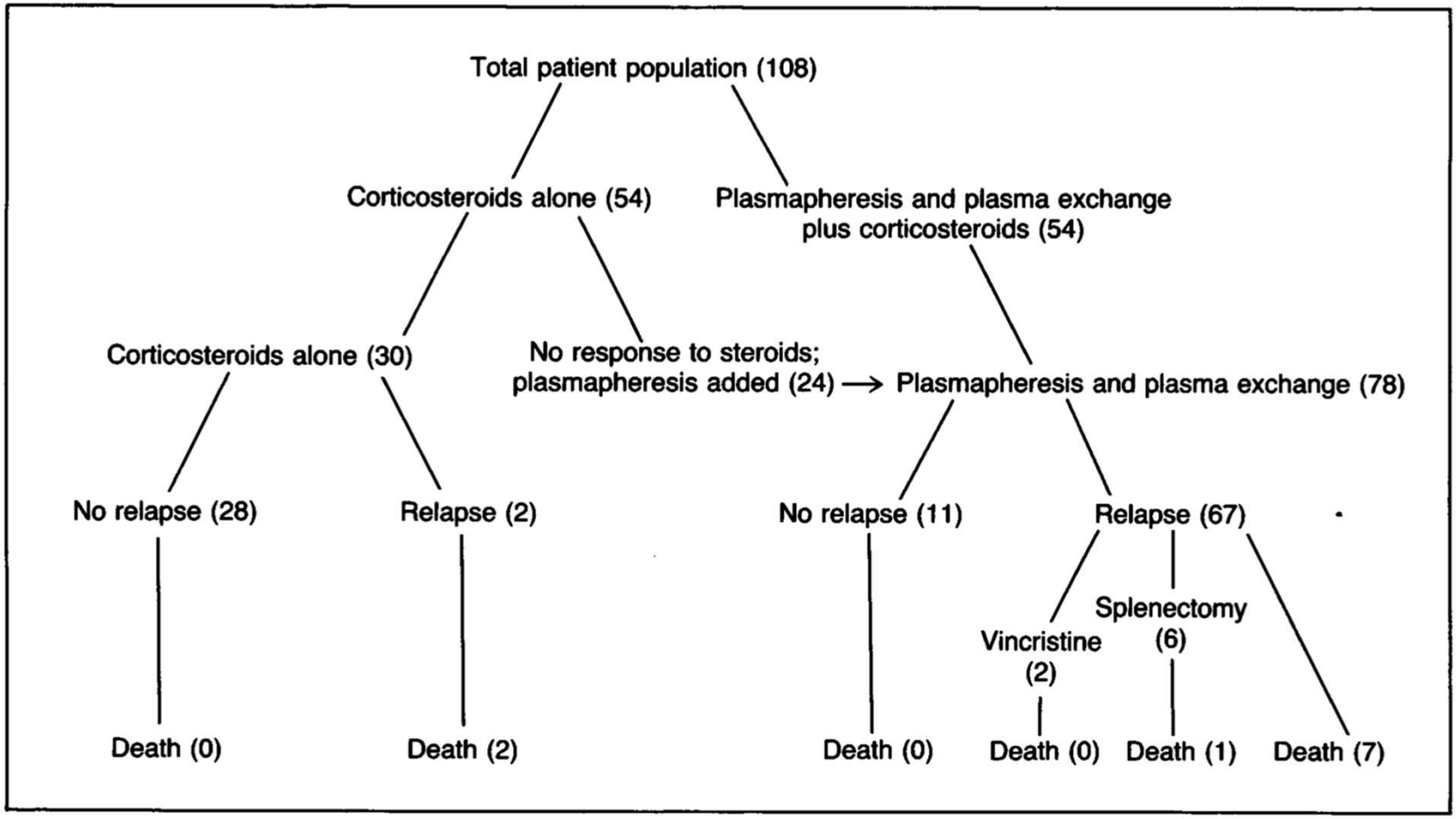

Figure 1. Flow Diagram of the Course of 108 Patients from the Time of Entry into the Study to Treatment and Final Outcome. The numbers in parentheses are the number of patients in each category.

Bell WR et al. N Engl J Med 1991;325:398-403

aTTP – Therapieoptionen

American Journal of Hematology 71:105–108 (2002)

Successful Treatment of Severe Thrombotic Thrombocytopenic Purpura With the Monoclonal Antibody Rituximab

Jens Chemnitz,* Andreas Draube, Christof Scheid, Peter Staib, Armin Schulz, Volker Diehl, and Dietmar Söhngen

Department I of Internal Medicine, University of Cologne, Germany

Chemnitz J et al. Am J Hemat 2002;71:105-108

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aTTP – Therapieoptionen

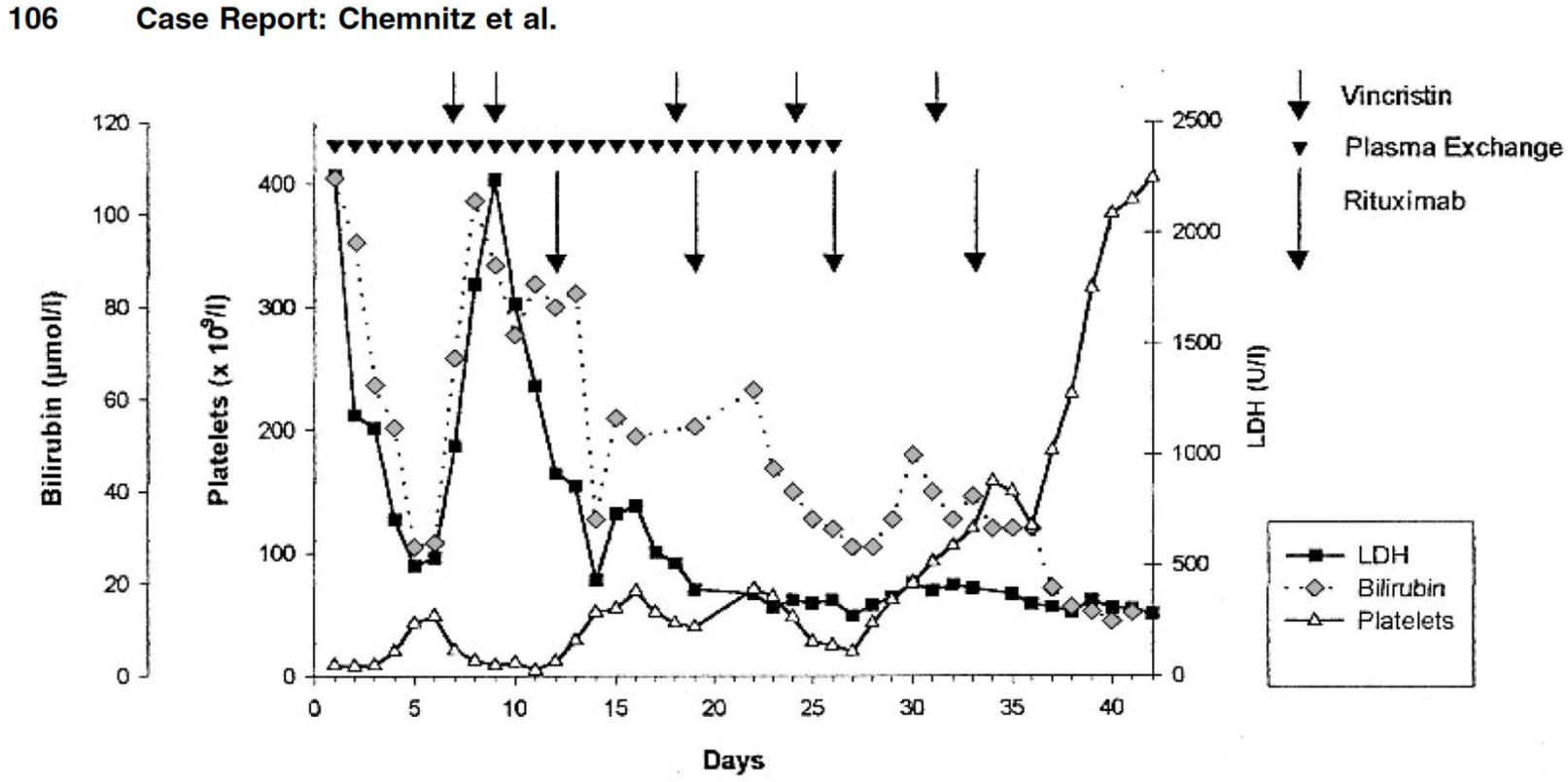

Fig. 1. Clinical course and treatment of patient 1.

