Thrombotic thrombocytopenic purpura: a look at the future

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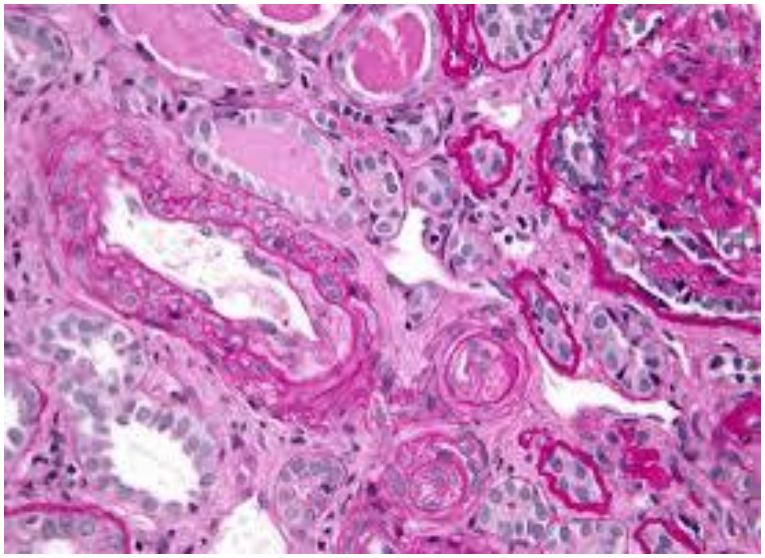
Thrombotic microangiopathies (TMAs)

Characterized by:

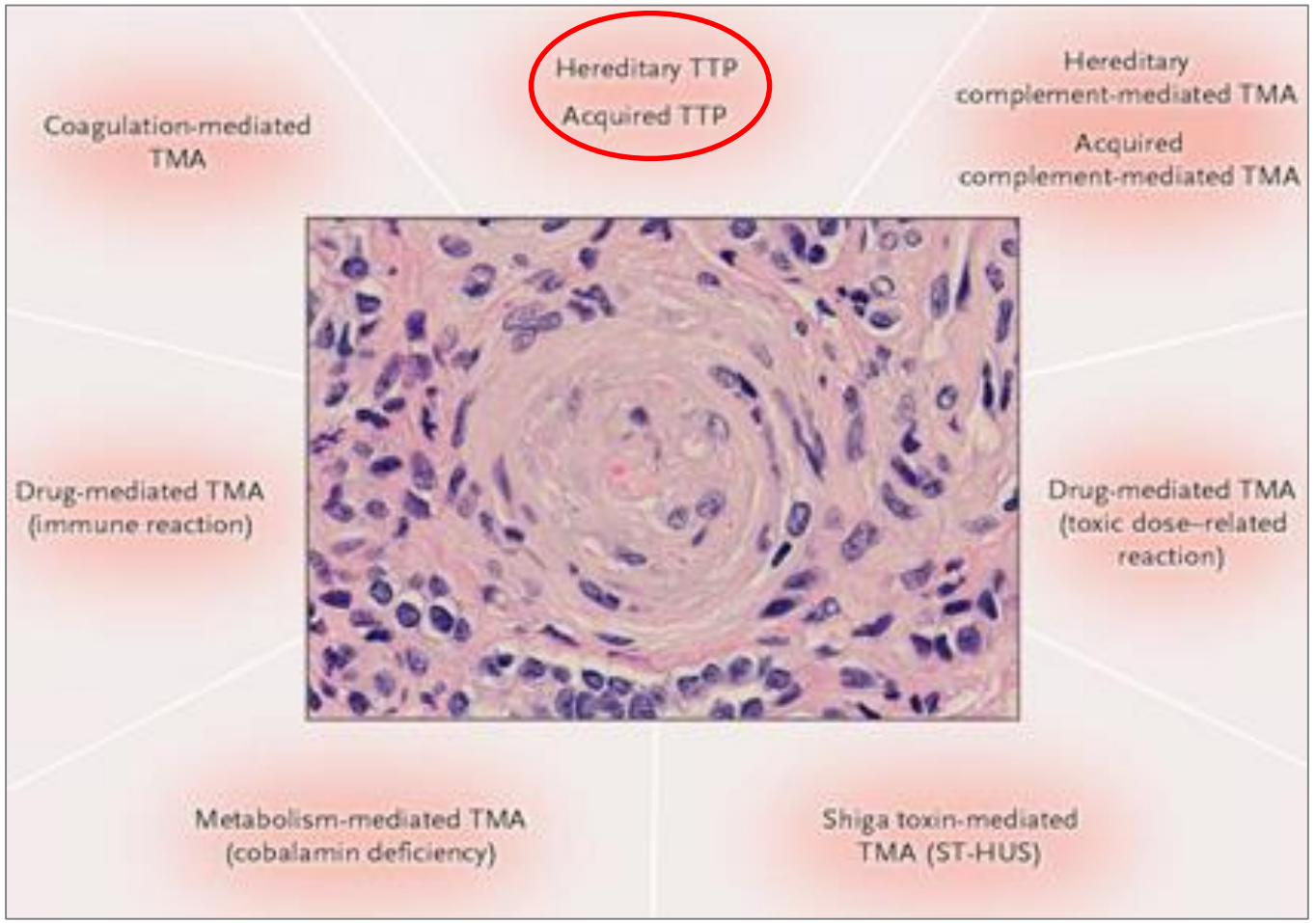
- **Widespread ischemic damage**
  (due to microthrombosis in arterioles)
- **Thrombocytopenia**
  (due to platelet trapping)
- **Microangiopathic hemolytic anemia**
  (due to red blood cell fragmentation)



George JN, Blood 2010

TMAs: one term, many diseases

Represent the final common pathway
of a multitude of clinical syndromes:



George JN, NEJM 2014

TTP

First described in 1924 by Moschcowitz, TTP is a thrombotic microangiopathy characterized by:

- Disseminated formation of platelet-rich thrombi in the microvasculature

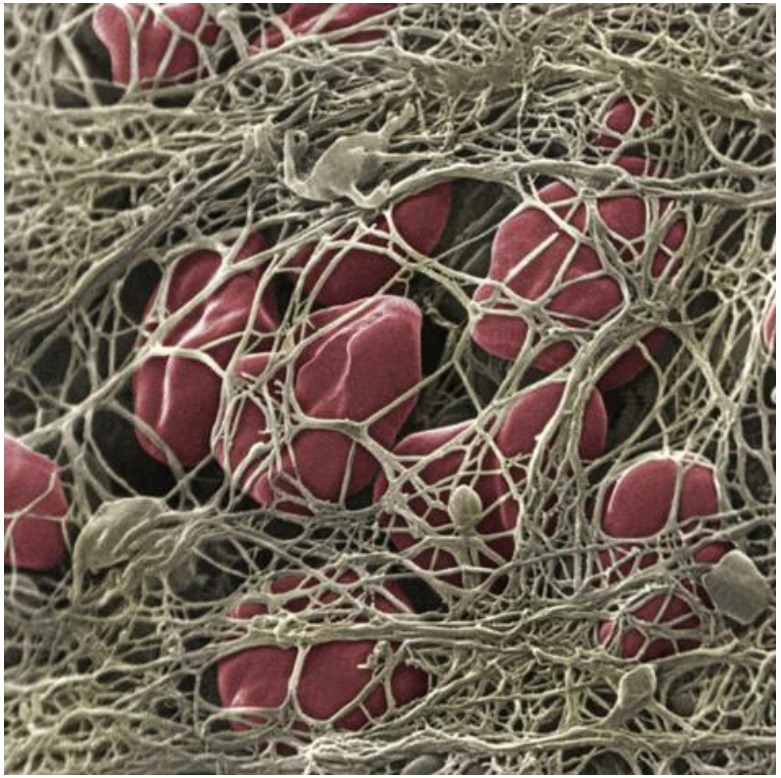
  → Tissue ischemia with neurological, myocardial, renal signs & symptoms

- Platelets consumption

  → Severe thrombocytopenia

- Red blood cell fragmentation

  → Hemolytic anemia



TTP epidemiology

- Acute onset
- Rare: 5-11 cases / million people / year
- Two forms: congenital (<5%), acquired (>95%)
- M:F ratio 1:3
- Peak of incidence: III-IV decades
- Mortality reduced from 90% to 10-20% with appropriate therapy
- Risk of recurrence: 30-35%

