TTP and other Thrombotic Microangiopathies

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Disclosures

- Research Support: BHF, Thrombosis UK, Anthos
- Advisory Boards (In past 5 years) Sanofi, Bayer, Anthos

Topics To Cover

1. TMA overview
2. TTP

Therapies

Long term effects and monitoring

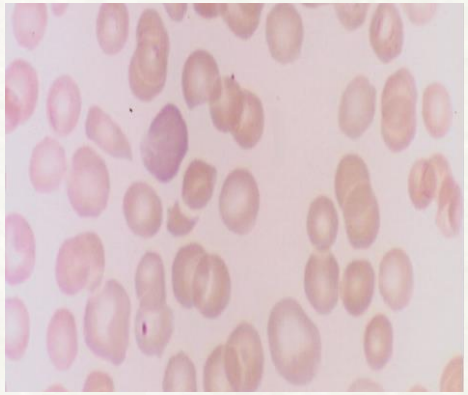
Congenital TTP

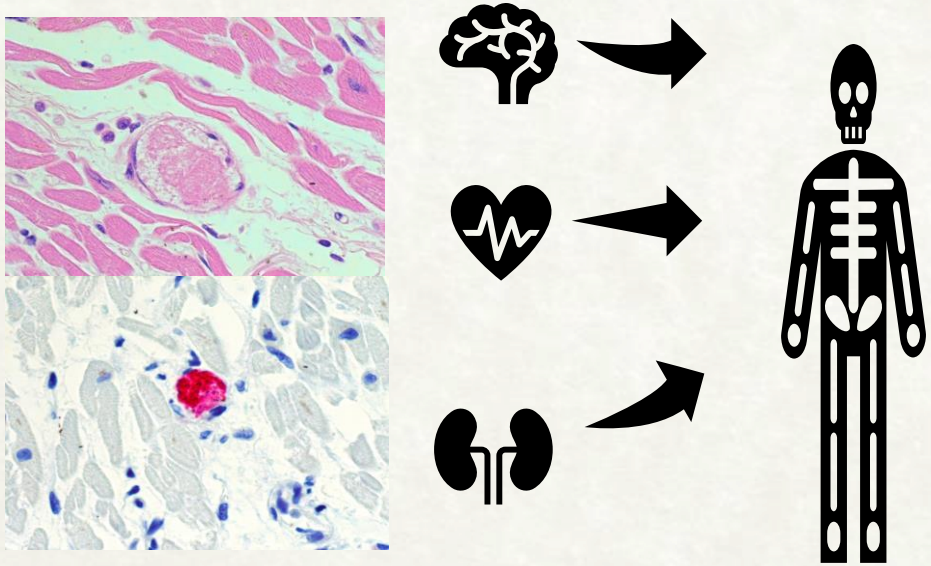
3. HUS
4. Other TMA

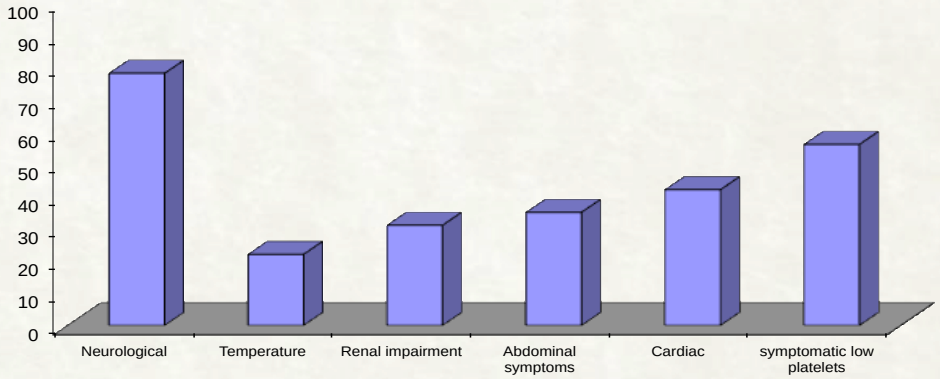
Current clinical diagnostic criteria of Thrombotic Microangiopathy

Thrombocytopenia

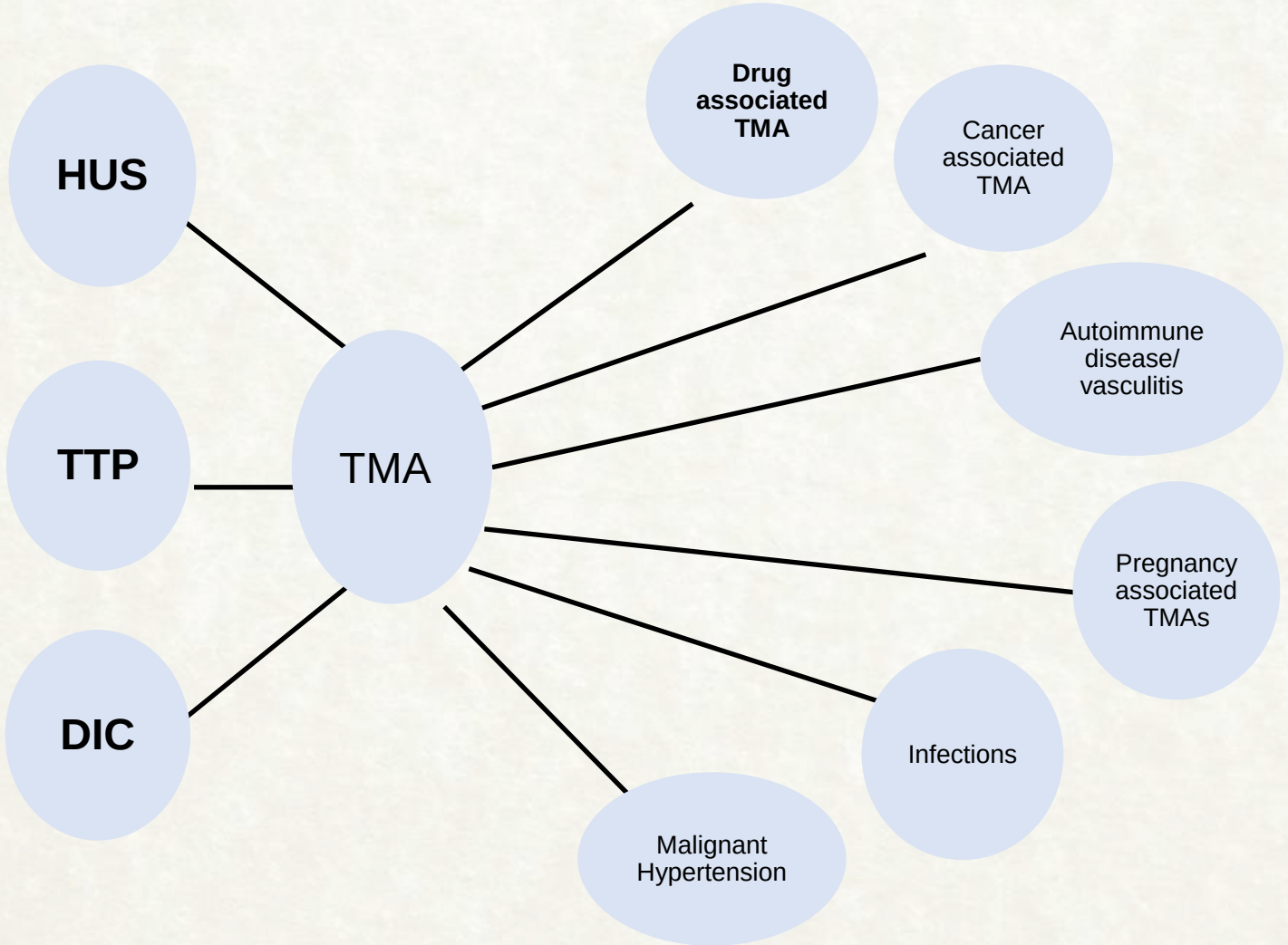
Microangiopathic haemolytic anaemia (MAHA)