Chemnitz J et al. Am J Hemat 2002;71:105-108

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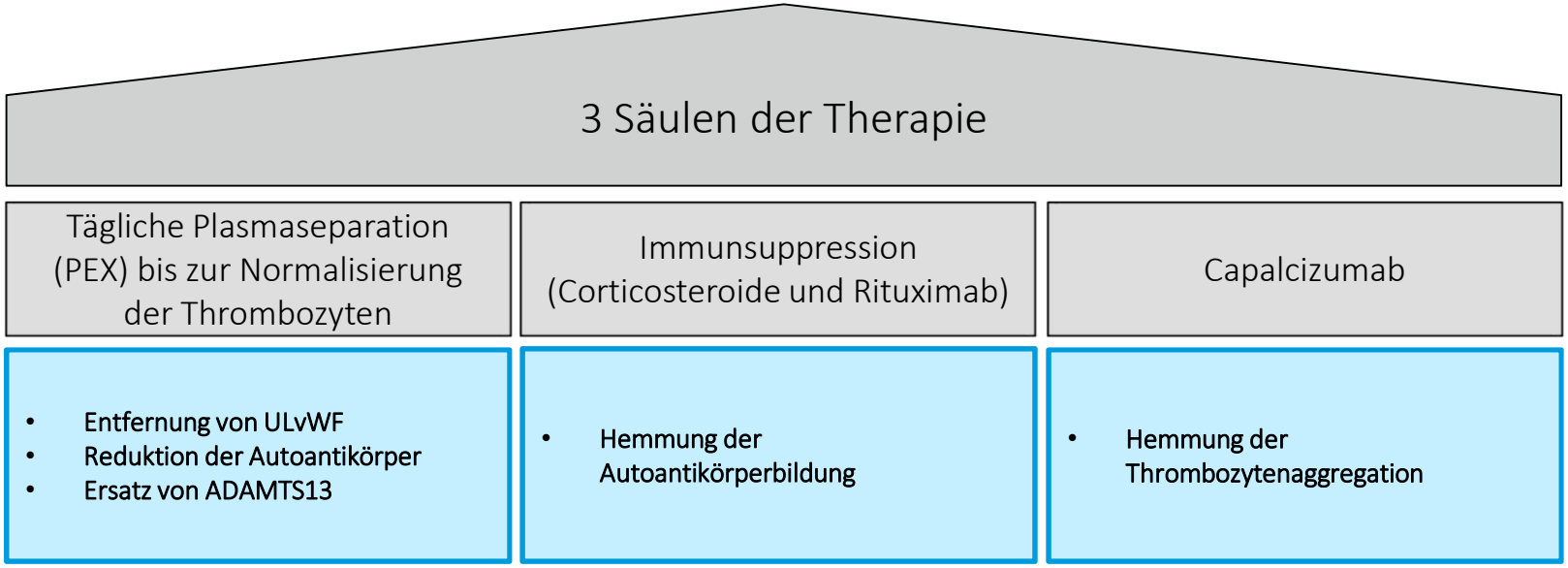
aTTP – neue Therapieoptionen



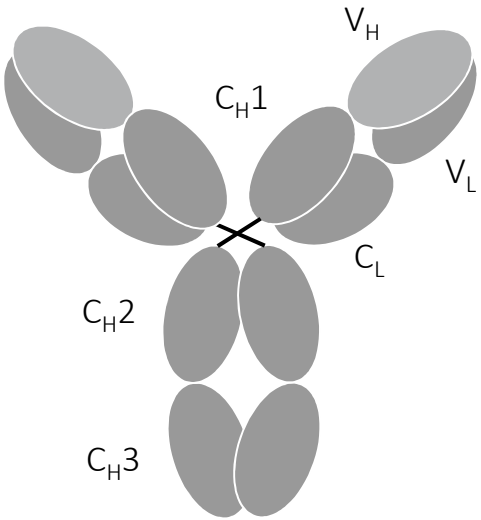
PEX: Plasmaseparation
ULvWF: Ultra-large von Willebrand Factor
ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13

nach Scully M et al. Br J Haematol. 2012; 158(3): 323-35.

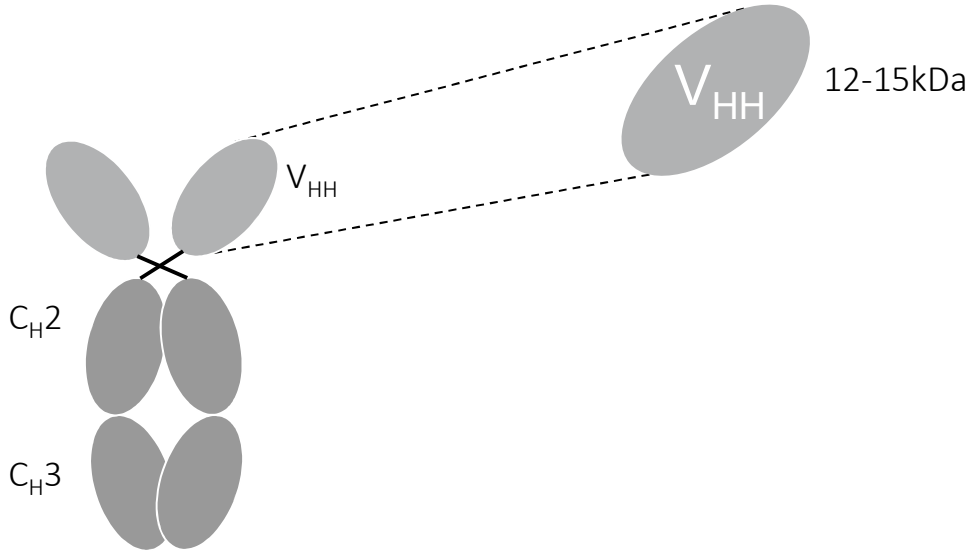
aTTP – neue Therapieoptionen

Caplacizumab: hoch potenter bivalenter anti-vWF Nanobody

- *"Camelid* heavy-chain only antibody"
- 28 kD bivalenter Nanobody
- Ziel: Thrombozytenbindende Domäne A1 von vWF
- Hergestellt in *E. coli*