Peyvandi et al, Haematologica 2010

TTP clinical features

Bleeding

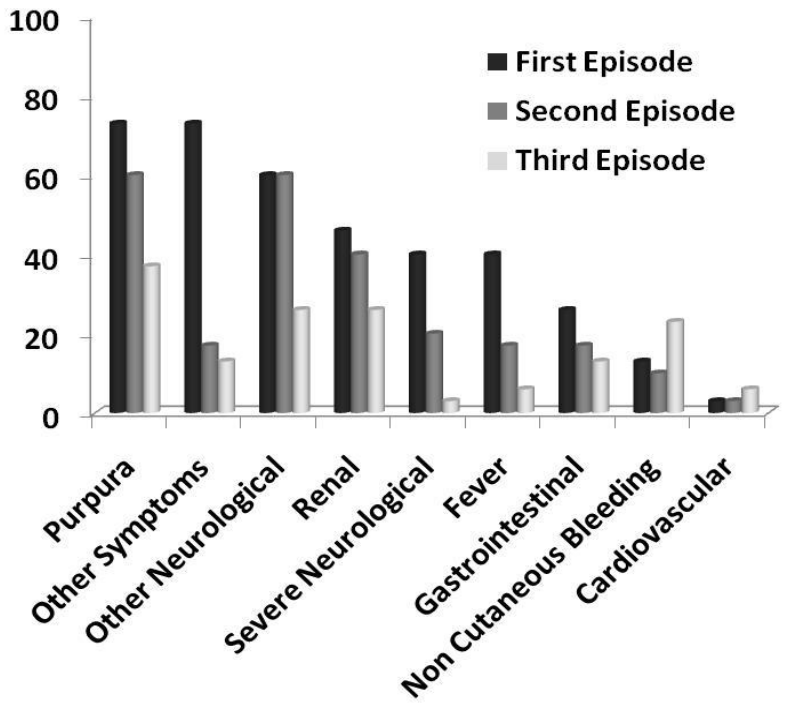
+

Thrombosis

“Old” diagnostic pentad:

- **Microangiopathic hemolytic anemia**
- **Thrombocytopenia**
- Fluctuating neurologic signs
- Fever
- Renal impairment

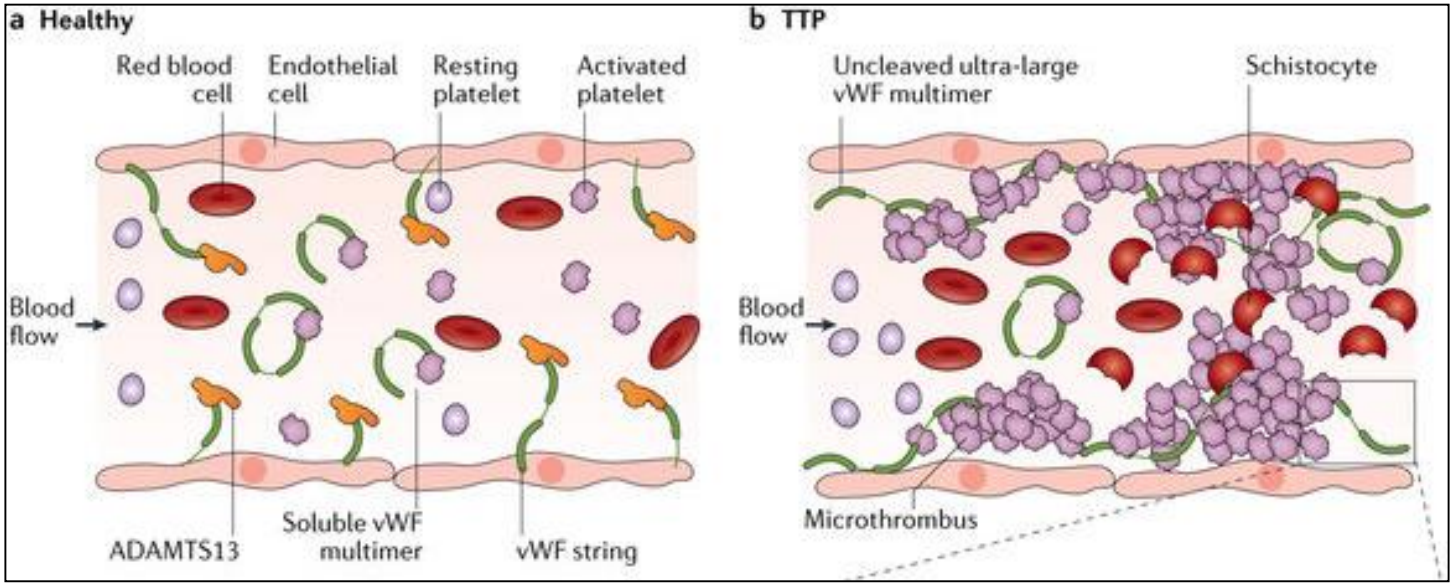
33 patients with ≥ 3 acute episodes



Scully et al, BJH 2010

TTP pathophysiology

- Caused by ADAMTS13 deficiency (A Disintegrin And Metalloproteinase with ThromboSpondin type 1 motifs, member 13)
- ADAMTS13 cleaves the VWF subunit at the Tyr1605–Met1606 peptide bond in the A2 domain



Furlan M, et al. Blood 1996; Tsai HM. Blood 1996; Zheng XL, et al. JBC 2001; Levy GG, et al. Nature 2001; Fujikawa K, et al. Blood 2001, Kremer Hovinga et al, Nat Rev Dis Primers 2017

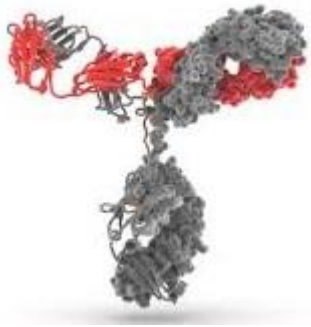
ADAMTS13 deficiency

ADAMTS13 deficiency
normal values 40-160%
severe deficiency <10%

Congenital
(<5%)

ADAMTS13 gene mutations

Acquired
(>95%)