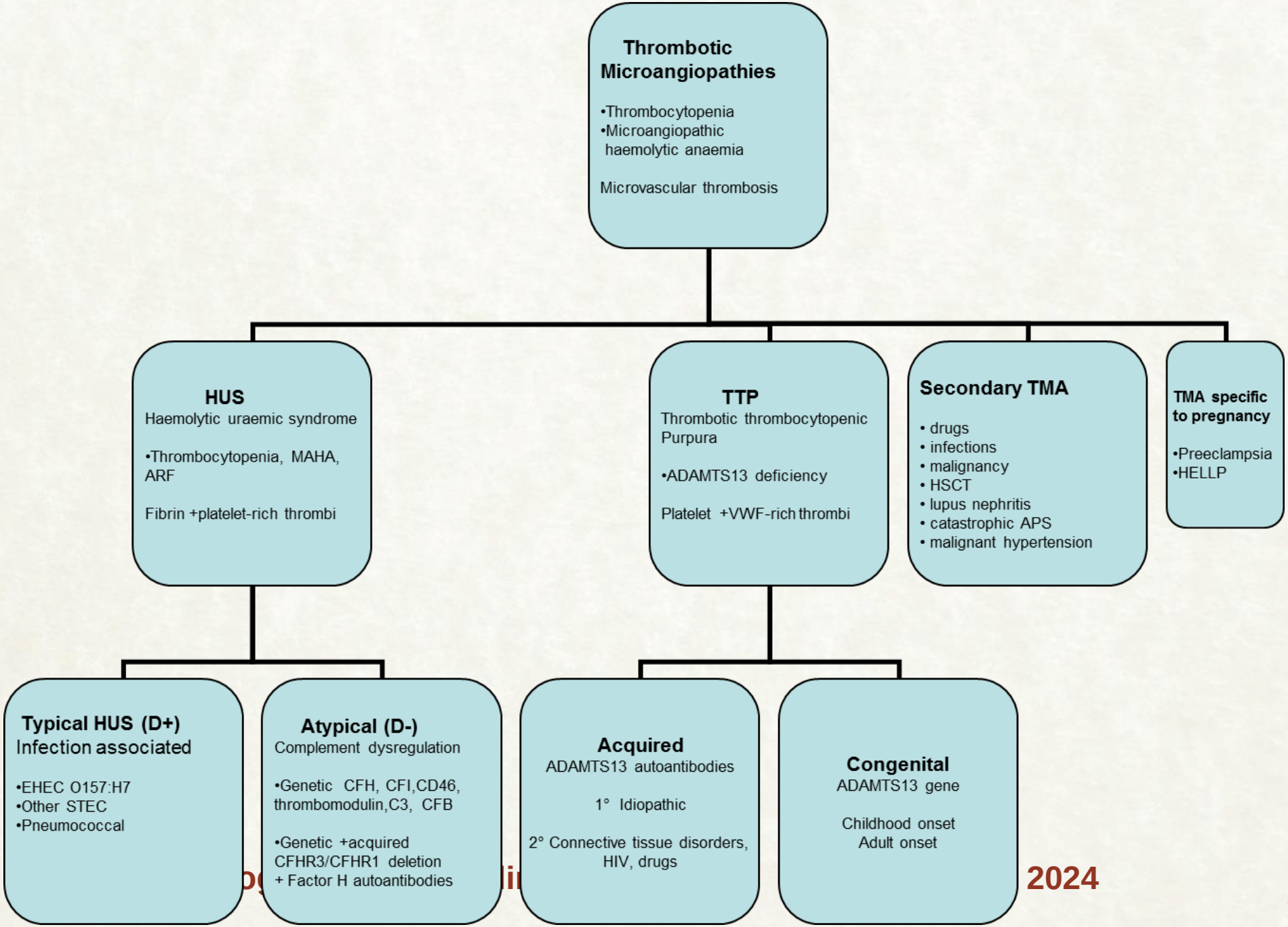






Differential Diagnosis of Thrombotic Microangiopathy

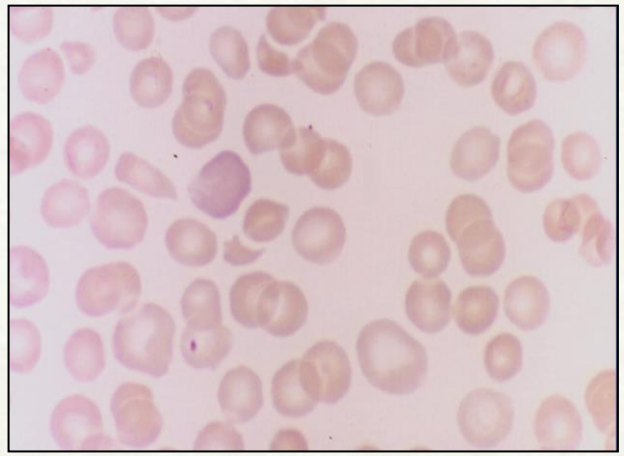



Thrombotic Microangiopathies
•Thrombocytopenia
•Microangiopathic haemolytic anaemia
Microvascular thrombosis
HUS
Haemolytic uraemic syndrome
•Thrombocytopenia, MAHA, ARF
Fibrin +platelet-rich thrombi
TTP
Thrombotic thrombocytopenic Purpura
•ADAMTS13 deficiency
Platelet +VWF-rich thrombi
Secondary TMA
• drugs
• infections
• malignancy
• HSCT
• lupus nephritis
• catastrophic APS
• malignant hypertension
TMA specific to pregnancy
•Preeclampsia
•HELLP
Typical HUS (D+)
Infection associated
•EHEC O157:H7
•Other STEC
•Pneumococcal
Atypical (D-)
Complement dysregulation
•Genetic CFH, CFI,CD46, thrombomodulin,C3, CFB
•Genetic +acquired CFHR3/CFHR1 deletion + Factor H autoantibodies
Acquired
ADAMTS13 autoantibodies
1° Idiopathic
2° Connective tissue disorders, HIV, drugs
Congenital
ADAMTS13 gene
Childhood onset
Adult onset

2024

Diagnosis of TTP – haematological emergency

- MAHA
- Thrombocytopenia
- Absence of underlying cause

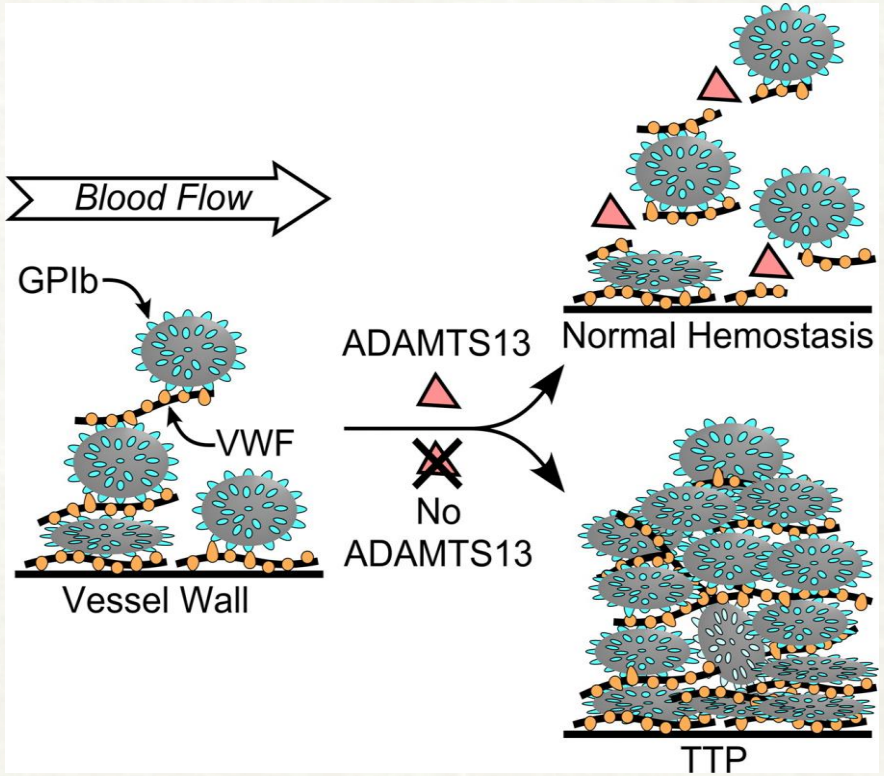


Assume TTP
Commence PEX urgently

TTP and ADAMTS13 - background

A Disintegrin And Metalloproteinase with ThromboSpondin type-1 repeats 13

- ADAMTS13 is a Zn^{2+}-dependent metalloprotease
- Secreted as active enzyme
- No natural inhibitor - long plasma ½-life
- Highly specific
  - Only cleaves VWF
  - Single site - A2 domain (Tyr1605-Met1606)
- Regulates VWF multimeric size/function in plasma



Sadler, Blood 2008

Laboratory tests

- FBC Anaemia & Thrombocytopenia ↑Reticulocytes
- Blood film MAHA - red cell fragmentation, polychromasia
- Normal coagulation
- -ve DAT
- ↑ bilirubin
- ↑ LDH
- Renal impairment
- Virology - HIV, Hepatitis A, B & C
- Pregnancy Test

ADAMTS13 assays

ADAMTS13 activity: in-house FRETS assay

- Synthetic fluorogenic 73aa VWF peptide including scissile bond (FRETS-VWF73).
- FRET design is a fluorescent molecule attached to a quenching group.
- If substrate is cleaved by ADAMTS13, then fluorescence is observed, but in the absence of ADAMTS13, cleavage does not occur and fluorescence is quenched

Kokame & Miyata, BJH, 2005

Anti-ADAMTS13 IgG: in-house ELISA

Diagnosis of TTP

French Score		Point
Platelet count: X10^9/L	<30	1
Creatinine: mmol/L	<225	1

*The PLASMIC Score for TTP Prediction	
Component	Point
Platelet count <30 x 10^9 per L	1
HemoLysis (indirect bilirubin >2 mg dL^{-1}, uncorrected reticulocyte > 2.5%, OR undetectable haptoglobin)	1
No Active cancer in previous year	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}	1