herkömmliche Antikörper



"Heavy chain only" Antikörper

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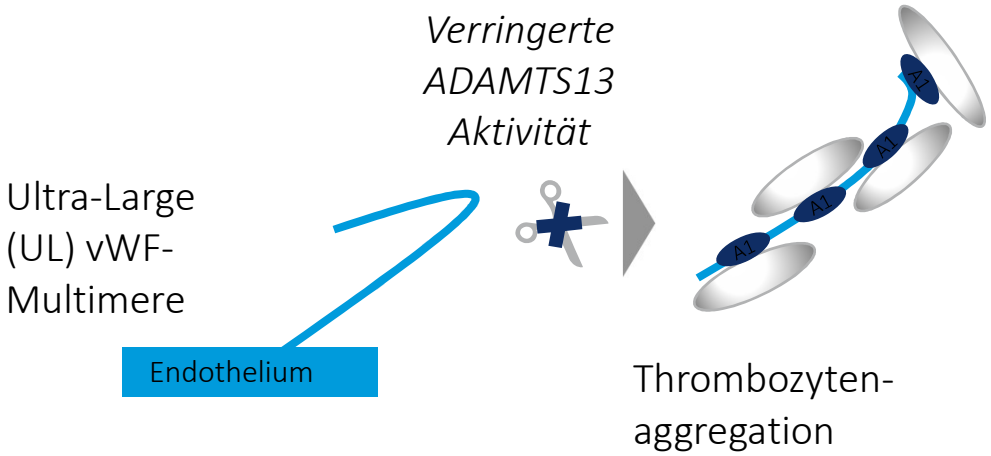
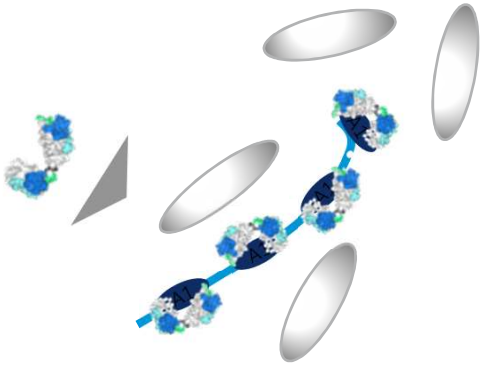
aTTP – neue Therapieoptionen

Caplacizumab blockiert die Interaktion zwischen Thrombozyten und vWF



Caplacizumab bindet an A1-Domäne von vWF und hemmt die Thrombozytenaggregation



nach Holz JB. Transfus Apher Sci. 2012; 46: 343-6.

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aTTP – neue Therapieoptionen (TITAN Studie)

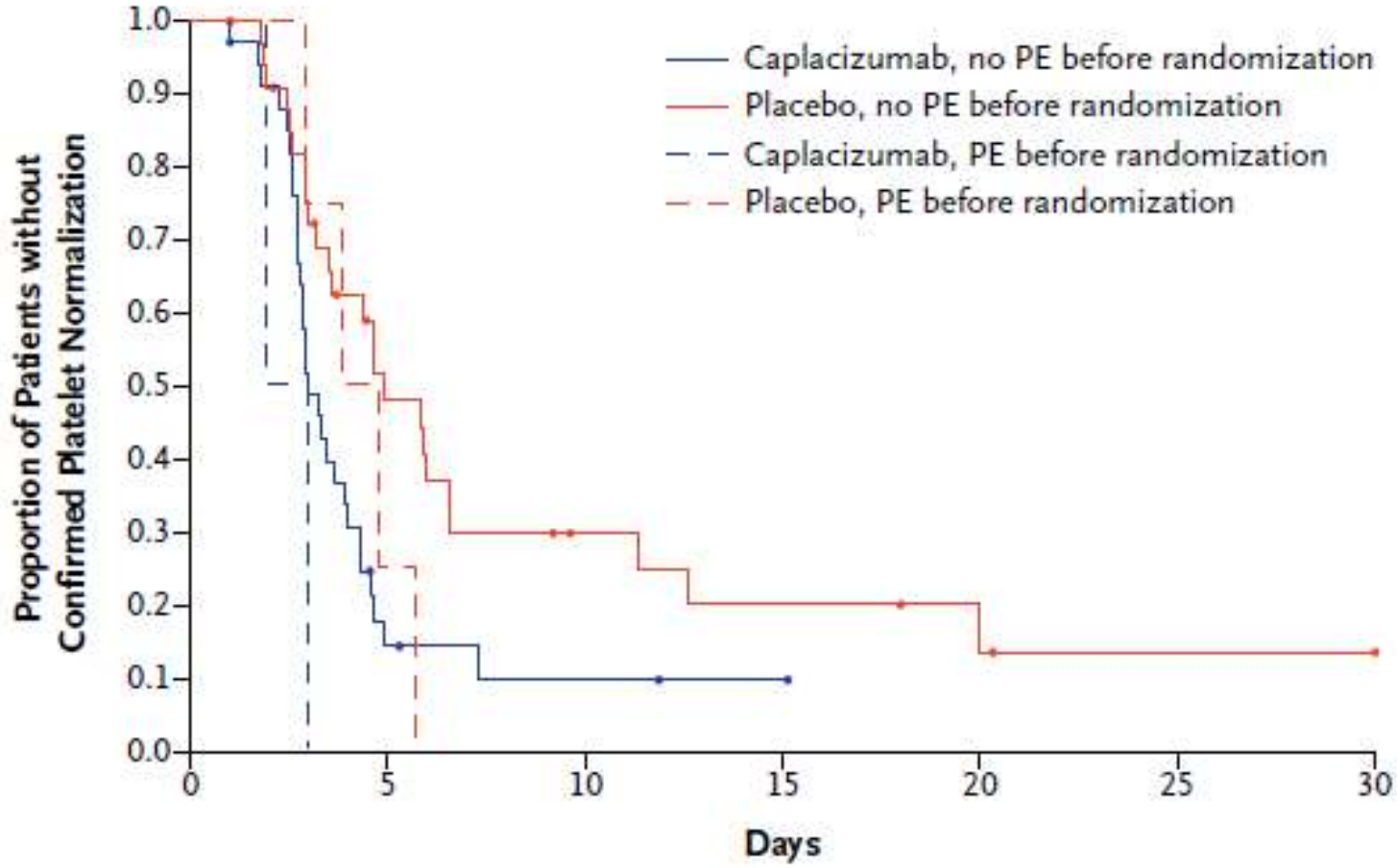
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2016 VOL. 374 NO. 6

Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

Flora Peyvandi, M.D., Ph.D., Marie Scully, M.D., Johanna A. Kremer Hovinga, M.D., Spero Cataland, M.D., Paul Knöbl, M.D., Haifeng Wu, M.D.,* Andrea Artoni, M.D., John-Paul Westwood, M.D., Magnus Mansouri Taleghani, M.D., Bernd Jilma, M.D., Filip Callewaert, Ph.D., Hans Ulrichts, Ph.D., Christian Duby, M.D., and Dominique Tersago, M.D., for the TITAN Investigators†

aTTP – TITAN Studie (primärer Endpunkt)