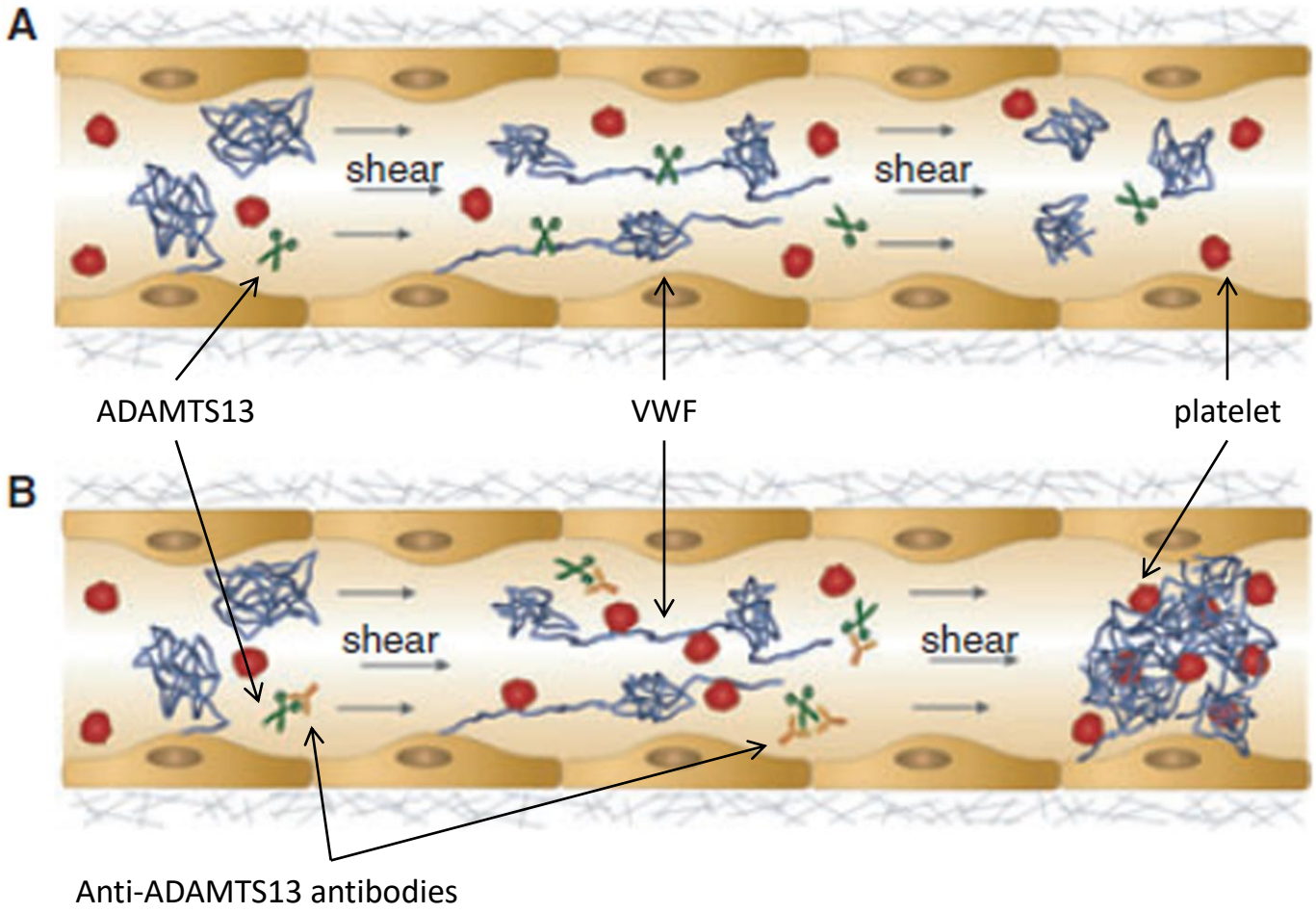


Anti-ADAMTS13 autoantibodies

TTP pathophysiology

Normal

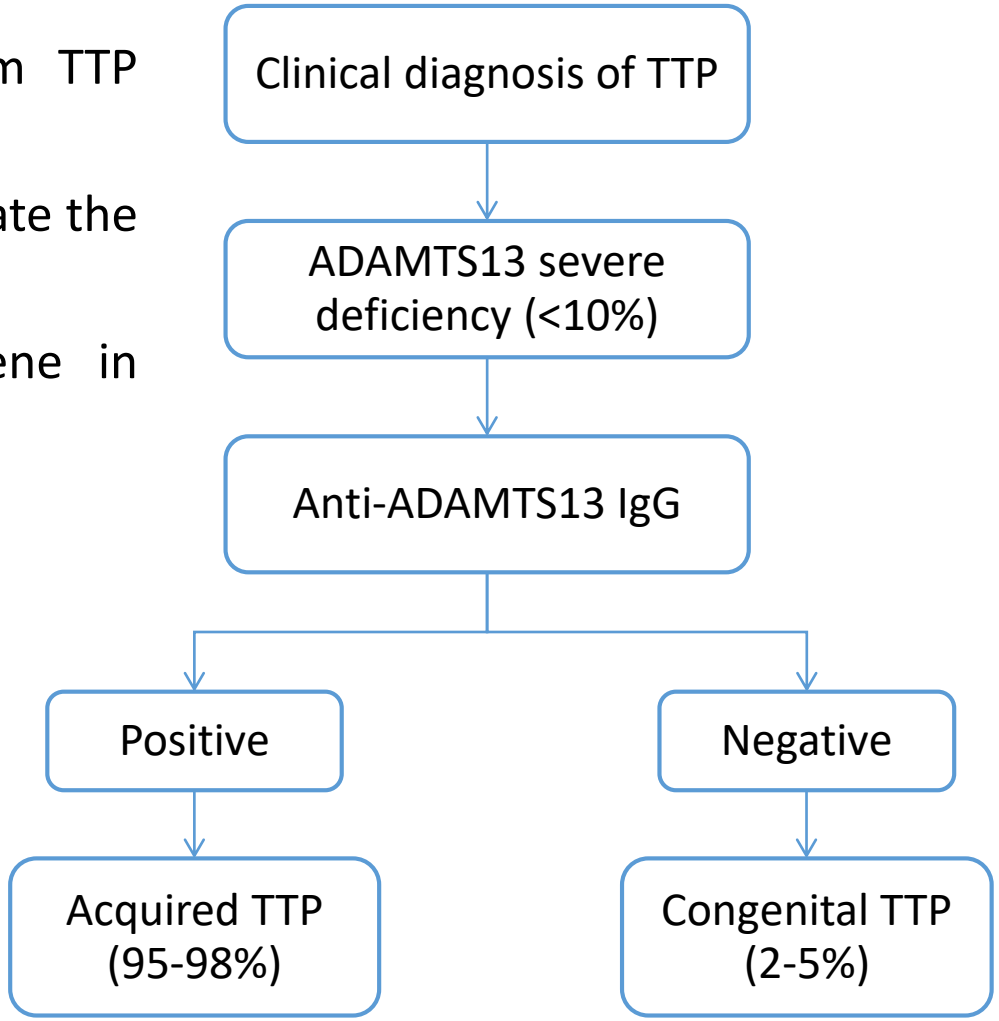
Acquired TTP
ADAMTS13 severe deficiency due anti-ADAMTS13 antibodies



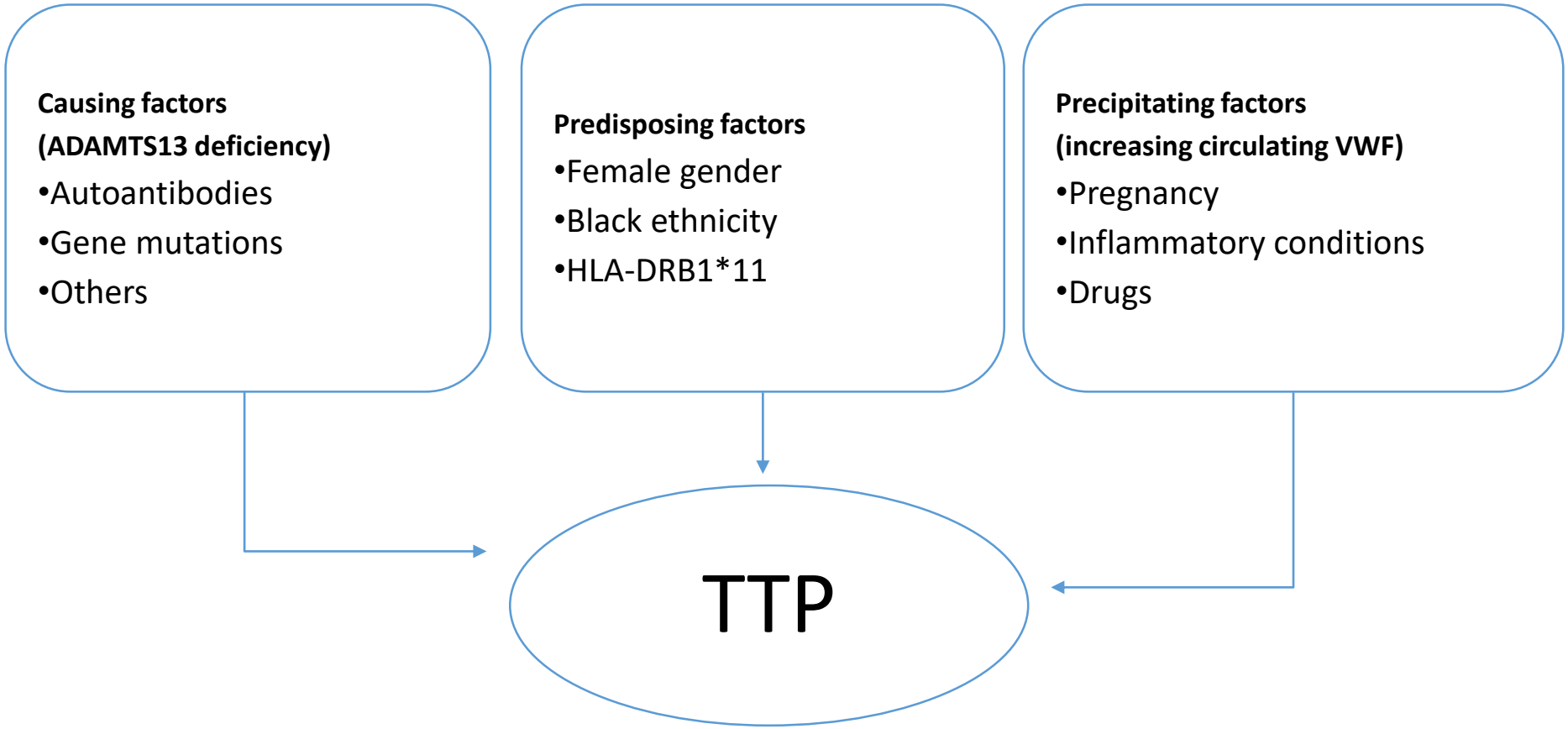
Adapted from Vanhoorelbeke and De Meyer, JTH 2013

TTP diagnostic flowchart

1) ADAMTS13 activity to confirm TTP clinical diagnosis
2) Anti-ADAMTS13 IgG to investigate the cause of ADAMTS13 deficiency
3) Sequencing of *ADAMTS13* gene in selected cases