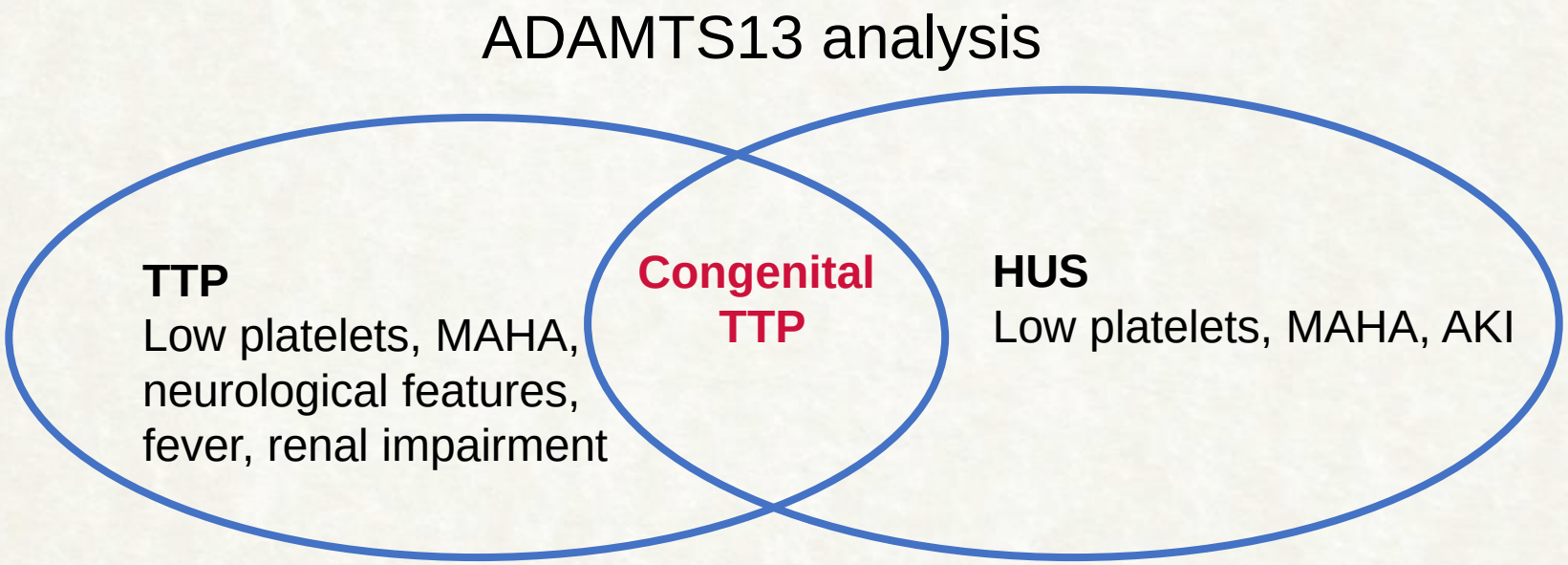
Prediction of severe ADAMTS13 deficiency (Activity <10%)

- 0 :2%
- 1: 70%
- 2: 94%

- High (**score 6 or 7**) vs low-intermediate risk (**score 0 to 5**)
- The model predicts severe ADAMTS-13 deficiency
- Positive predictive value of 72%
- Negative predictive value of 98%
- Sensitivity of 90%
- Specificity of 92%

➢ a. Bendapudi PK, et al. *Lancet Hematol.* 2017;4:e157-e164; b. Hassan S, et al. *Br J Haematol.* 2015;171:830-835.

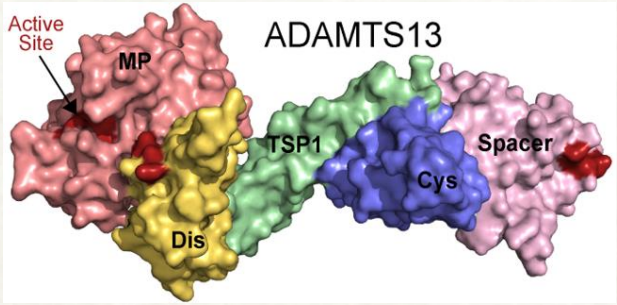
Role of ADAMTS13 analysis in TTP/TMA diagnosis



'Serum creatinine level >150–200 μmol/l or a platelet count >30,000/mm^3 almost eliminates a diagnosis of severe ADAMTS13 deficiency'

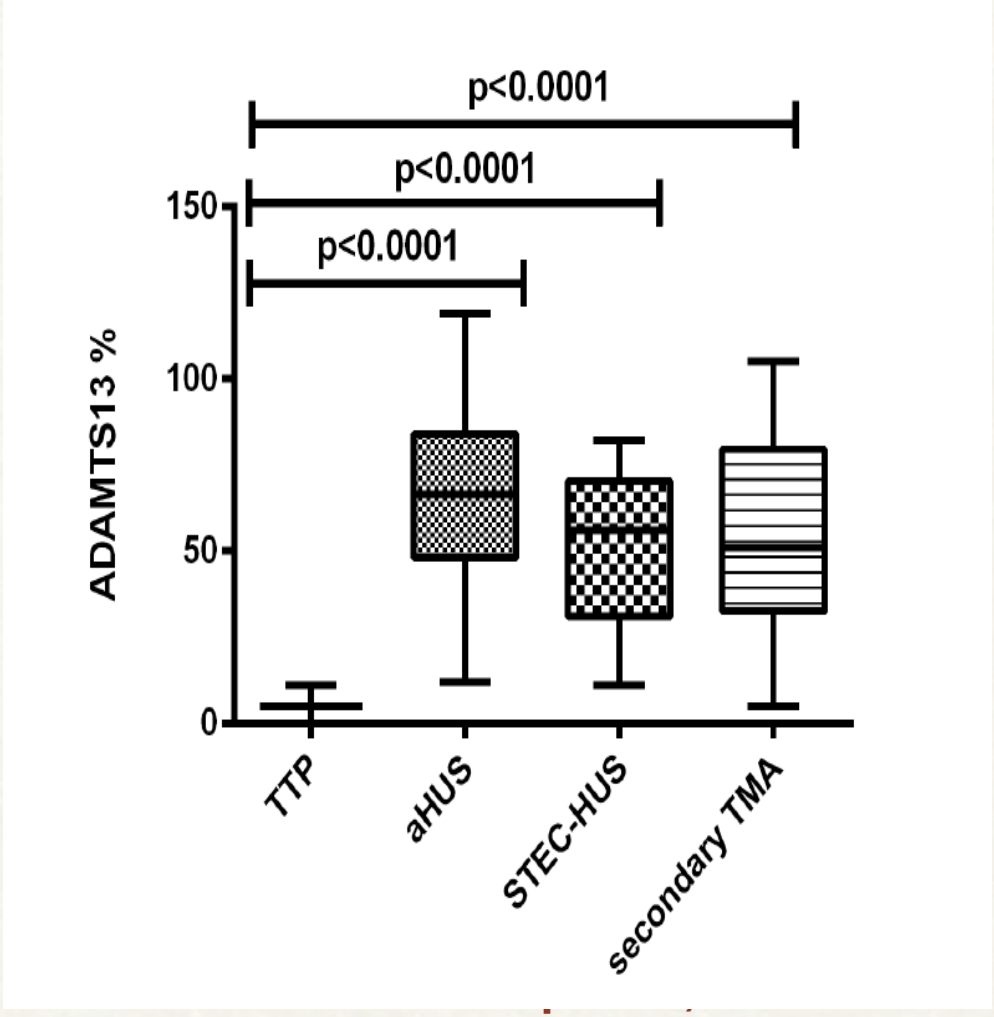
Zuber J et al. Nat Rev Nephrol 2012;7

ADAMTS13 levels in TTP, HUS and TMAs



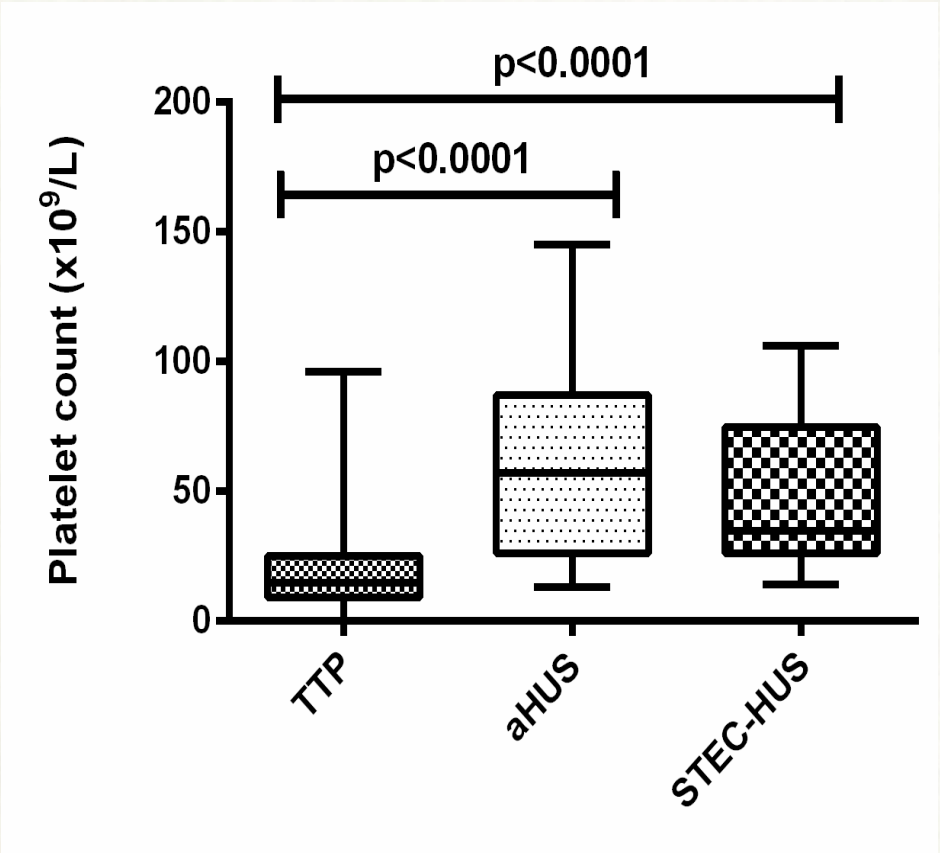
Patients with TTP had significantly lower median ADAMTS13 levels than aHUS, HUS or MAHA/TMA.

No significant difference in ADAMTS13 levels between patients in the aHUS, HUS or MAHA/TMA groups.