Peyvandi F et al. N Engl J Med 2016; 374: 511-522

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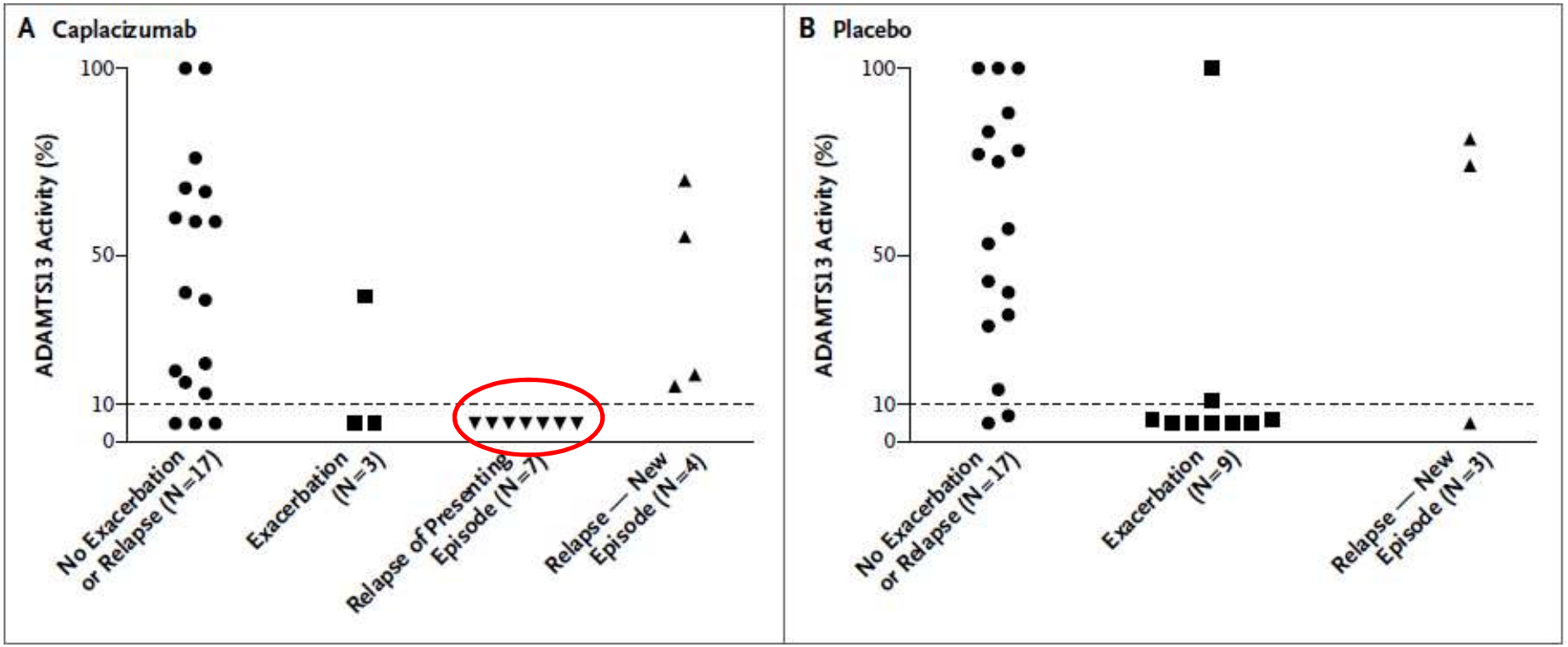
aTTP – TITAN Studie (sekundäre Endpunkte)

Table 2. Primary and Secondary Efficacy End Points in the Intention-to-Treat Population.

End Point	Caplacizumab (N=36)	Placebo (N=39)
Primary end point		
Time to response: caplacizumab vs. placebo		
Event rate ratio (95% CI)*	2.20 (1.28–3.78)	
P value†	0.005	
Patients with no PE before randomization		
Median time to response (95% CI) — days	3.0 (2.7–3.9)	4.9 (3.2–6.6)
Confirmed response — no. (%)	29 (81)	24 (62)
Data censored at 30 days — no. (%)	5 (14)	11 (28)
Patients with one PE before randomization		
Median time to response (95% CI) — days	2.4 (1.9–3.0)	4.3 (2.9–5.7)
Confirmed response — no. (%)	2 (6)	4 (10)
Data censored at 30 days — no. (%)	0	0
Secondary end points		
Exacerbation of TTP — no. (%)‡	3 (8)	11 (28)
Relapse — no. (%)		
During 1-mo follow-up period	8 (22)	0
During 12-mo follow-up period§	11 (31)	3 (8)
Complete remission after initial daily PE — no. (%)¶	29 (81)	18 (46)
Mean no. of PE days (range)		
During daily PE period	5.9 (3–15)	7.9 (2–35)
During overall study-drug treatment period	7.7 (3–21)	11.7 (2–43)
During the first 30 days of follow-up	10.2 (4–29)	11.7 (2–43)

Peyvandi F et al. N Engl J Med 2016; 374: 511-522

aTTP – TITAN Studie (ADAMTS13 Aktivität)



Peyvandi F et al. N Engl J Med 2016; 374: 511-522

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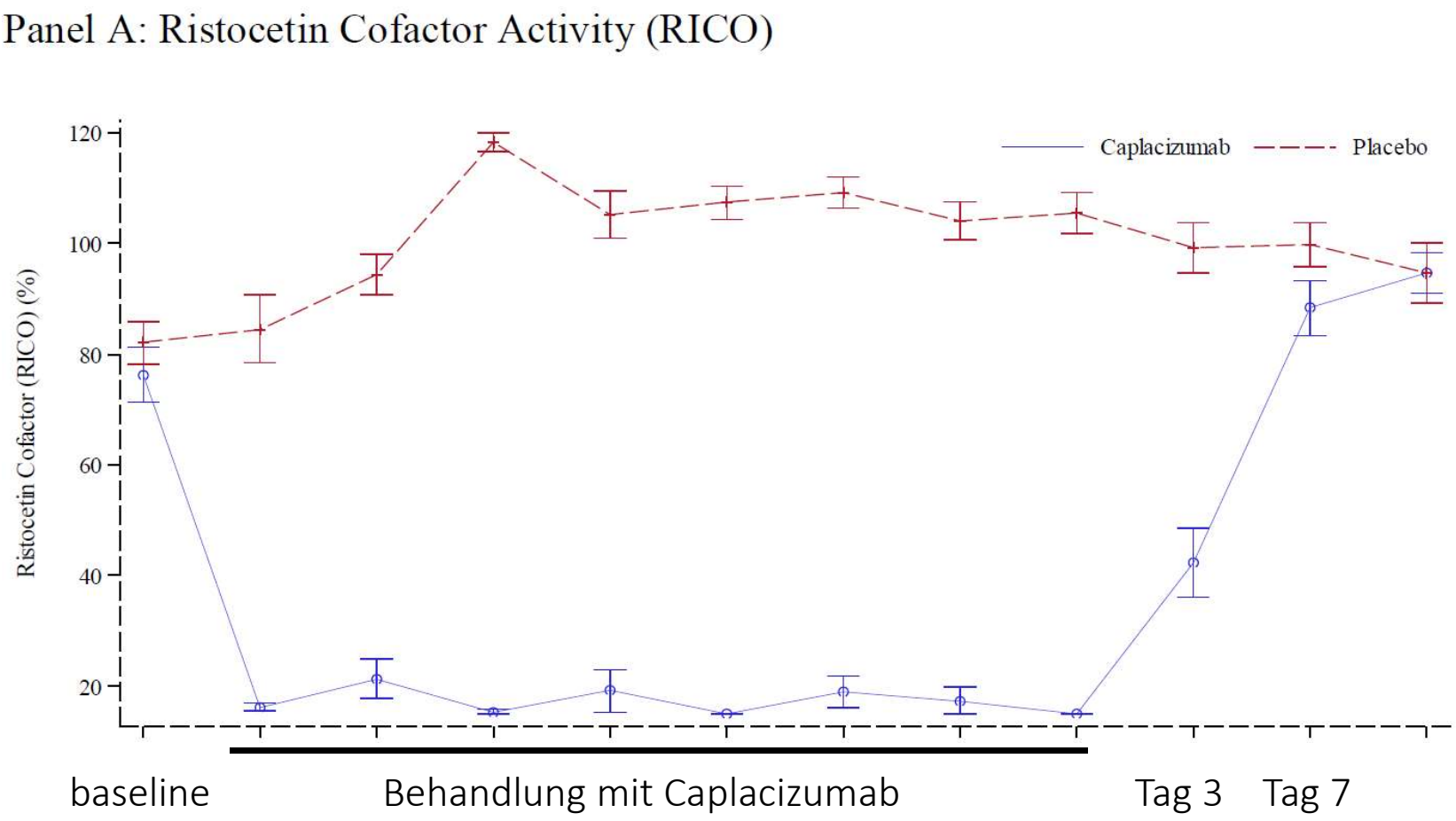
aTTP – TITAN Studie (Pharmakokinetik)