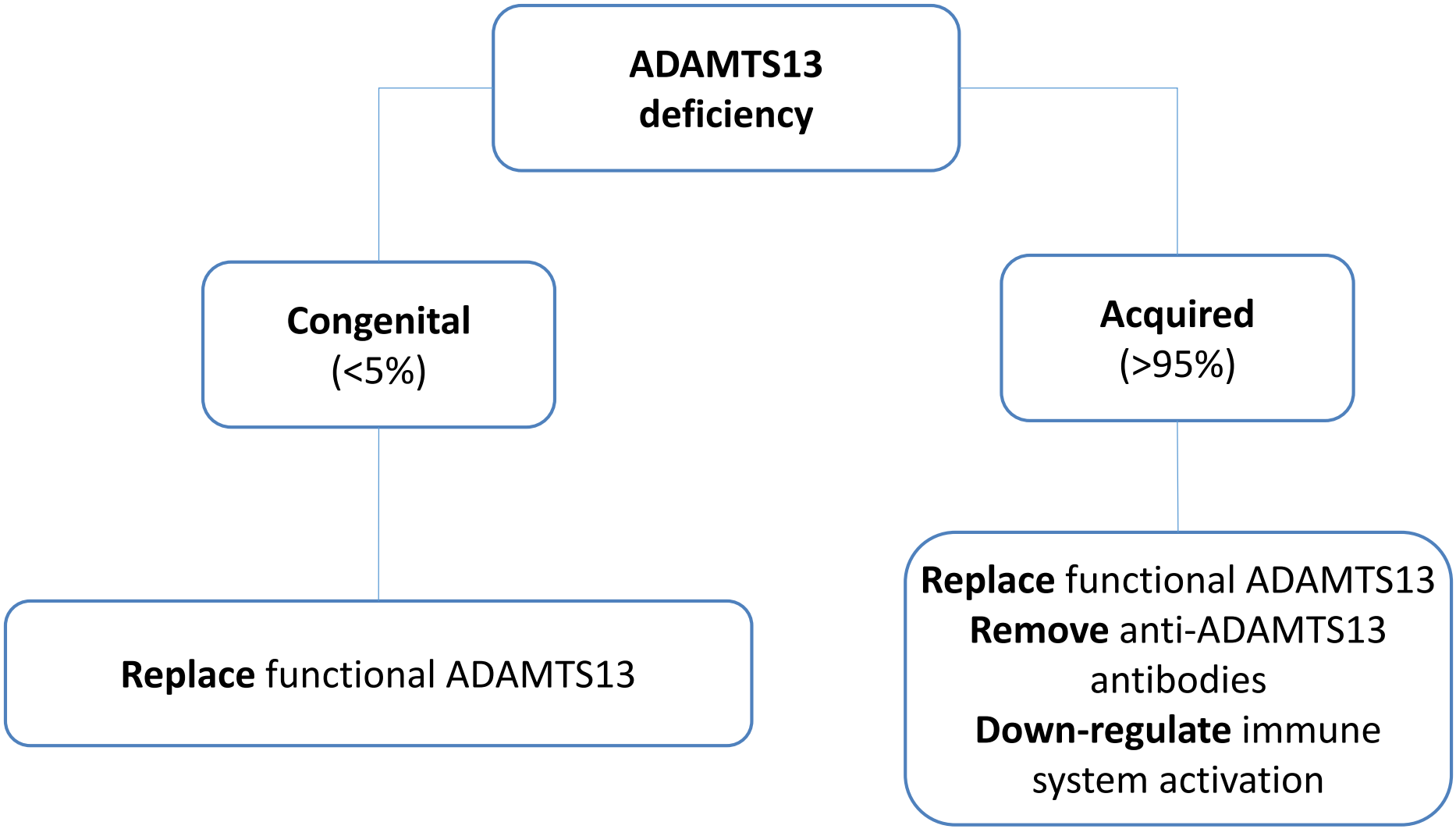


The known players

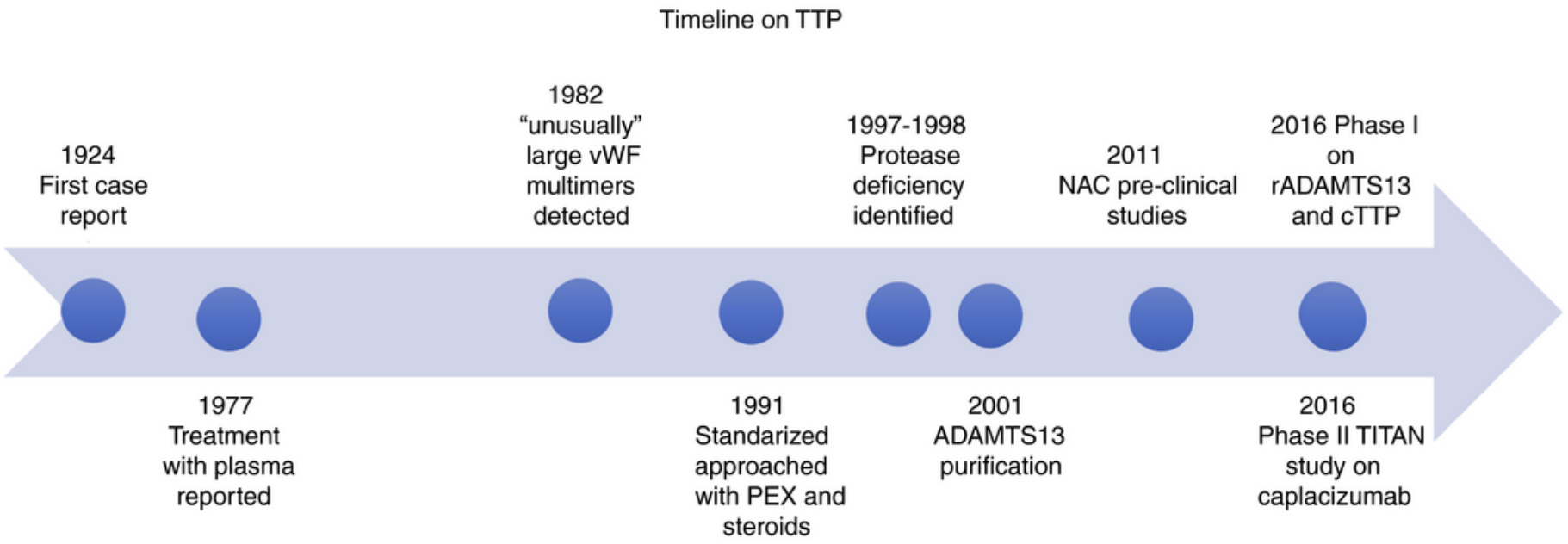


Adapted from Joly et al, Blood 2017

TTP treatment

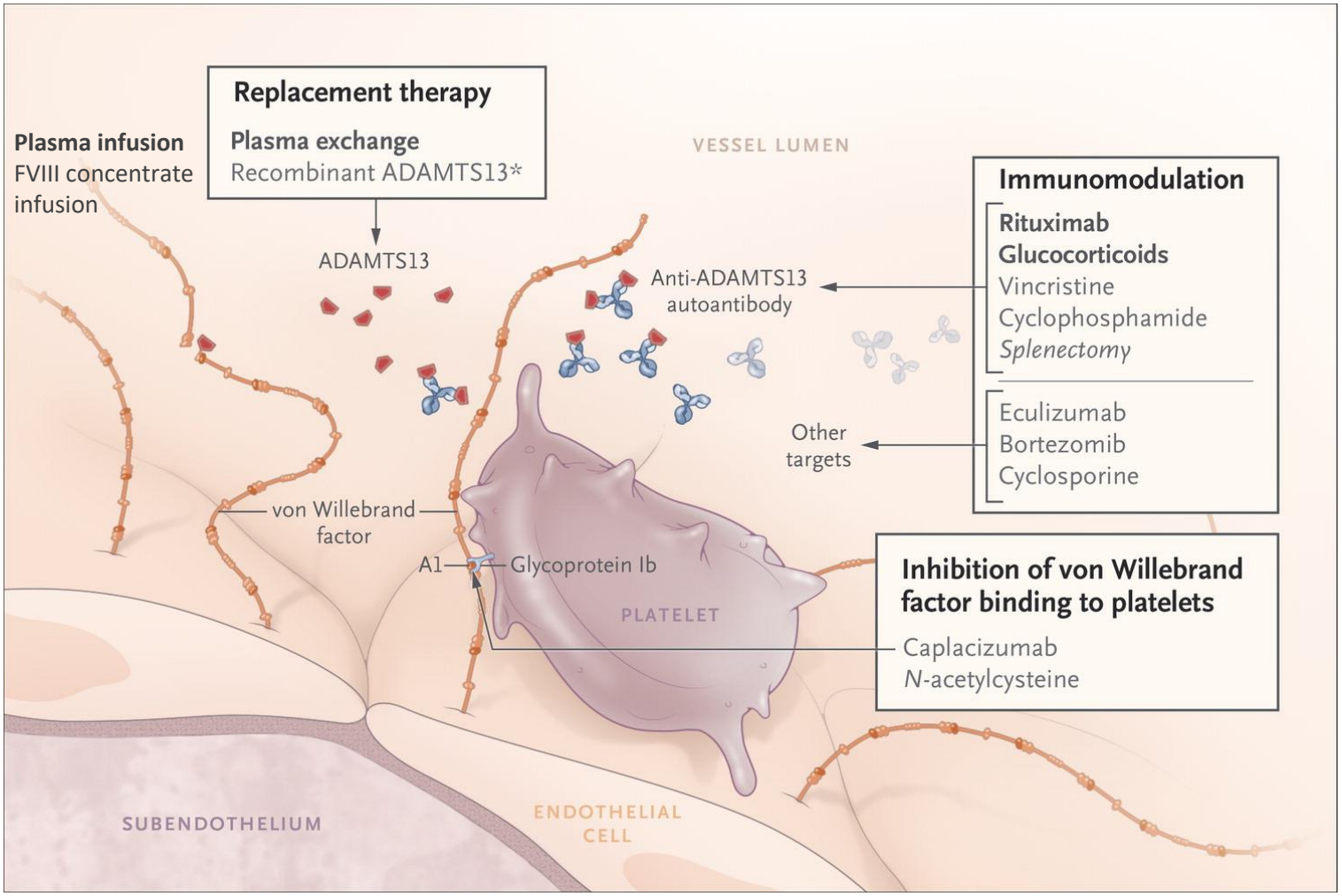


Novel therapies in thrombotic thrombocytopenic purpura



Research and Practice in Thrombosis and Haemostasis, 2017

Current and novel therapies



Adapted from Veyradier, NEJM 2016

Current and novel therapies: acquired TTP/ acute phase

Current therapies

- Plasma exchange
- Immunosuppressors

Novel therapies

- **Caplacizumab**
- N-acetylcysteine
- Eculizumab
- Bortezomib

Acquired TTP: unmet needs

From **ACUTE PHASE**

Disease duration is variable

Clinical response usually achieved after 9-16 days of PEX

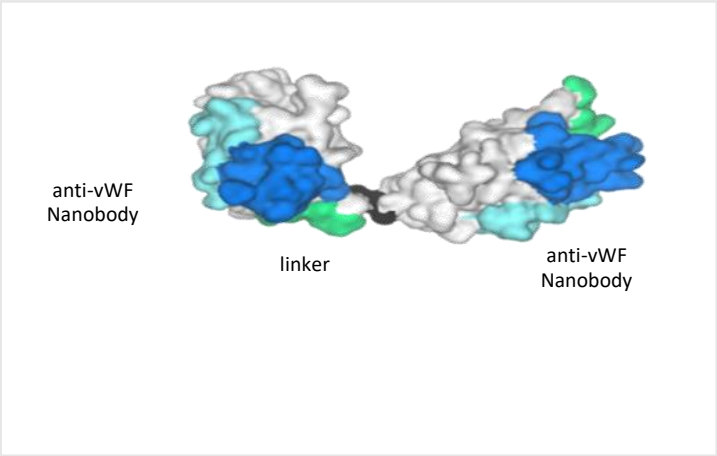
Mortality highest in the first days from disease onset

Risk of **exacerbation** (new clinical signs and symptoms within 30 days after normalisation of PLT count)

Still 10% mortality despite standard of care

To **REMISSION PHASE**