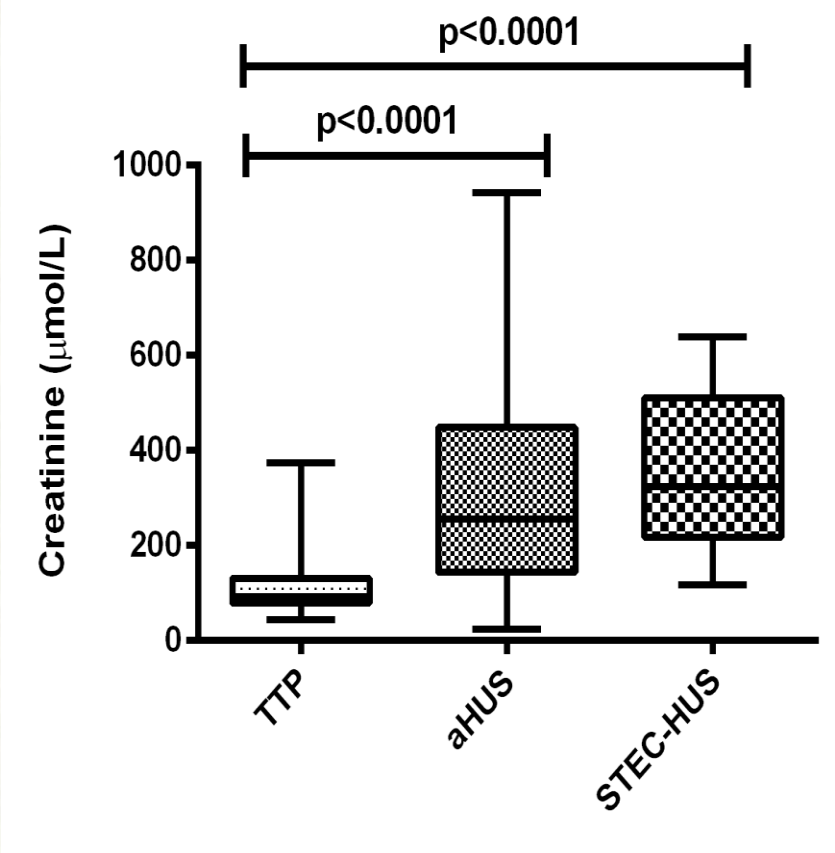


Hassan et al Br J Haematol. 2015;171(5):830-5

Platelets & Creatinine: from UK TTP Registry



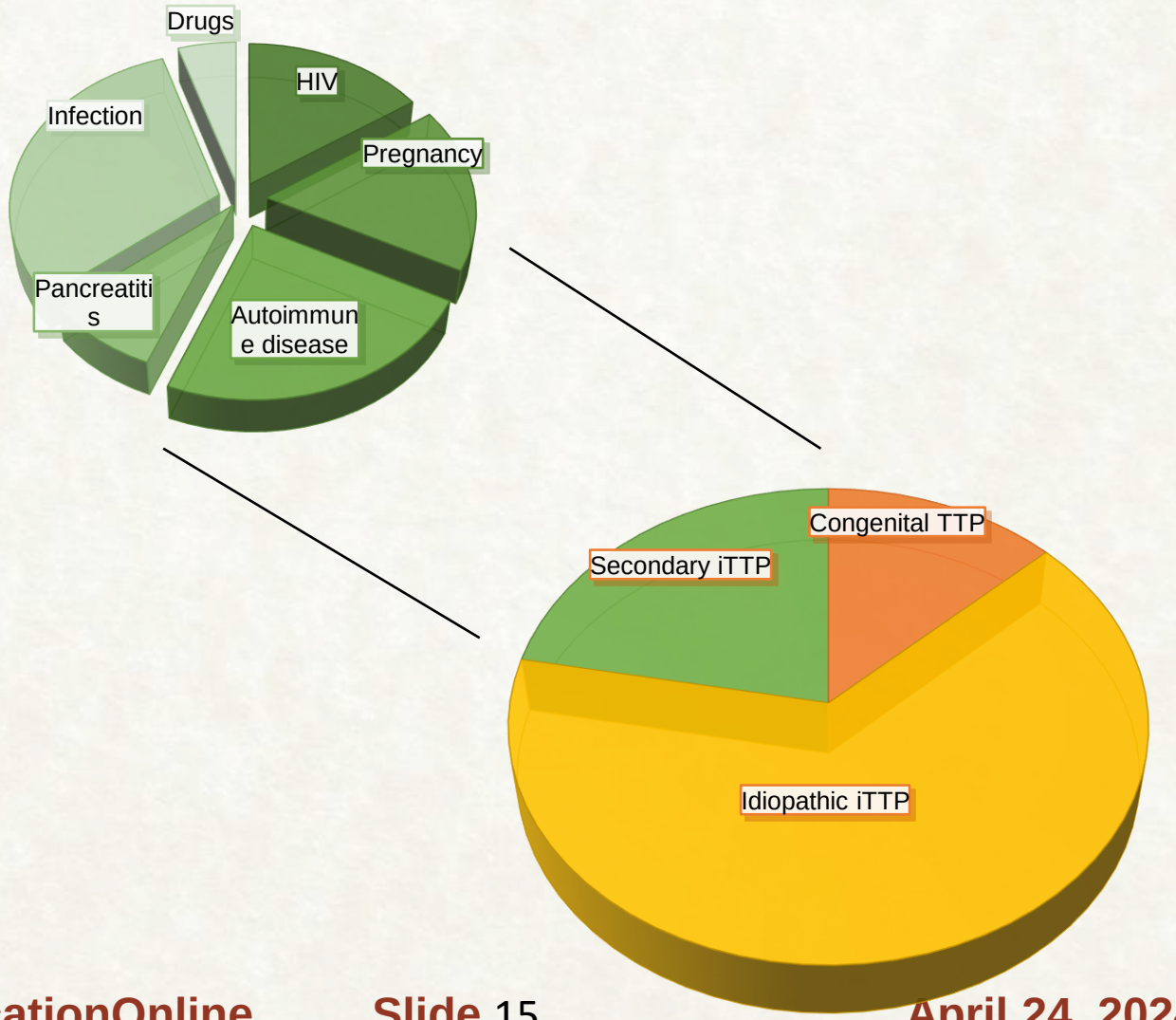
35.3% aHUS group: platelet count <30 x 10^9/L
17.3% of TTP had a platelet count >30 x 10^9/L



15.3% of TTP had a Creatinine >150 µmol/L

Hassan et al Br J Haematol. 2015;171(5):830-5

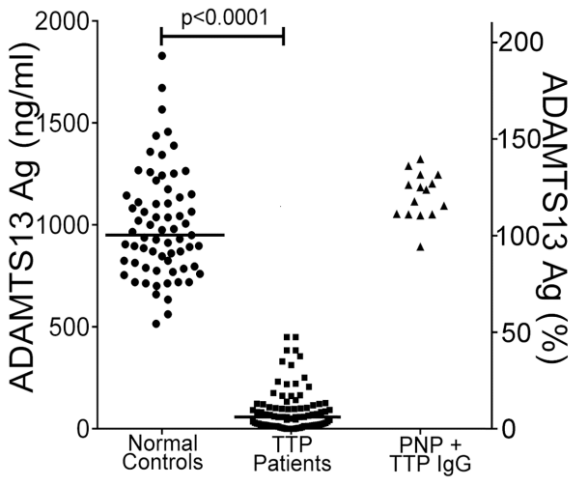
Subgroups of TTP

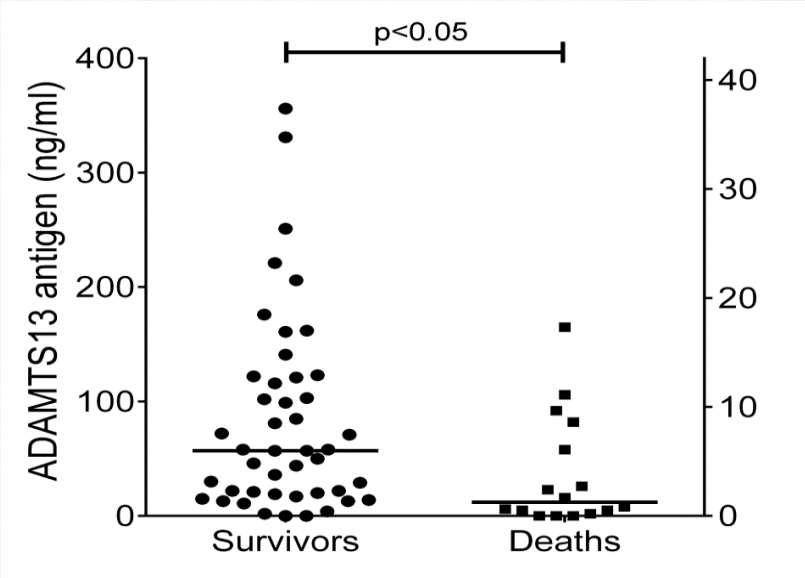


Anti-ADAMTS13 IgG are NOT all inhibitory

Group	N or C	Inhibitory potential	Number of patients
I	N	Inhibitory	10
II	N+C	Inhibitory	9
III	N+C	Mildly inhibitory	9
IV	N+C	Non-inhibitory	12
V	C	Non-inhibitory	3

- 15/43 patients had autoantibodies with no detectable inhibitory action
- 9/43 had only mildly inhibitory antibodies