Peyvandi F et al. N Engl J Med 2016; 374: 511-522

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aTTP – TITAN Studie (Patientencharakteristika)

Table 1. Baseline Characteristics and Therapy in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=36)	Placebo (N=39)	Total (N=75)
Mean age (range) — yr	41 (19–72)	42 (21–67)	42 (19–72)
Female sex — no. (%)	24 (67)	20 (51)	44 (59)
Race — no. (%)†			
White	32 (89)	34 (87)	66 (88)
Black	4 (11)	5 (13)	9 (12)
Presenting episode of TTP — no. (%)			
Initial	24 (67)	27 (69)	51 (68)
Recurrent	12 (33)	12 (31)	24 (32)
Mean platelet count (range) — per mm^3‡	21,100 (2000–70,000)	28,000 (5000–84,000)	24,600 (2000–84,000)
Mean LDH (range) — U/liter§	1277 (240–3874)	1270 (247–4703)	1274 (240–4703)
ADAMTS13 activity — no. (%)			
<10%	28 (78)	30 (77)	58 (77)
≥10%	2 (6)	6 (15)	8 (11)
Missing data	6 (17)	3 (8)	9 (12)
PE tapering — no. (%)	11 (31)	11 (28)	22 (29)
Glucocorticoids during daily PE — no. (%)	32 (89)	36 (92)	68 (91)
Rituximab during daily PE — no. (%)¶	2 (6)	9 (23)	11 (15)

Peyvandi F et al. N Engl J Med 2016; 374: 511-522

aTTP – neue Therapieoptionen (HERCULES Studie)

The NEW ENGLAND JOURNAL of MEDICINE

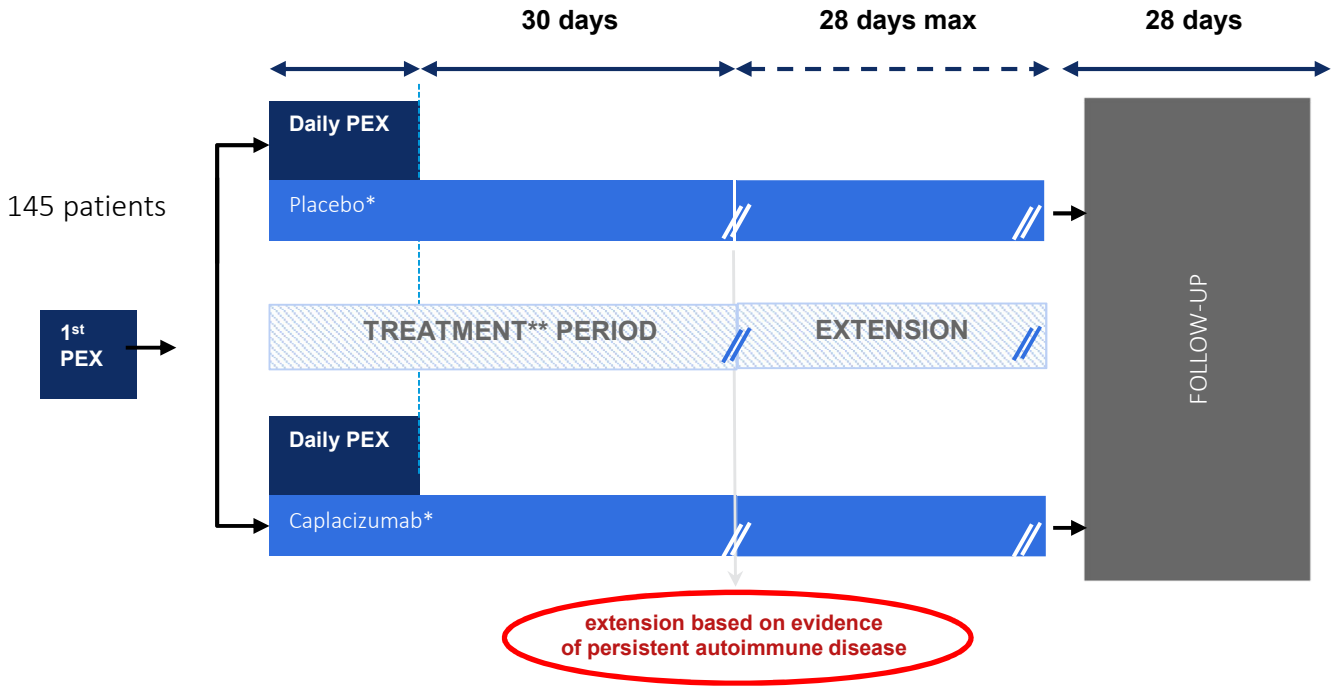
ORIGINAL ARTICLE

Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura

M. Scully, S.R. Cataland, F. Peyvandi, P. Coppo, P. Knöbl, J.A. Kremer Hovinga, A. Metjian, J. de la Rubia, K. Pavenski, F. Callewaert, D. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

N ENGL J MED 380;4 NEJM.ORG JANUARY 24, 2019

aTTP – Caplacizumab Phase III Studie (HERCULES)



** iv bolus (10mg) followed by daily sc (10mg) ** including corticosteroids at start of daily PEX until underlying disease activity resolved*

Primary endpoint: time to confirmed normalisation of platelet count response

Secondary endpoints:
- aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period
- recurrence of aTTP in the overall study period
- refractoriness to treatment
- time to normalisation of 3 organ damage markers

nach Scully M (Vortrag ASH 2018)

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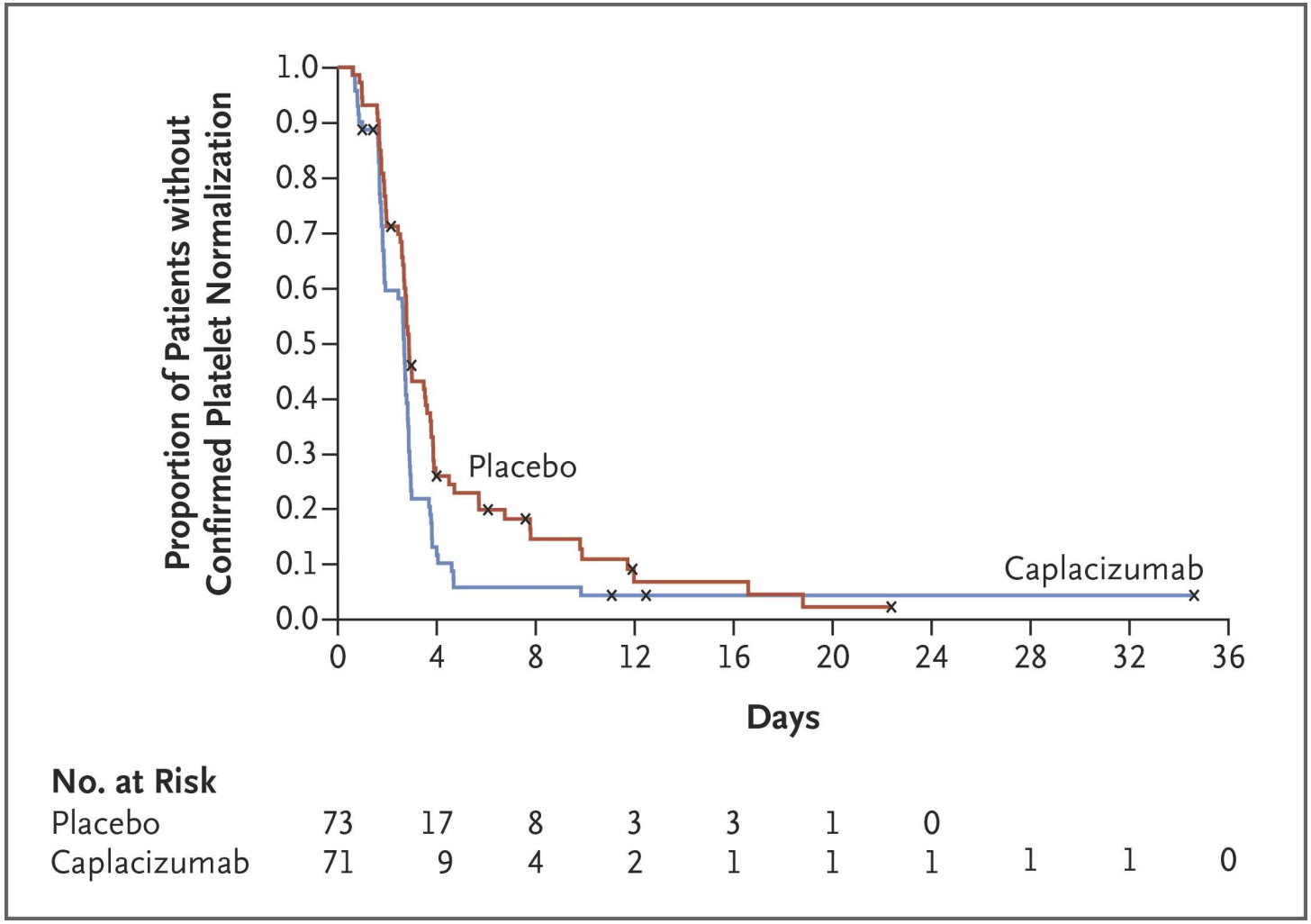
Primärer Endpunkt
Dauer bis zur Normalisierung der Thrombozyten