Novel therapies: Caplacizumab

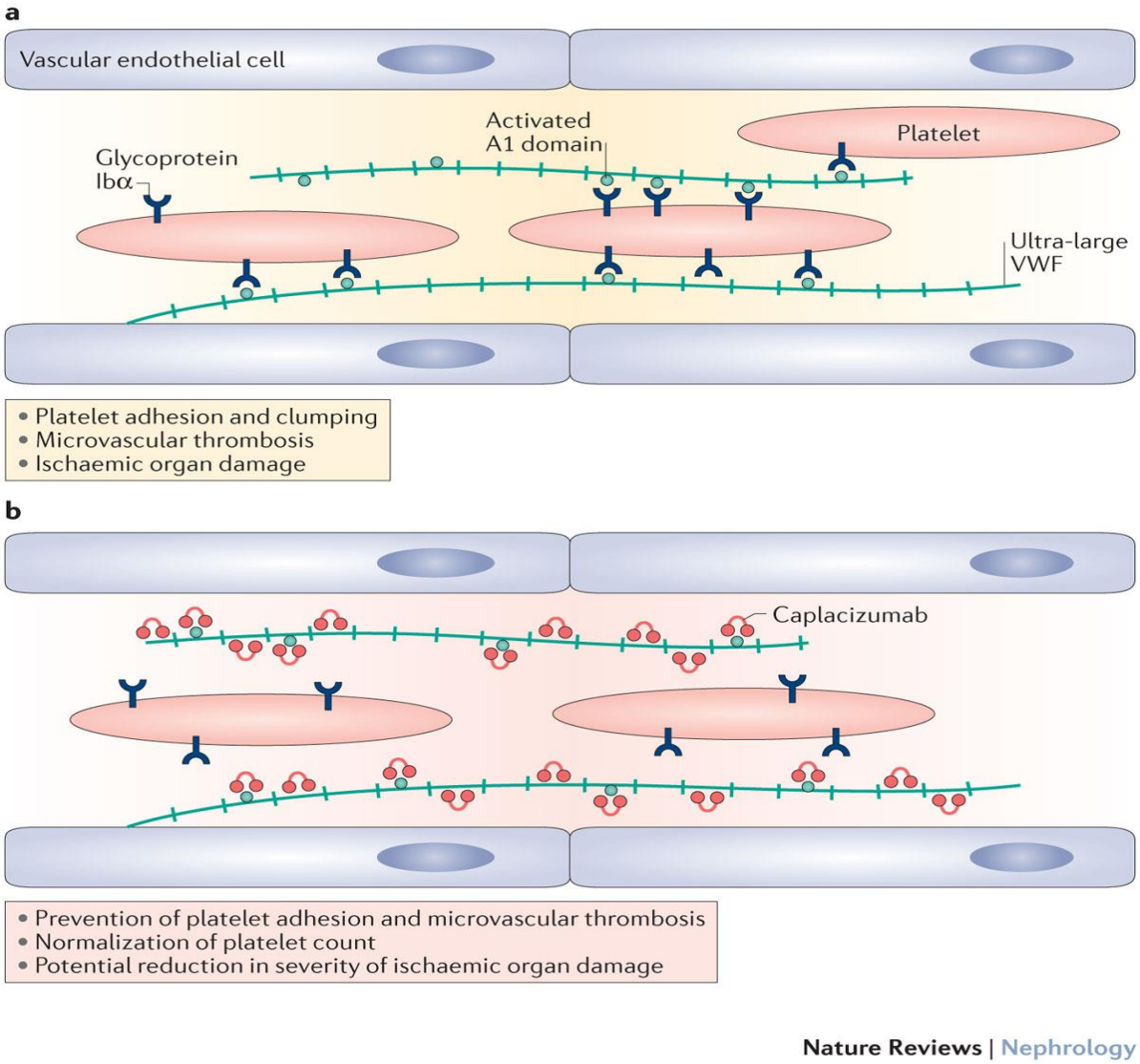


Caplacizumab is a anti-VWF nanobody

(Nanobody is a biologic derived from heavy chain only antibodies)

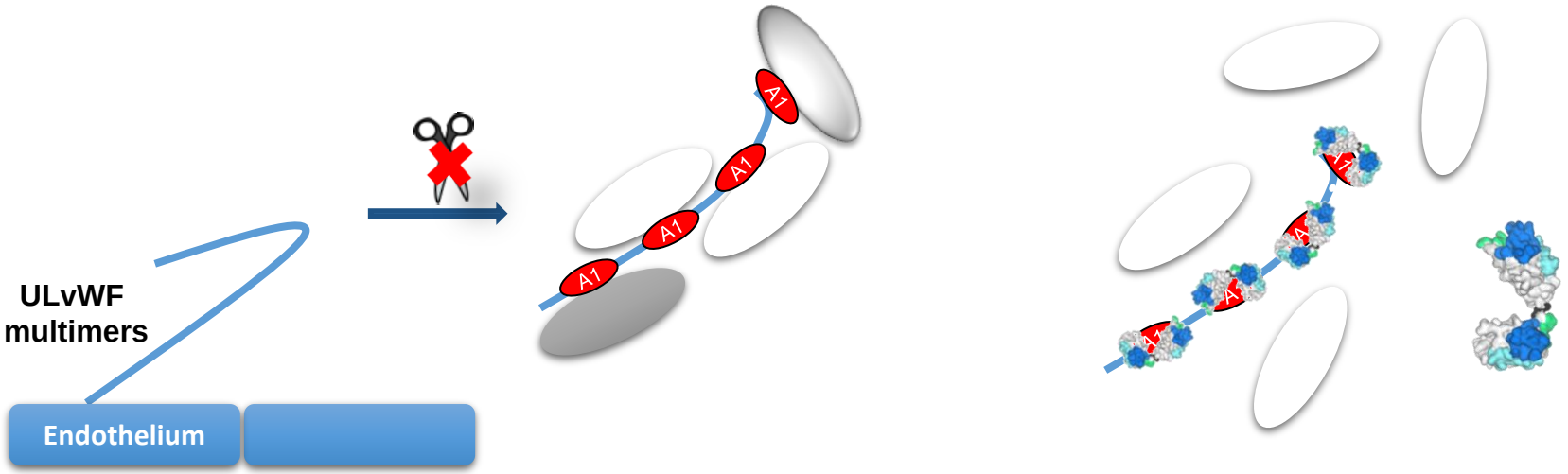
- Caplacizumab binds to A1 domain of vWF
- Immediate inhibition of platelet string formation and consumption of platelets

Mechanism of action of caplacizumab

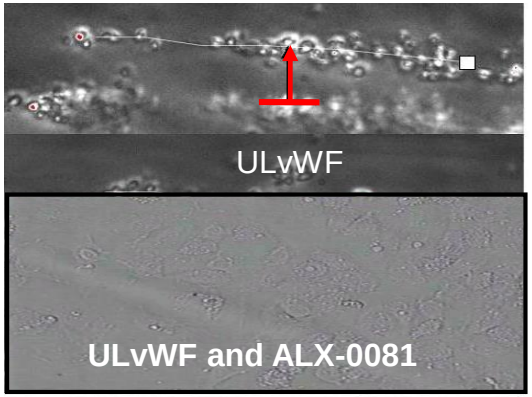


Lämmle, B. (2016) Caplacizumab accelerates resolution of acute acquired TTP *Nat. Rev. Nephrol.*

Caplacizumab: mode of action in TTP



***In vivo* platelet string formation**



The TITAN trial

The NEW ENGLAND JOURNAL of MEDICINE

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Caplacizumab for Acquired Thrombotic Thrombocytopenic Purpura

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Background

- Thrombotic thrombocytopenic purpura is often caused by an autoantibody to ADAMTS13, resulting in **ultralarge von Willebrand factor**, which induces **platelet aggregation**.