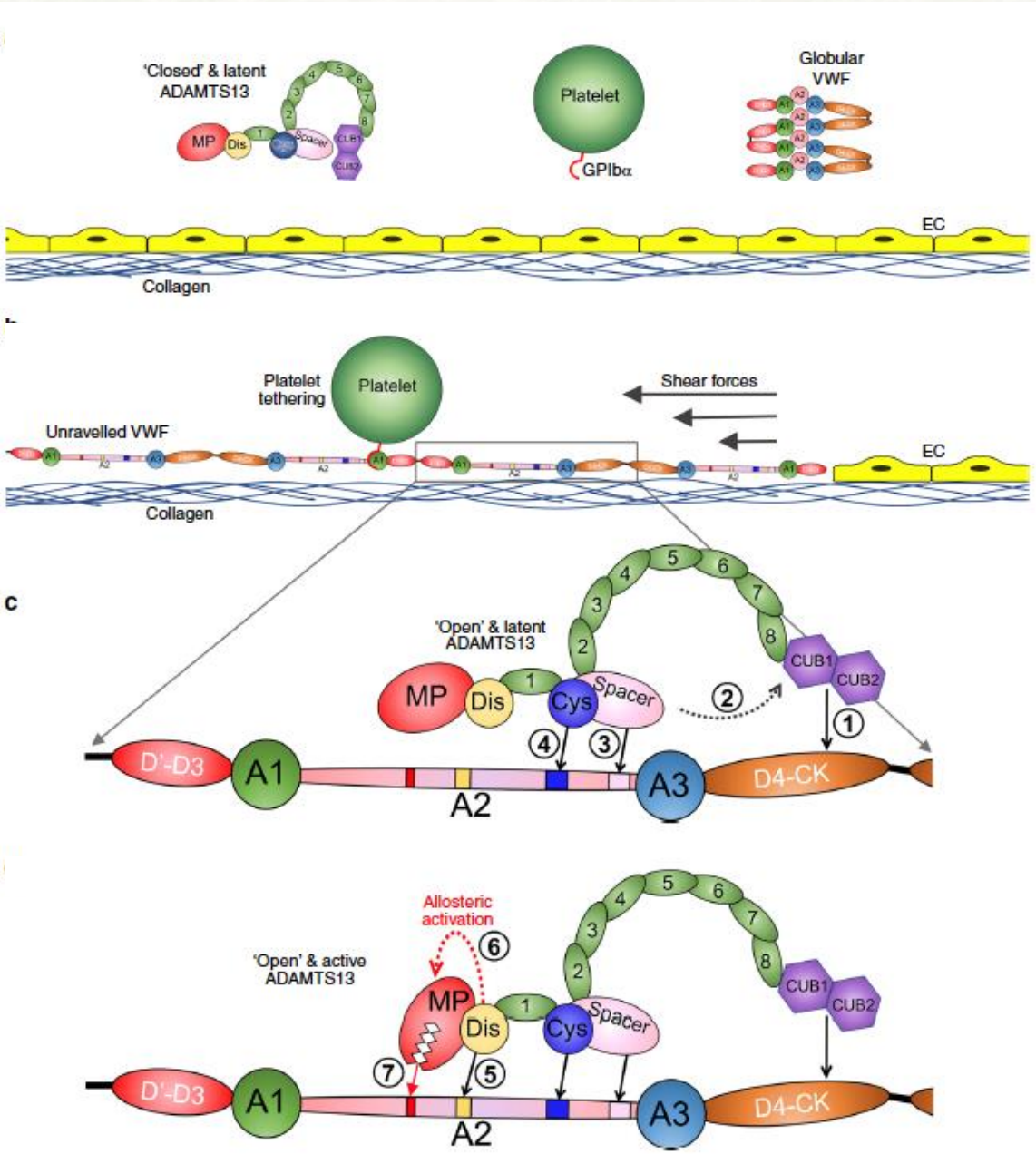




ADAMTS13 antigen <13.5ng/ml
↑likelihood of mortality
OR 5.7
(95% CI 1.5-21.8; p<0.05)

Thomas *et al* EBioMED 2015

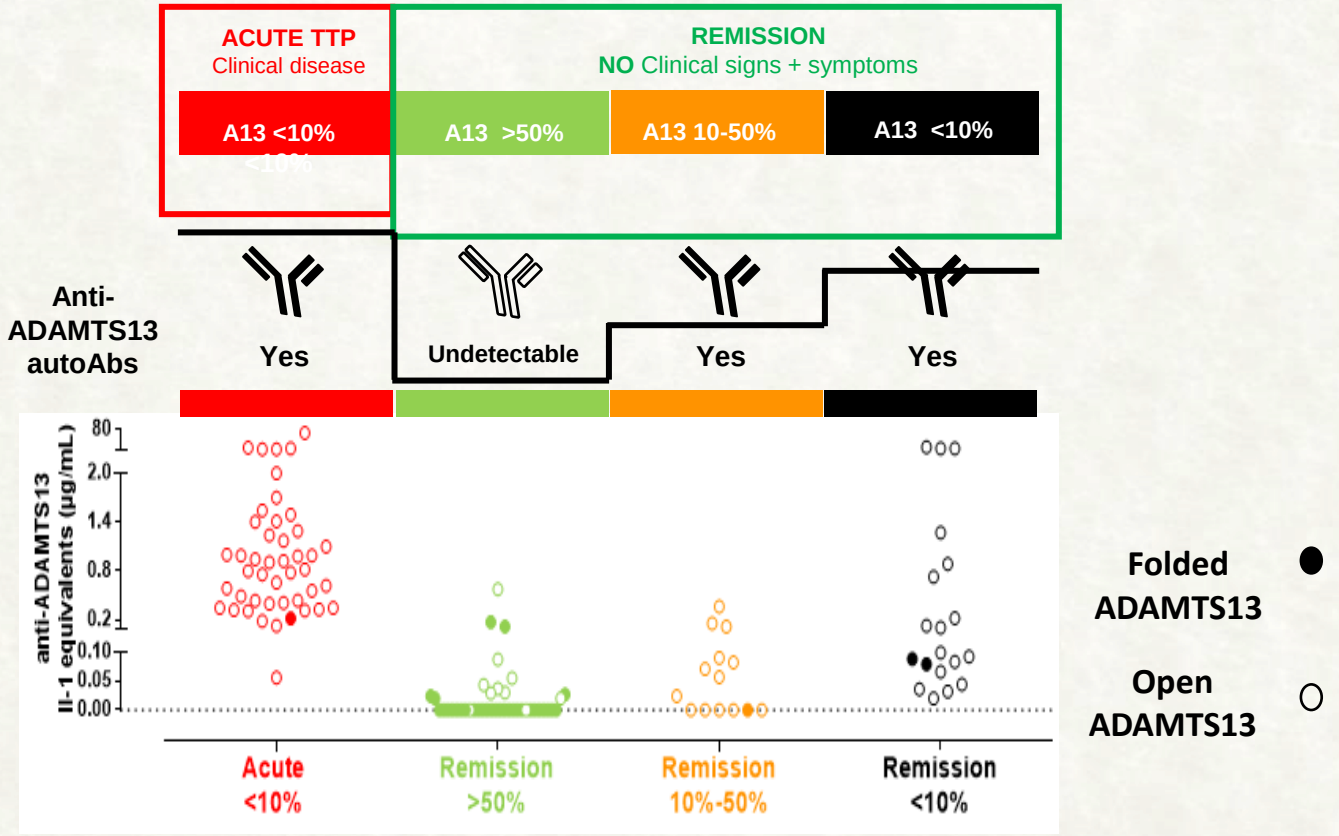
Mode of action of ADAMTS13 – open and closed conformation



Petri et al Nat Comm 2019

April 24, 2024

ADAMTS13 confirmation and TTP disease state



Roose *et al* JTH 2020

Prognostic Factors in acute iTTP

- ↑**Troponin** 68% at presentation 6 fold ↑ in mortality
- ↓**GCS** 28% at presentation 9 fold ↑ in mortality
- **Anti ADAMTS13 IgG levels**

Q1 (<20%) → Q2 → Q3 → Q4 (>77%)

Q4

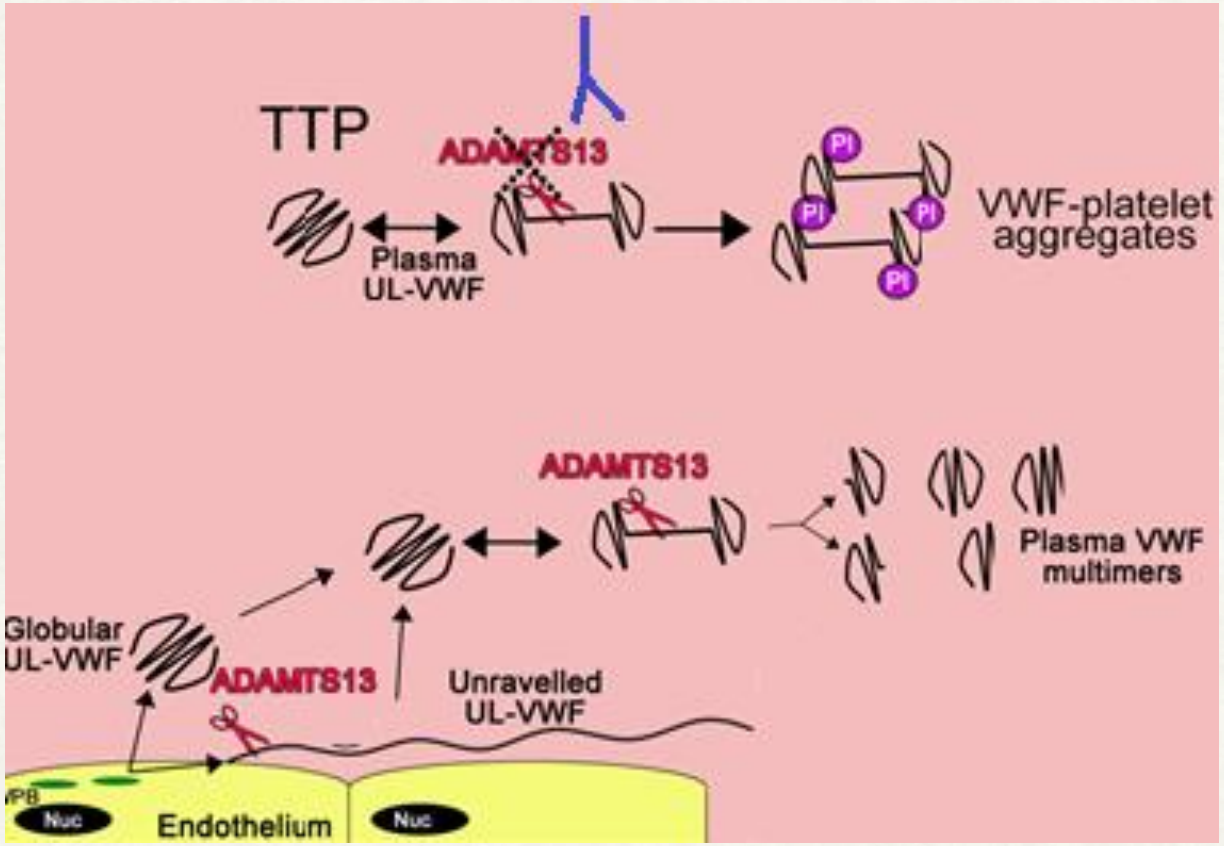
- More likely to have ↑troponin (44% vs 87%, p<0.0001)
- More likely to have ↓GCS (19% vs 41%, p=0.035)
- More PEX to remission (10 vs. 20, p=0.006)
- Increased mortality (5.0% vs 16.9%)