Scully M et al. N Engl J Med 2019;380:335-346

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Primärer Endpunkt

Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population.

Outcome	Caplacizumab (N = 72)	Placebo (N = 73)	P Value
Primary outcome			
Time to normalization of platelet count			
25th Percentile (95% CI) — days	1.75 (1.65–1.87)	1.94 (1.70–2.64)	
50th Percentile (95% CI) — days	2.69 (1.89–2.83)	2.88 (2.68–3.56)	
75th Percentile (95% CI) — days	2.95 (2.85–3.81)	4.50 (3.78–7.79)	
Rate ratio for normalization of platelet count, caplacizumab vs. placebo (95% CI)*	1.55 (1.09–2.19)		0.01

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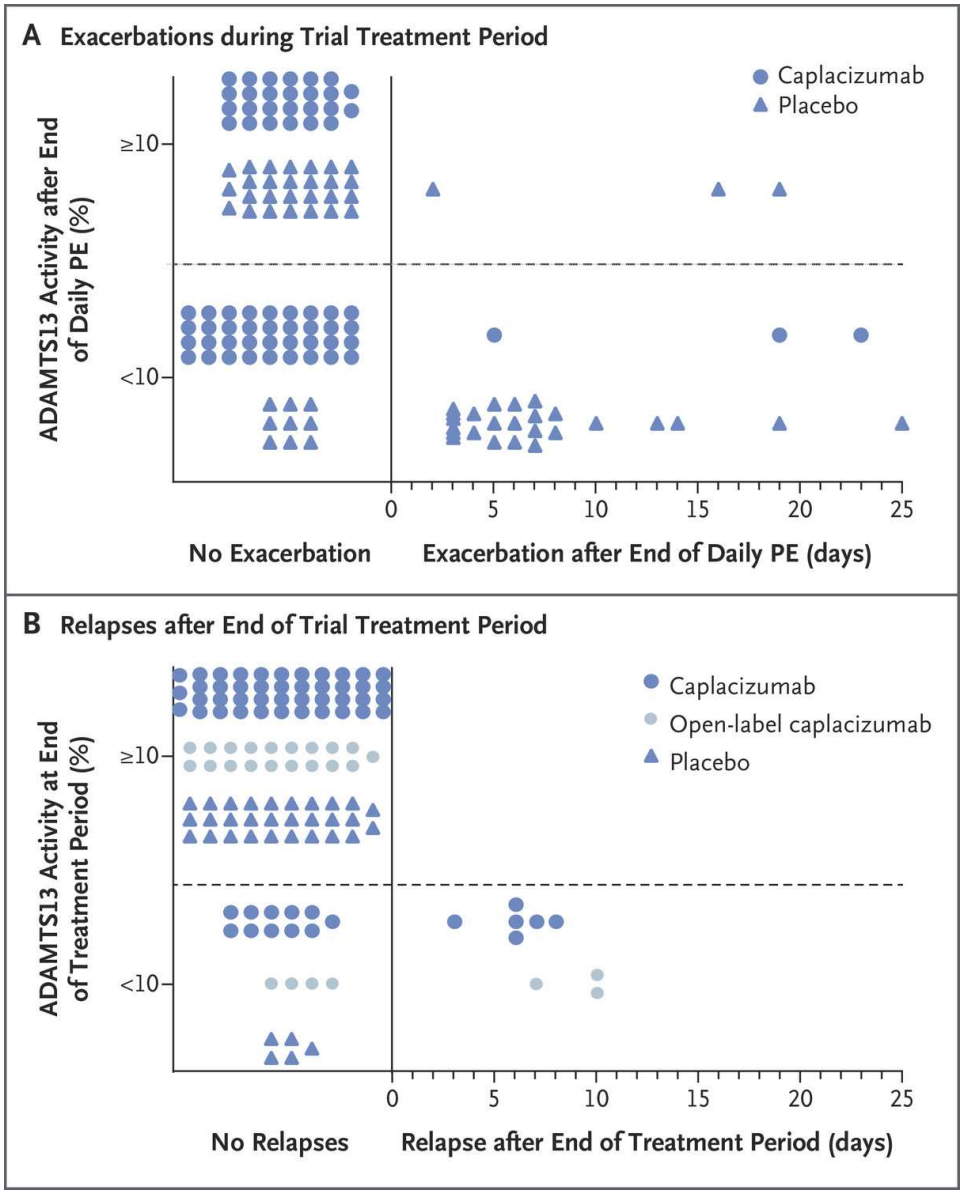
Sekundäre Endpunkte

Table 2. Primary and Secondary Efficacy Outcomes in the Intention-to-Treat Population.

Outcome	Caplacizumab (N = 72)	Placebo (N = 73)	P Value
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP, or major thromboembolic event during the double-blind treatment period — no. (%)	9 (12)	36 (49)	<0.001
TTP-related death	0	3 (4)	
Recurrence of TTP: exacerbation†	3 (4)	28 (38)	
Major thromboembolic event	6 (8)	6 (8)	
Recurrence of TTP at any time during the trial — no. (%)†	9 (12)	28 (38)	<0.001
During the double-blind treatment period: exacerbation	3 (4)	28 (38)	
During the follow-up period: relapse‡	6 (8)	0	
Refractory TTP — no. (%)§	0	3 (4)	0.06
Median time to normalization of organ-damage markers (95% CI) — days	2.86 (1.93–3.86)	3.36 (1.88–7.71)	
Other secondary outcomes¶			
Number of days of plasma exchange			
Mean (95% CI)	5.8 (4.8–6.8)	9.4 (7.8–11.0)	
Median (range)	5.0 (1.0–35.0)	7.0 (3.0–46.0)	
Volume of plasma exchanged — liters			
Mean (95% CI)	21.3 (18.1–24.6)	35.9 (27.6–44.2)	
Median (range)	18.1 (5.3–102.2)	26.9 (4.0–254.0)	
No. of days of hospitalization			
Mean (95% CI)	9.9 (8.5–11.3)	14.4 (12.0–16.9)	
Median (range)	9.0 (2.0–37.0)	12.0 (4.0–53.0)	
Patients admitted to the intensive care unit — no. (%)‖	28 (39)	27 (37)	
No. of days in the intensive care unit			
Mean (95% CI)	3.4 (2.6–4.2)	9.7 (5.3–14.1)	
Median (range)	3.0 (1.0–10.0)	5.0 (1.0–47.0)	