- Caplacizumab **blocks** platelet aggregation

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

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)

* Baseline was defined as before the first administration of the study drug. The intention-to-treat population comprised all patients randomly assigned to a study group, including three patients who did not receive the assigned study drug. There were no significant differences between the study groups in the listed baseline characteristics except as noted below. LDH denotes lactate dehydrogenase, PE plasma exchange, and TTP thrombotic thrombocytopenic purpura.

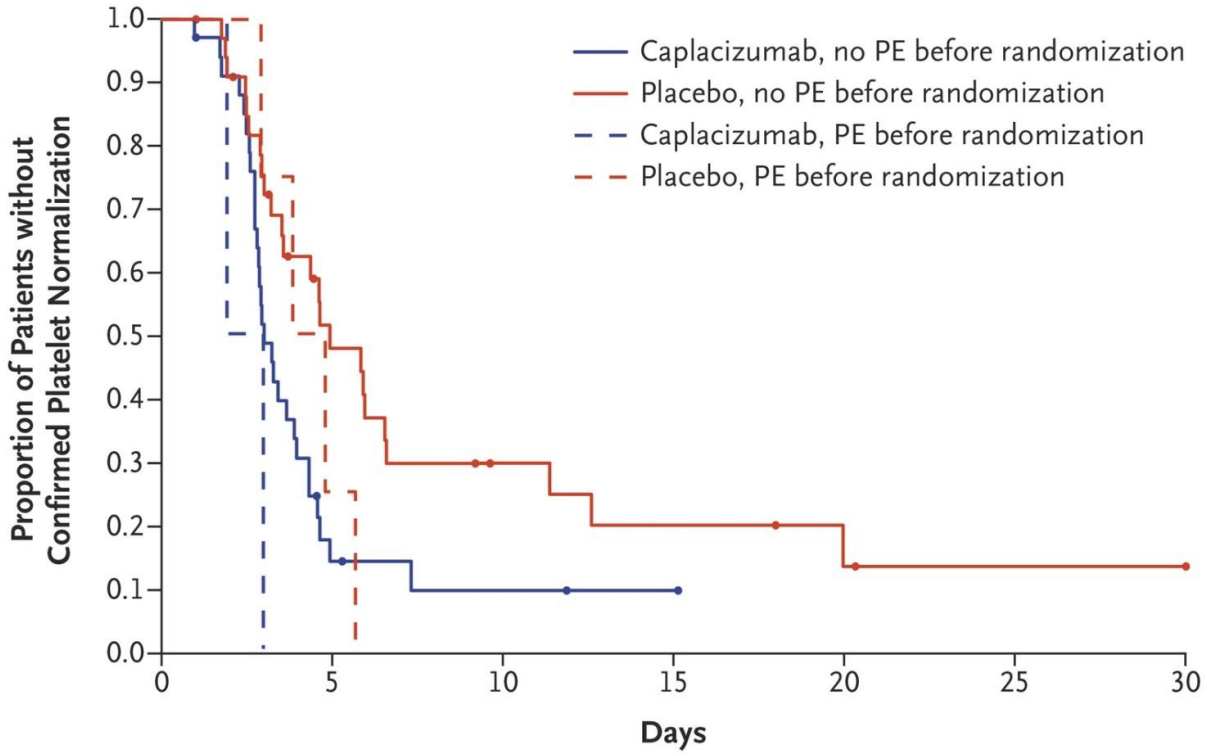
† Race was determined by the investigator.

‡ Data on platelet count were available for 72 patients (35 in the caplacizumab group and 37 in the placebo group).

§ Data on LDH were available for 69 patients (34 in the caplacizumab group and 35 in the placebo group).

¶ The proportion of patients who received rituximab during daily PE differed significantly between the two groups ($P<0.05$). The imbalance may have been a site effect, since one site used rituximab as part of the standard of care starting on day 2 of daily plasma exchange, and this site recruited seven patients, five of whom were randomly assigned to the placebo group.

Time to Confirmed Normalization of Platelet Count in the Intention-to-Treat Population.

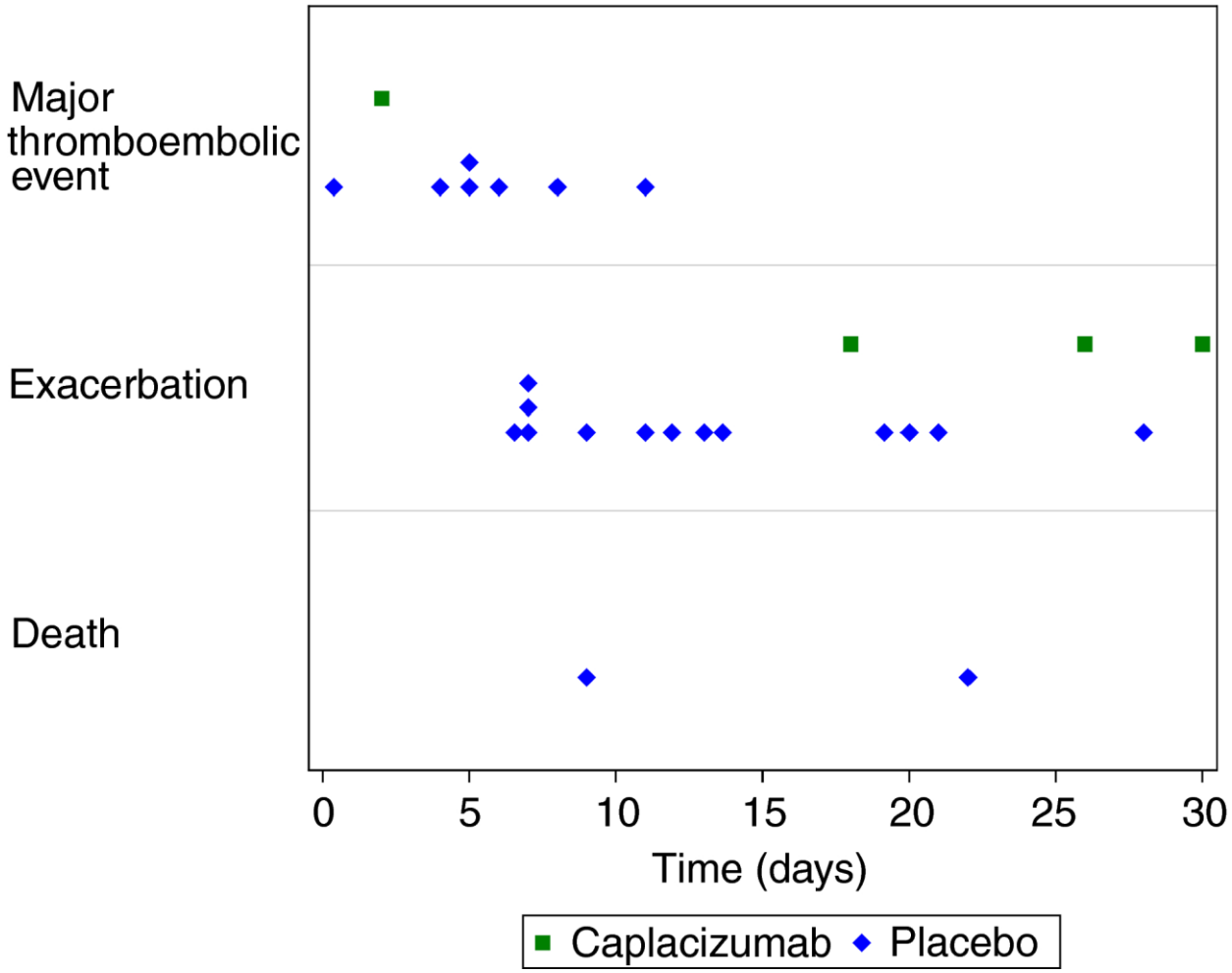


No. at Risk

Caplacizumab, no PE before randomization	34	4	2	1	0	0	0
Placebo, no PE before randomization	35	13	6	4	2	1	1
Caplacizumab, PE before randomization	2	0	0	0	0	0	0
Placebo, PE before randomization	4	1	0	0	0	0	0

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

Caplacizumab reduces the frequency of major thromboembolic events, exacerbations and death in patients with acquired thrombotic thrombocytopenic purpura