- **ADAMTS13 antigen levels**

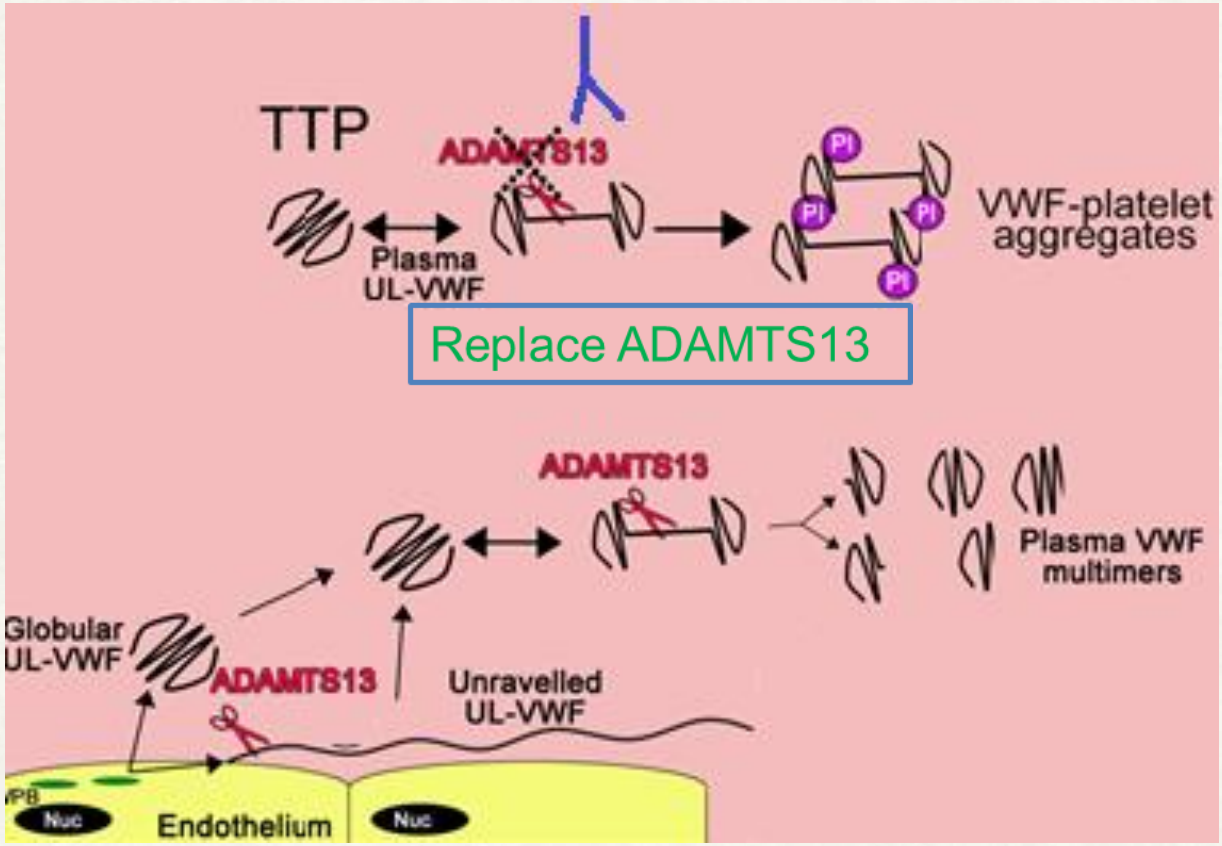
Highest mortality = ADAMTS 13 IgG >77% (Q4) and ADAMTS13 antigen <1.5% (Q1)
Mortality = 27.3%