Scully M et al. N Engl J Med 2019

HERCULES Studie – Exazerbationen / Relapse



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Patientencharakteristika (1)

Table 1. Demographic and Baseline Disease Characteristics and Concomitant Treatments for TTP in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=72)	Placebo (N=73)	Total (N=145)
Demographic and baseline disease characteristics			
Mean age (range) — yr	45 (18–77)	47 (21–79)	46 (18–79)
Female sex — no. (%)	49 (68)	51 (70)	100 (69)
Mean body-mass index (range)†	30 (18–53)	30 (19–59)	36 (18–59)
Race — no. (%)‡			
White	47 (65)	50 (68)	97 (67)
Black	15 (21)	13 (18)	28 (19)
Asian	4 (6)	0	4 (3)
Other	3 (4)	1 (1)	4 (3)
Data missing	3 (4)	9 (12)	12 (8)
Hispanic or Latino ethnic group — no. (%)‡	4 (6)	2 (3)	6 (4)
Presenting episode of TTP — no. (%)§			
Initial	48 (67)	34 (47)	82 (57)
Recurrent	24 (33)	39 (53)	63 (43)
Median platelet count (range) — per mm^3¶‖	24,000 (3,000–119,000)	25,000 (9,000–133,000)	24,000 (3,000–133,000)
Median lactate dehydrogenase (range) — U per liter‖	449 (120–2525)	403 (151–3343)	422 (120–3343)
Median cardiac troponin I (range) — μg per liter‖	0.09 (0.01–75.96)	0.07 (0.01–7.28)	0.08 (0.01–75.96)
Median serum creatinine (range) — μmol per liter‖	77 (35–717)	82 (52–482)	80 (35–717)
ADAMTS13 activity — no. (%)‖**			
<10%	58 (81)	65 (89)	123 (85)
≥10%	13 (18)	7 (10)	20 (14)
Data missing	1 (<1)	1 (<1)	2 (1)
Glasgow Coma Scale score — no. (%)††			
≤12	6 (8)	5 (7)	11 (8)
13 to 15	65 (90)	67 (92)	132 (91)
Data missing	1 (<1)	1 (<1)	2 (1)

Scully M et al. N Engl J Med 2019

Patientencharakteristika (2)

Table 1. Demographic and Baseline Disease Characteristics and Concomitant Treatments for TTP in the Intention-to-Treat Population.*

Characteristic	Caplacizumab (N=72)	Placebo (N=73)	Total (N=145)
Immunosuppressive therapy — no. (%)			
Glucocorticoids	69 (96)	71 (97)	140 (97)
Rituximab	28 (39)	35 (48)	63 (43)
Frontline, started by trial day 3	9 (12)	16 (22)	25 (17)
During daily plasma exchange, started after trial day 3	3 (4)	7 (10)	10 (7)
After the period of daily plasma exchange	11 (15)	6 (8)	17 (12)
During daily plasma exchange among patients who had exacerbation	0	1 (1)	1 (1)
After the period of daily plasma exchange among patients who had exacerbation	0	2 (3)	2 (1)
During the follow-up period	5 (7)	3 (4)	8 (6)
Mycophenolate mofetil	6 (8)	0	6 (4)
Hydroxychloroquine	2 (3)	1 (1)	3 (2)
Bortezomib	2 (3)	0	2 (1)
Cyclophosphamide	1 (1)	1 (1)	2 (1)
Cyclosporin	1 (1)	1 (1)	2 (1)
Other treatments for TTP — no. (%)			
Splenectomy			
Performed before the start of the trial	0	5 (7)	5 (3)
Performed during the trial	2 (3)	1 (1)	3 (2)
Immune globulin concentrate infusion	4 (6)	0	4 (3)
Immunoadsorption	1 (1)	0	1 (1)

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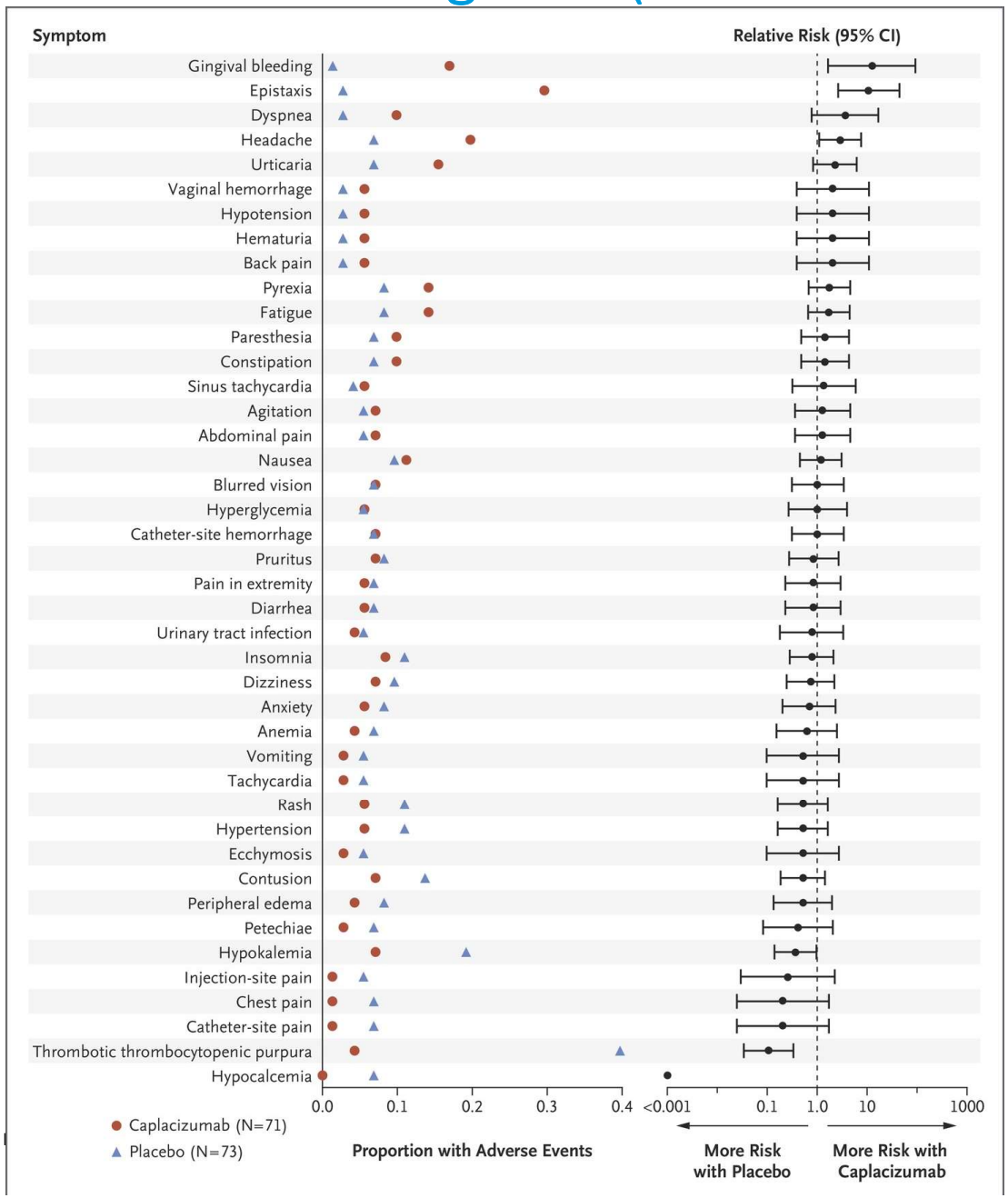
Unerwünschte Ereignisse (*adverse events*)