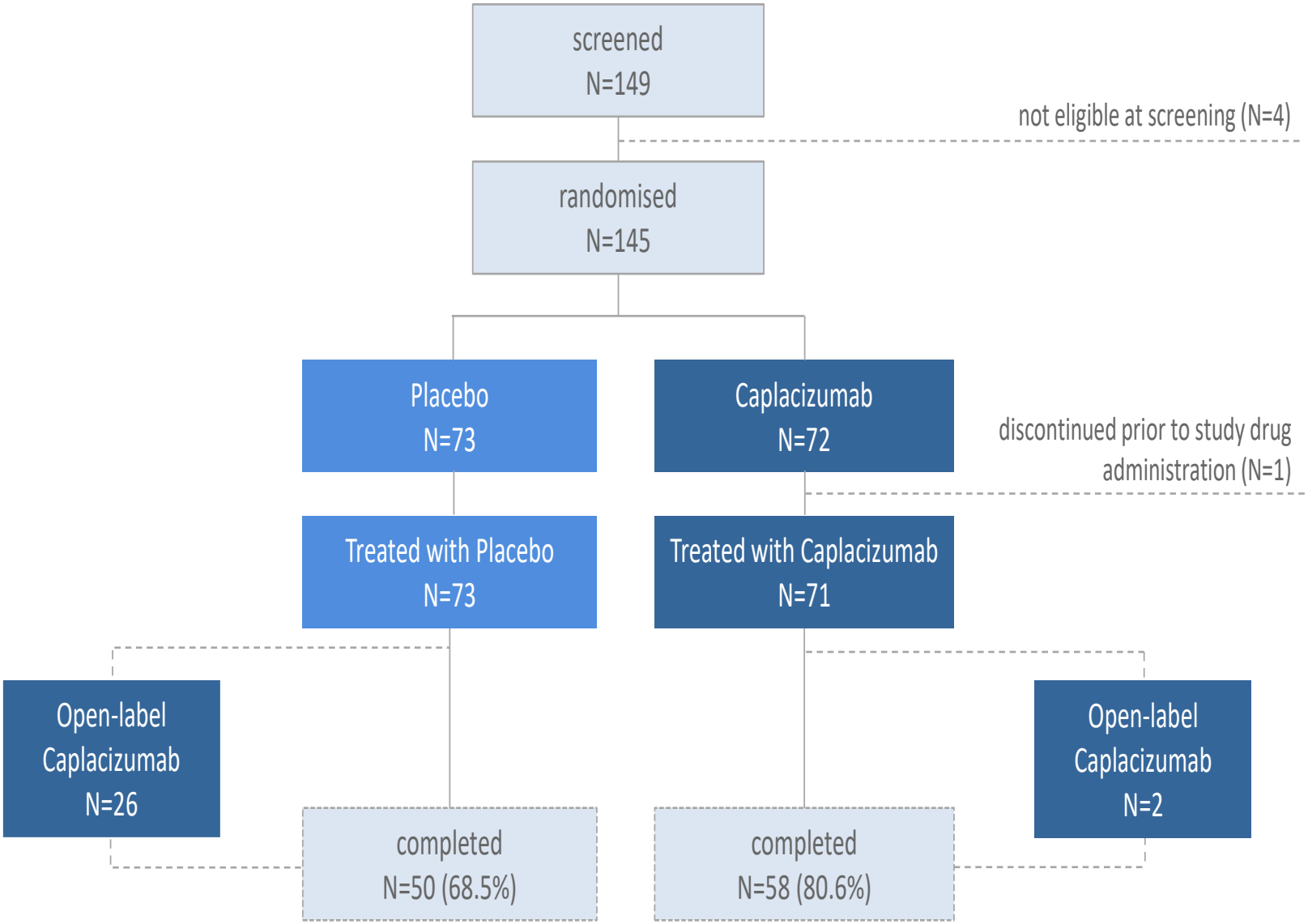
Peyvandi et al, JTH 2017

Conclusions- the TITAN trial

- Caplacizumab induced a **faster resolution** of the acute TTP episode than did placebo.
- The **platelet-protective effect** of caplacizumab was maintained during the treatment period.
- Caplacizumab was associated with an increased tendency toward **bleeding**, as compared with placebo.

HERCULES TRIAL

Recruitment flow

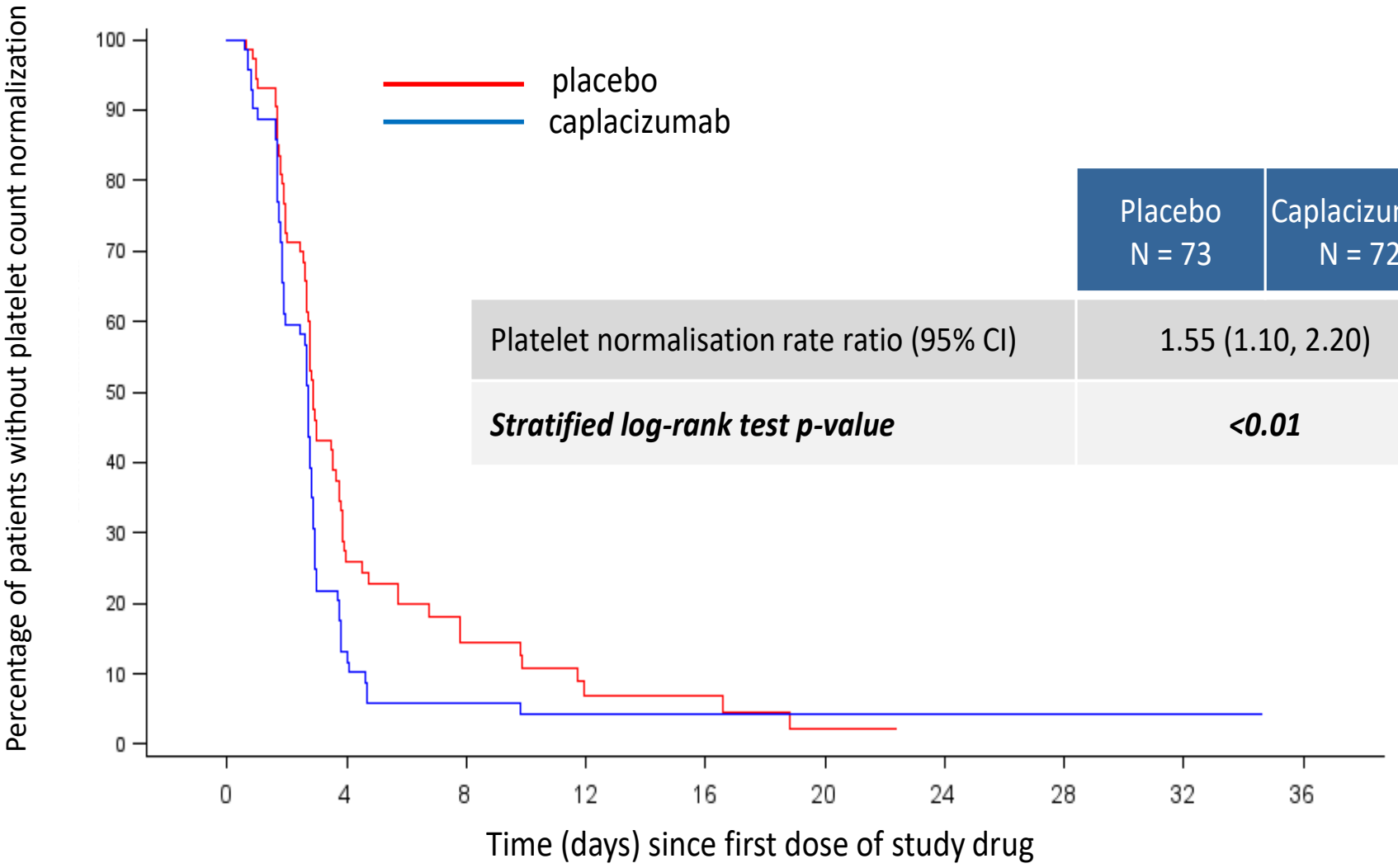


Demographics and baseline disease characteristics

	Placebo N=73	Caplacizumab N=72
Mean age (SD)	47.3 (14.1)	44.9 (13.5)
Females – N (%)	51 (69.9)	49 (68.1)
Baseline platelet count (10^9/L) - mean (SD)	39.1 (29.1)	32.0 (27.2)
Previous aTTP episode(s) – N (%)		
- initial	34 (46.6)	48 (66.7)
- recurrent	39 (53.4)	24 (33.3)
ADAMTS13 activity at baseline – N (%)		
- <10%	65 (90.3)	58 (81.7)
- ≥10%	7 (9.7)	13 (18.3)
Disease severity at baseline – N (%)*		
- Less severe	48 (65.8)	42 (58.3)
- Very severe	25 (34.2)	30 (41.7)