Alwan *et al*, Blood 2017

How drugs work in TTP

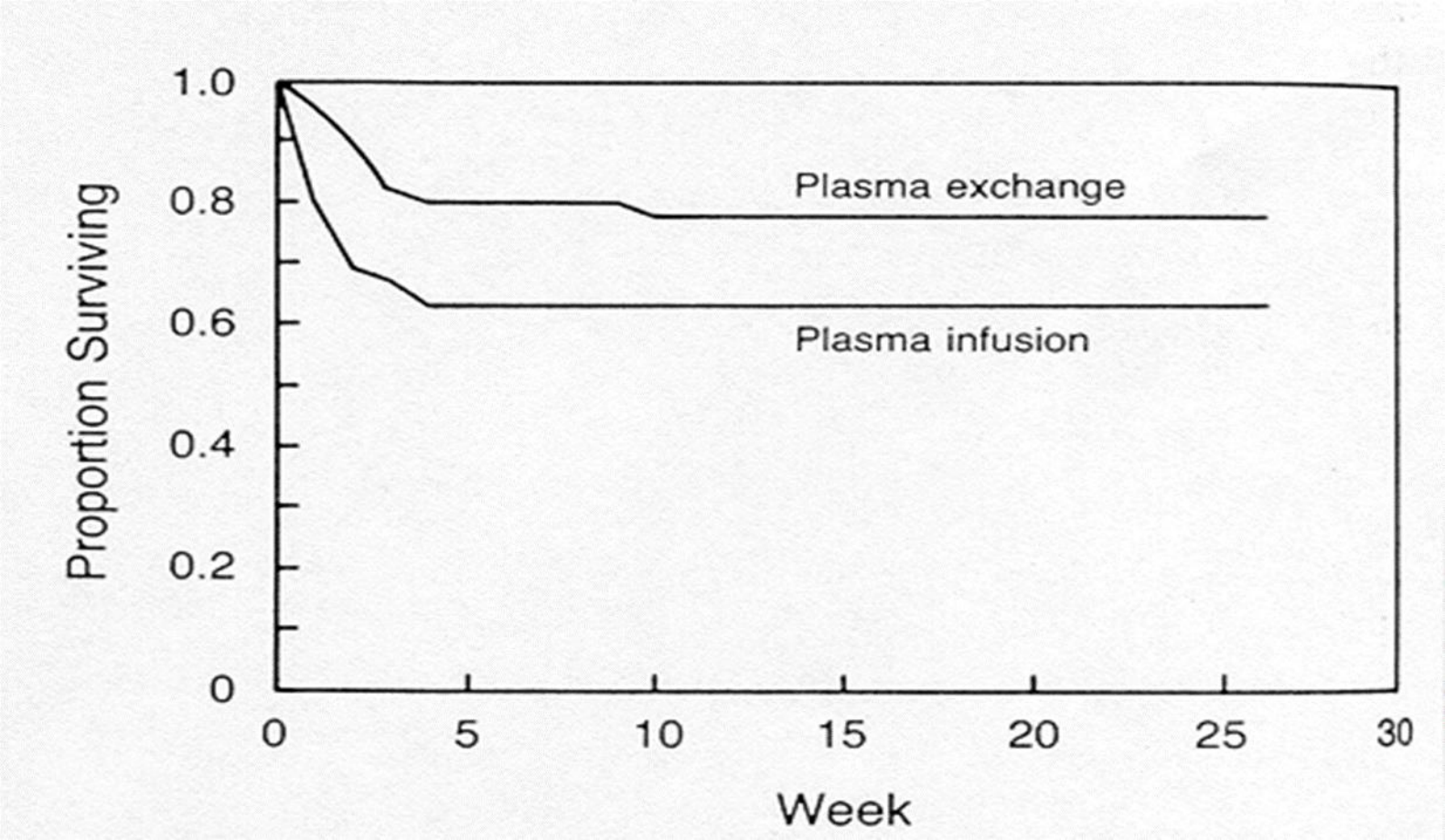


How drugs work in TTP

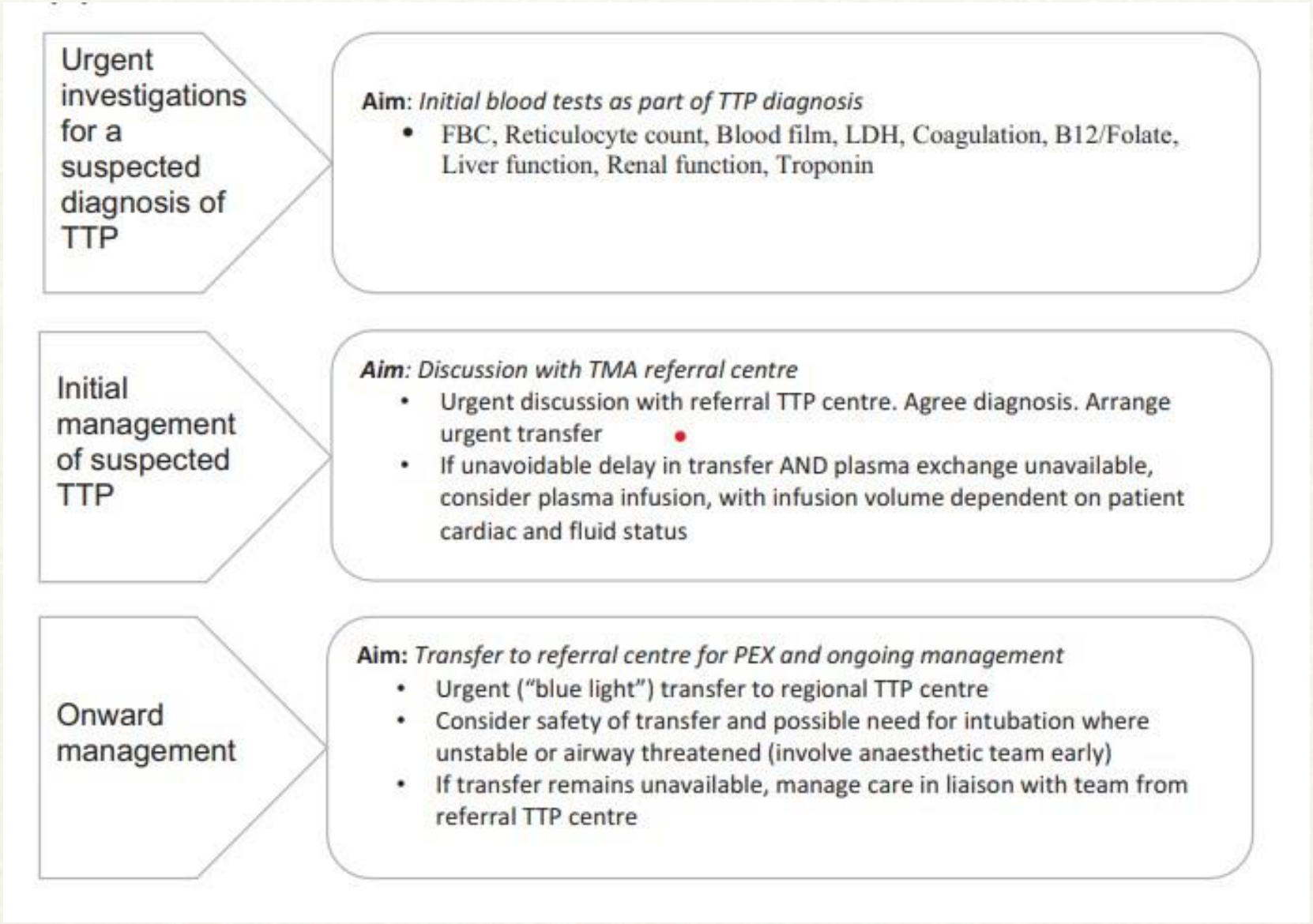


Treatment of TTP

Survival of patients with thrombotic thrombocytopenic purpura

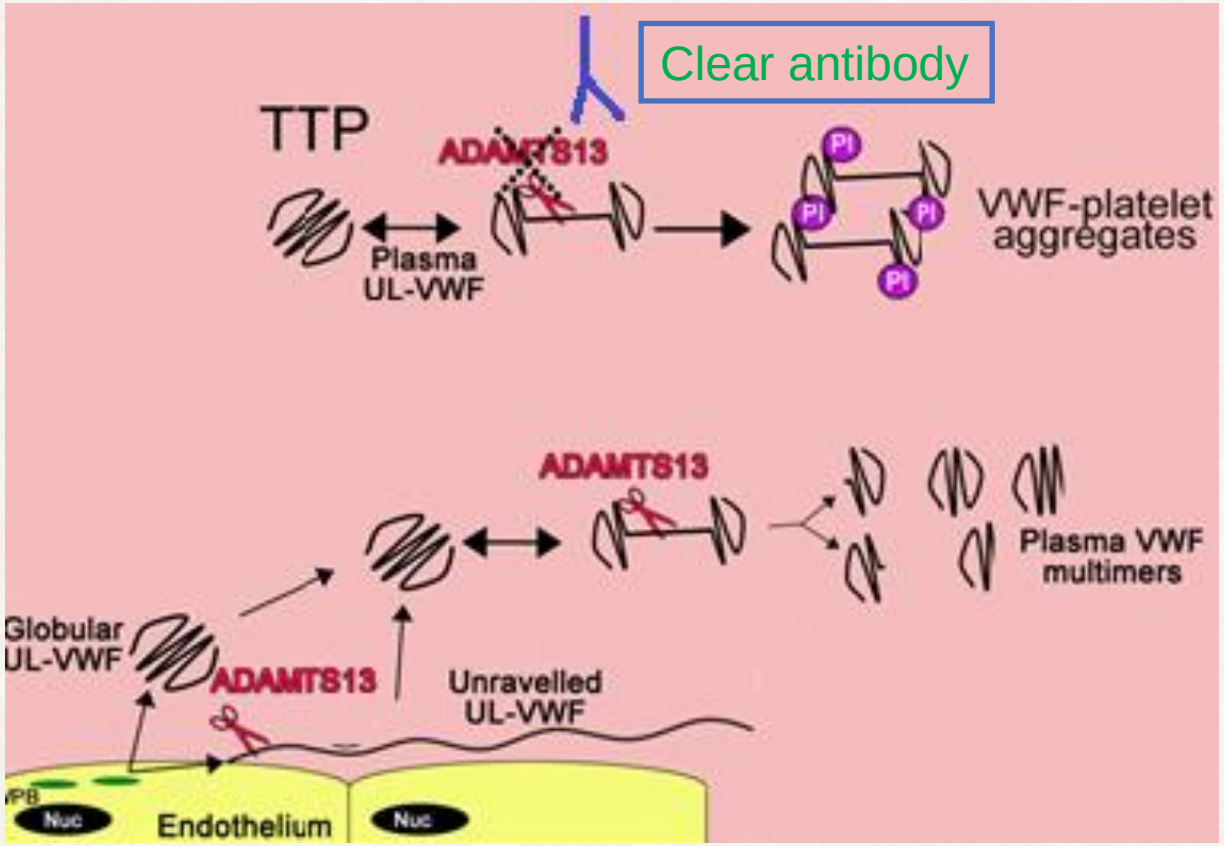


Rock *et al*, NEJM 1991

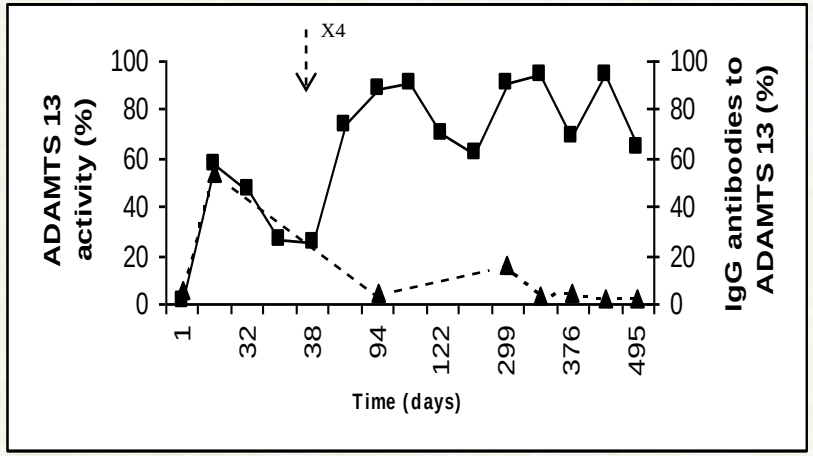


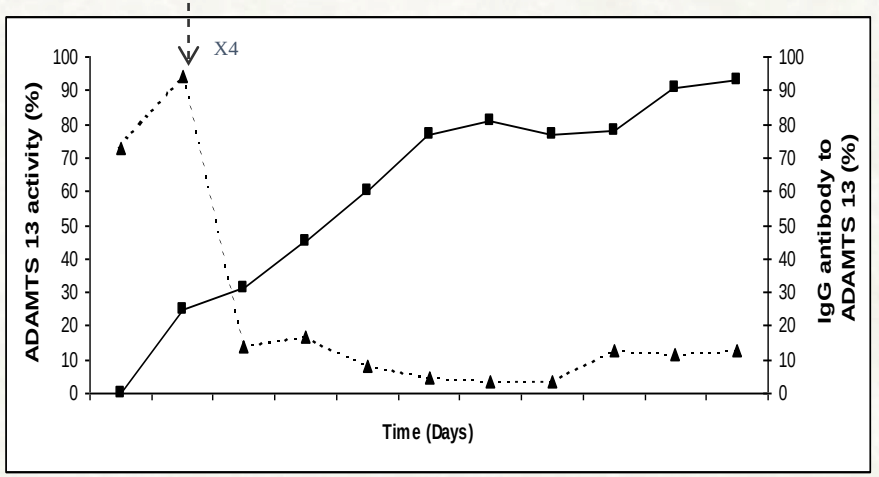
Scully *et al*, BJH 2024

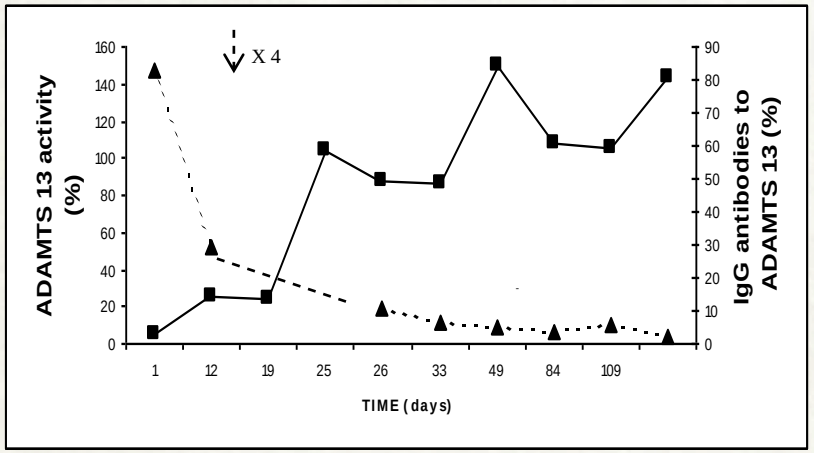
How drugs work in TTP

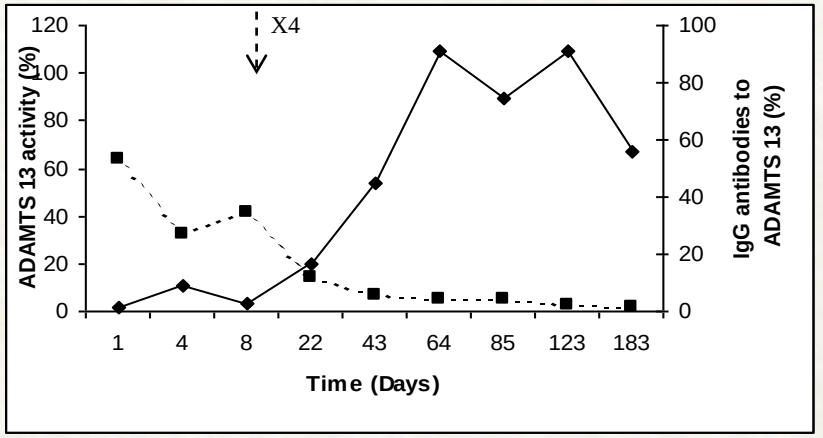


ADAMTS13 activity & anti ADAMTS13 IgG antibodies and response to Rituximab in refractory TTP