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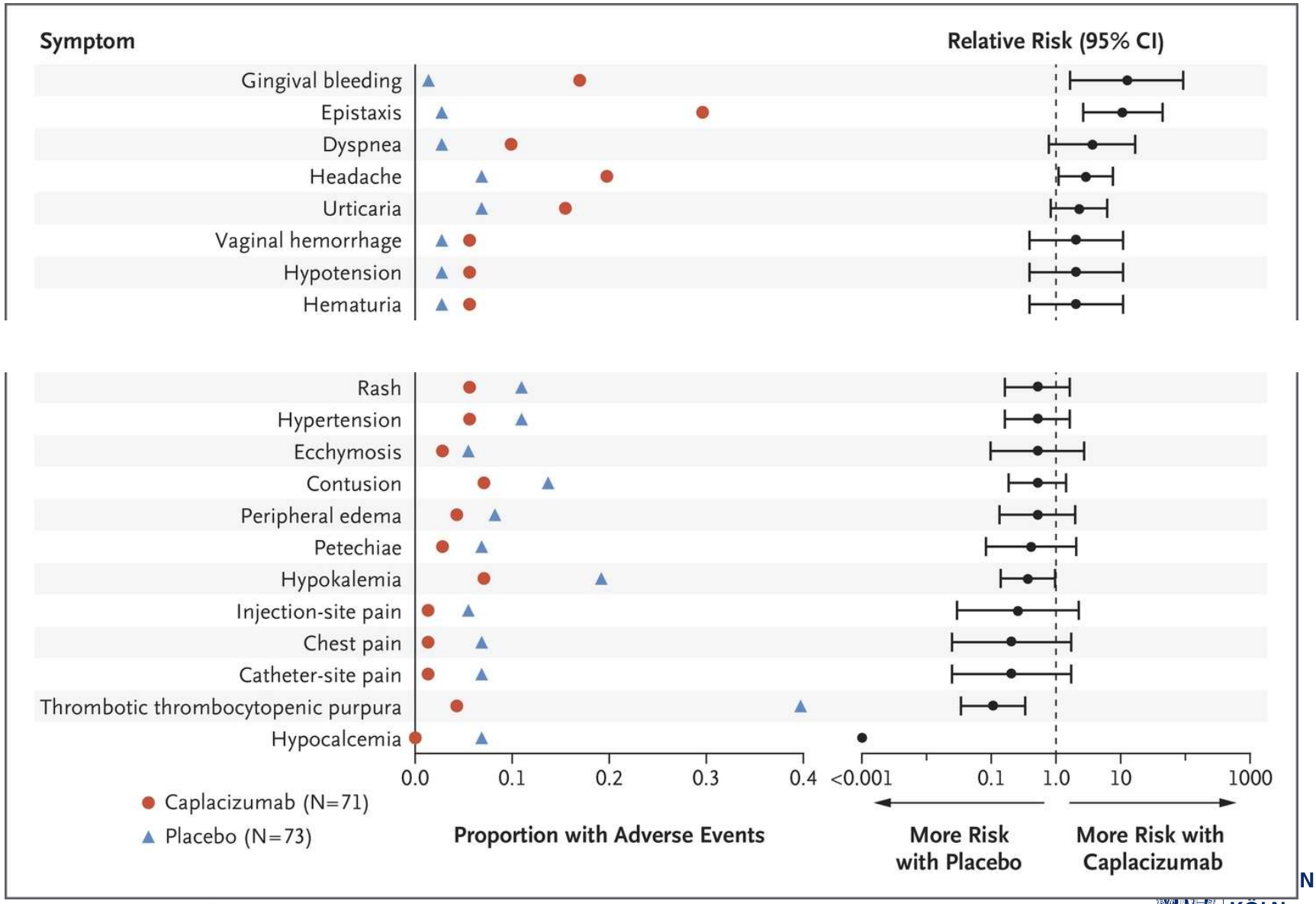
Unerwünschte Ereignisse (*adverse events*)



Phase III HERCULES Studie – Schlussfolgerungen

- Signifikant schneller Normalisierung der Thrombozytenzahlen im Rahmen einer akuten aTTP Episode
- Signifikante Reduktion der aTTP-assozierten Mortalität, aTTP-Exazerbation sowie von schweren, thrombembolischen Ereignissen
- Verbesserte Prävention von erneuten aTTP Episoden (*relapse*)
- Signifikant reduzierter Plasmaverbrauch
- Signifikant reduzierte ITS Aufenthalte / Krankenhausverweildauer
- Akzeptables Sicherheitsprofi

Zulassung durch die EMA

- Zulassung von Caplacizumab (Cablivi®) durch die EMA als Orphan Drug seit 1.10.2018 in der Behandlung einer erworbenen TTP (aTTP)

„Cablivi wird zur Behandlung von Erwachsenen, die an einer Episode von erworbener thrombotisch-thrombozytopenischer Purpura (acquired thrombotic thrombocytopenic purpura, aTTP) leiden, in Verbindung mit Plasmapherese und Immunsuppression angewendet."

- Erstdosis i.v. 10 mg Caplacizumab vor der Plasmapherese
- Folgedosen: Tägliche s.c. Gabe 10 mg Caplacizumab nach jeder Plasmapherese.
  Danach tägliche s.c. Injektion von 10 mg Caplacizumab über 30 Tage nach Beendigung der täglichen Plasmapherese.
- Fortsetzung je nach Anzeichen einer noch vorhandenen immunologischen Erkrankung

Zusammenfassung

- Capalcizumab als dritte Säule der aTTP-Therapie
- Signifikant schneller Normalisierung der Thrombozytenzahlen
- Reduktion der aTTP-assozierten Morbidität und Mortalität

Zusammenfassung

Offene Fragen:

- Caplacizumab für alle aTTP Fälle oder nur bei ”schweren” Fällen ?

Zusammenfassung

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- Caplacizumab für alle aTTP Fälle oder nur bei ”schweren” Fällen ?

- Stellenwert der ADAMTS13 Aktivität zur Steuerung der Therapiedauer ?

….Therapie mit Caplacizumab beenden wenn ADAMTS13 Aktivität >20-30%

….Therapie mit Caplacizumab verlängern (bis zu 58 Tage) wenn ADAMTS13 anhaltend <10% sowie engmaschige Kontrollen nach Absetzen der Therapie

Zusammenfassung

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- Beendigung der Plasmaseparation ?
  - Ansteigende Thrombozytenzahlen ?
  - Normalisierung der Thrombozytenzahlen ?
  - 150 Tsd plus 2?
  - Plateau?

Zusammenfassung

Offene Fragen:

- Caplacizumab für alle aTTP Fälle oder nur bei ”schweren” Fällen ?

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- Beendigung der Plasmaseparation ?
  - Ansteigende Thrombozytenzahlen ?
  - Normalisierung der Thrombozytenzahlen ?
  - 150 Tsd plus 2?
  - Plateau?

- Stellenwert der Rituximab-Therapie ?
  - – firstline innerhalb der ersten Tage vs. im Verlauf / nur bei “schweren” Fällen

Vielen Dank!

paul.brinkkoetter@uk-koeln.de

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