** Very severe was defined as: French severity score ≥3 (cerebral involvement: yes=1 / no=0, LDH: >10xULN=1 / ≤10xULN=0, age: >60 years=2 / >40 and ≤60 years=1 / ≤40 years=0), or severe neurological involvement at baseline, or cardiac involvement (cTnI > 2.5 x upper limit of normal)*

Primary endpoint: time to platelet count response



	Placebo N = 73	Caplacizumab N = 72
Platelet normalisation rate ratio (95% CI)	1.55 (1.10, 2.20)	
Stratified log-rank test p-value	***<0.01***	

First key secondary endpoint

Subjects with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
Total number of subjects with at least one of the events[1]	**36 (49.3)**	**9 (12.7)**
aTTP-related death[2]	3 (4.1)	0
recurrence (exacerbation) of aTTP[3]	28 (38.4)	3 (4.2)
at least one treatment emergent major thromboembolic event[2]:	6 (8.2)	6 (8.5)
- cerebrovascular accident	*3 (4.1)*	*2 (2.8)*
- myocardial infarction	*1 (1.4)*	*1 (1.4)*
- pulmonary embolism	*0*	*1 (1.4)*
- deep venous thrombosis (spontaneous)	*1 (1.4)*	*0*
- deep venous thrombosis (catheter-associated)	*2 (2.7)*	*3 (4.2)*
p-value	***<0.0001***	

* percentages are based on 71 subjects entering the study drug treatment period; 1 patients could have more than 1 event; 2 adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee; 3 recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX

Second key secondary endpoint

Subjects with **aTTP recurrence** during the overall study period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72
aTTP recurrence[1]	28 (38.4)	9 (12.7)
During the study drug treatment period (exacerbations)	28 (38.4)	3 (4.2)
During the follow-up period (relapses)	0	6 (9.1)[2]
p-value	<0.001	

1 recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX

2 ADAMTS-13 activity levels were <10% at the end of the study drug treatment period in all of these patients

Third key secondary endpoint
Percentage of subjects with **refractory aTTP**

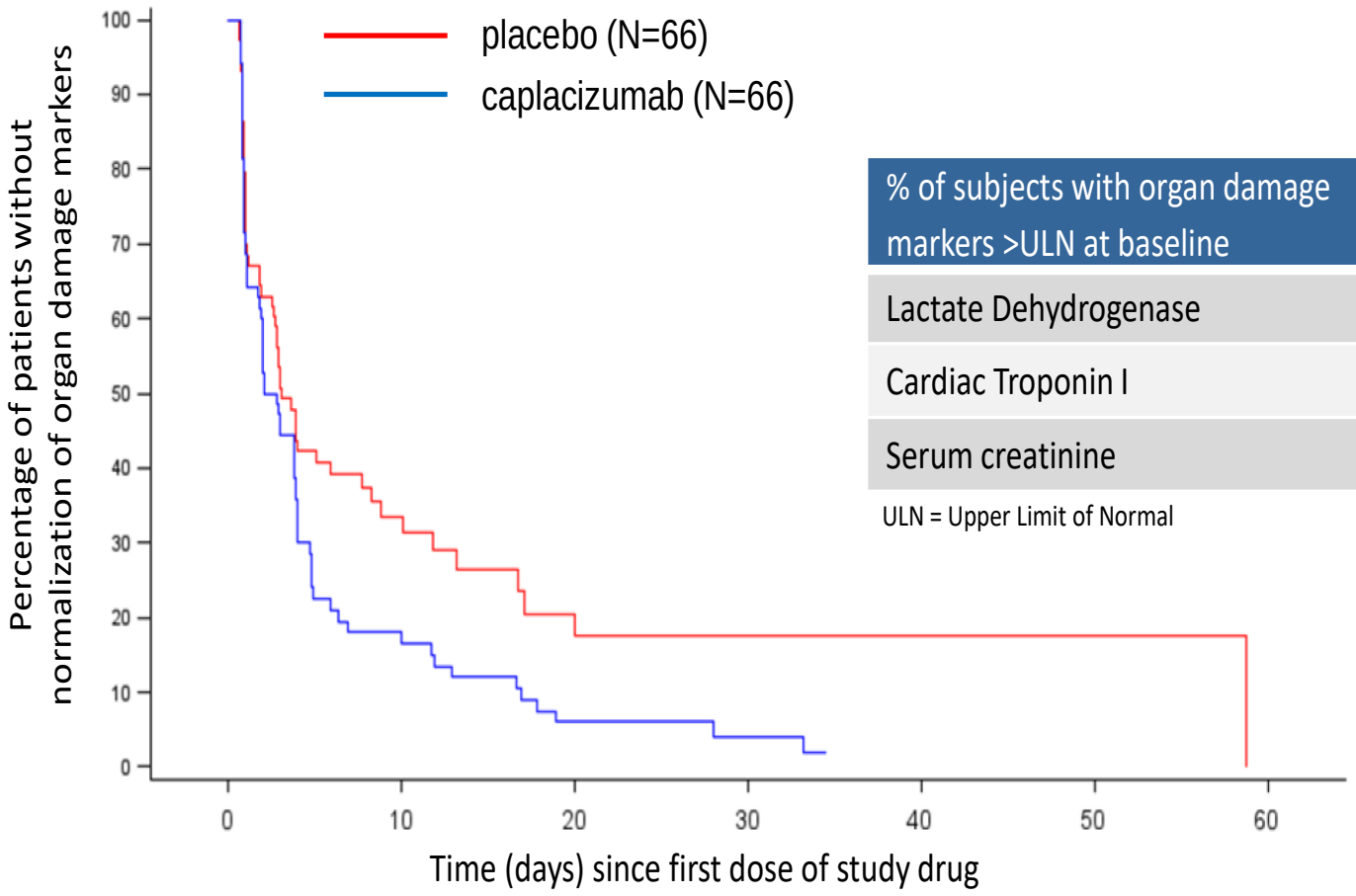
Protocol-specified key secondary endpoint (Benhamou et al., 2015)

Number of subjects (%)	Placebo N=73	Caplacizumab N=72
Refractory aTTP[1]	3 (4.2)	0
p-value	0.057	

1 refractory TTP = absence of platelet count doubling after 4 days of standard treatment and LDH > ULN

Fourth key secondary endpoint

Time to normalization of organ damage markers



% of subjects with organ damage markers >ULN at baseline	All subjects N=145
Lactate Dehydrogenase	87.1%
Cardiac Troponin I	53.8%
Serum creatinine	22.7%

ULN = Upper Limit of Normal

Other secondary endpoints

Overall study drug treatment period (mean±SE)	Placebo N=73	Caplacizumab N=71	% relative reduction
Number of days of Plasma Exchange	9.4±0.8	5.8±0.5	↓38%
Volume of plasma (L)	35.9±4.2	21.3±1.6	↓41%
Number of days in Intensive Care Unit	9.7±2.1 (n=27)	3.4±0.4 (n=28)	↓65%
Number of days in Hospital	14.4±1.2	9.9±0.7	↓31%

Safety

Overall summary of Treatment-Emergent Adverse Events (TEAEs)

Number of subjects (%) with	Placebo N=73	Caplacizumab N=71
At least one TEAE	71 (97.3)	69 (97.2)
At least one study drug-related TEAE	32 (43.8)	41 (57.7)
At least one TEAE leading to study drug discontinuation	9 (12.3)	5 (7.0)
At least one SAE	39 (53.4)	28 (39.4)
At least one study drug-related SAE	4 (5.5)	10 (14.1)
At least one SAE leading to death	3 (4.1)	1 (1.4)[1]

Safety

Bleeding-related TEAEs*

	Placebo - n (%)	Caplacizumab - n (%)
Bleeding-related TEAEs (by SMQ)[1]	**17 (23.3)**	**33 (45.6)**
Epistaxis	1 (1.4)	17 (23.9)
Gingival bleeding	0	8 (11.3)
Bruising	3 (4.1)	5 (7.0)
Hematuria	1 (1.4)	4 (5.6)
Vaginal hemorrhage	1 (1.4)	3 (4.2)
Menorrhagia	1 (1.4)	2 (2.8)
Catheter site hemorrhage	3 (4.1)	2 (2.8)
Injection site bruising	2 (2.7)	2 (2.8)
Hematochezia	0	2 (2.8)
Hematoma	0	2 (2.8)

- Treatment emergent adverse events occurring in at least 2 subjects in either group
- 1 Standardized MedDRA Query “Hemorrhage”

HERCULES study-Conclusions

- Faster resolution of an aTTP episode with shorter time to platelet count response
- Clinically relevant reduction in aTTP-related death, exacerbation of aTTP or a major thromboembolic event
- Prevention of aTTP relapses when treatment is extended until resolution of underlying disease
- Potential to prevent refractory disease and speed normalization of markers of organ damage
- Reduction in use of plasma exchange and length of stay in the ICU and hospital
- Safety profile in line with previous study results and mechanism of action

Acquired TTP: a look at the future

- TTP is still an extremely challenge disease
- The understanding of the pathophysiology of the disease is helping to modify therapeutic approach
- New drugs will be soon available to further reduce mortality and morbidity

To **REMISSION PHASE**