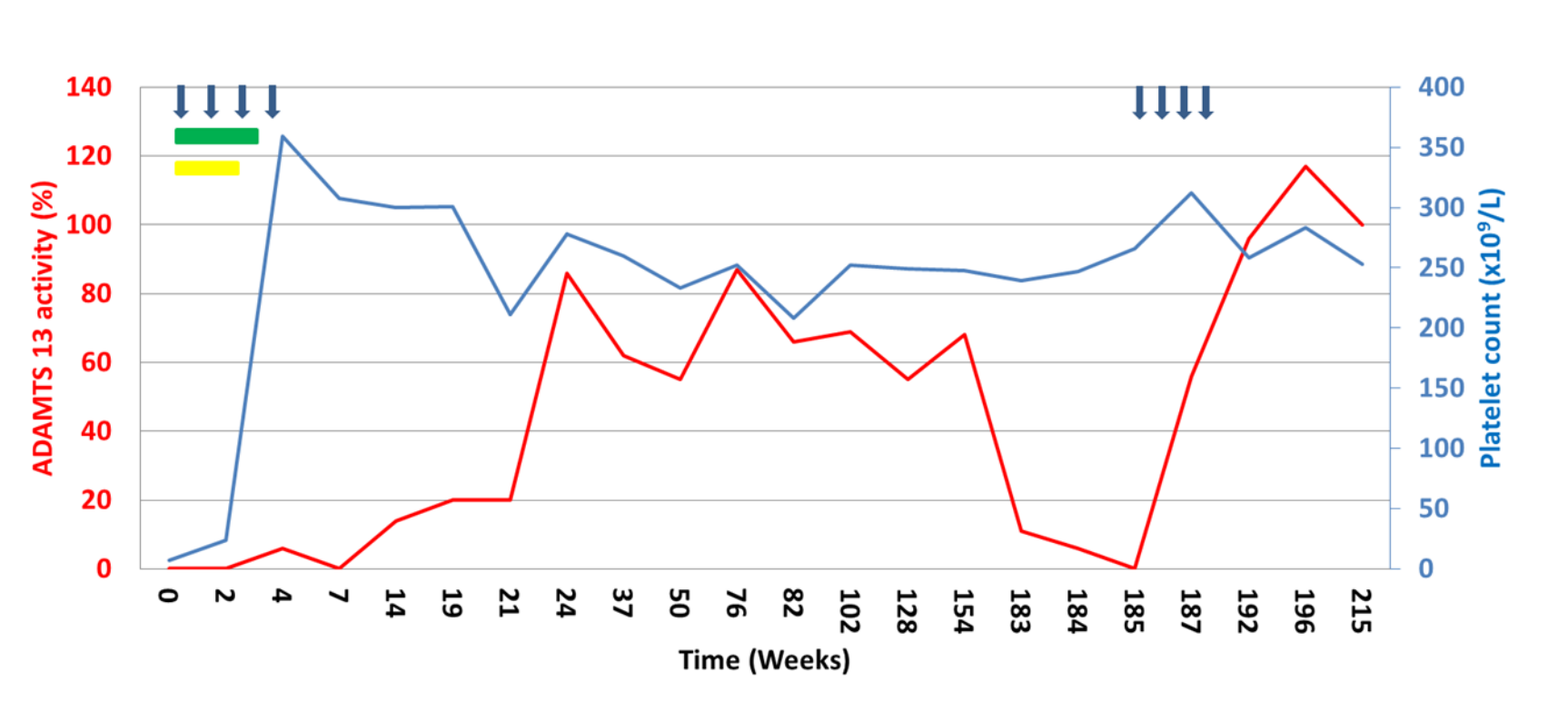
Scully *et al* BJH 2007

Upfront Rituximab - timing and outcome

	≤3 days from admission (n=52)	>3 days from admission (n=30)	
Median No. of PEX to CR (range)	16 (4-36)	24 (6-40)	p=0.03
Median Length of admission (range)	16 (4-86)	23 (7-52)	p=0.01
Median Time to CR from admission (range)	12 (4-52)	20 (4-42)	P<0.001
Median Time to CR from first infusion (range)	10 (2-50)	9 (0-30)	P=0.67

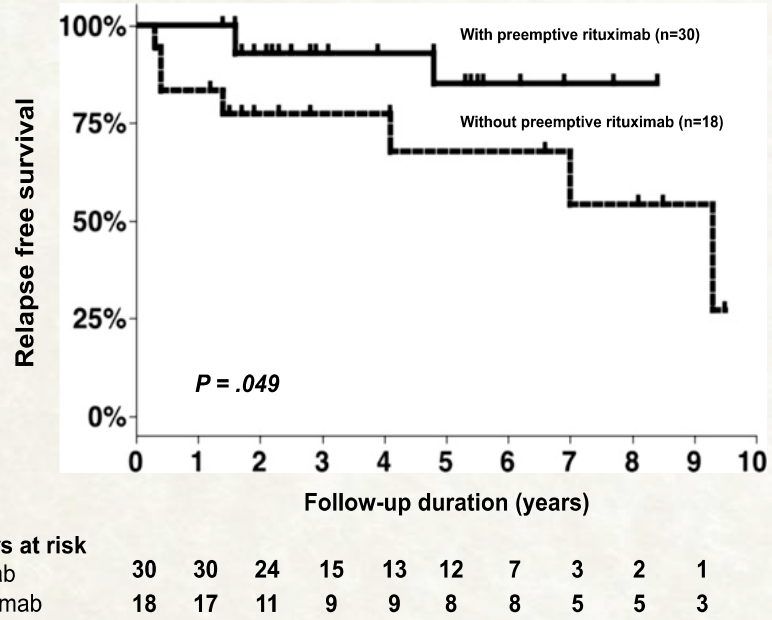
Westwood *et al* JTH 2013

Elective Rituximab

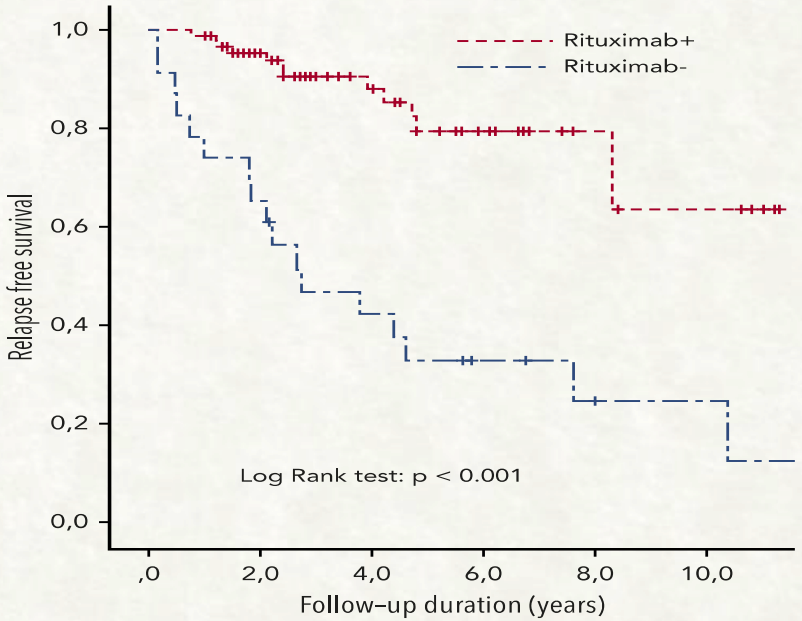


Elective Rituximab

Hie *et al*
Blood 2014



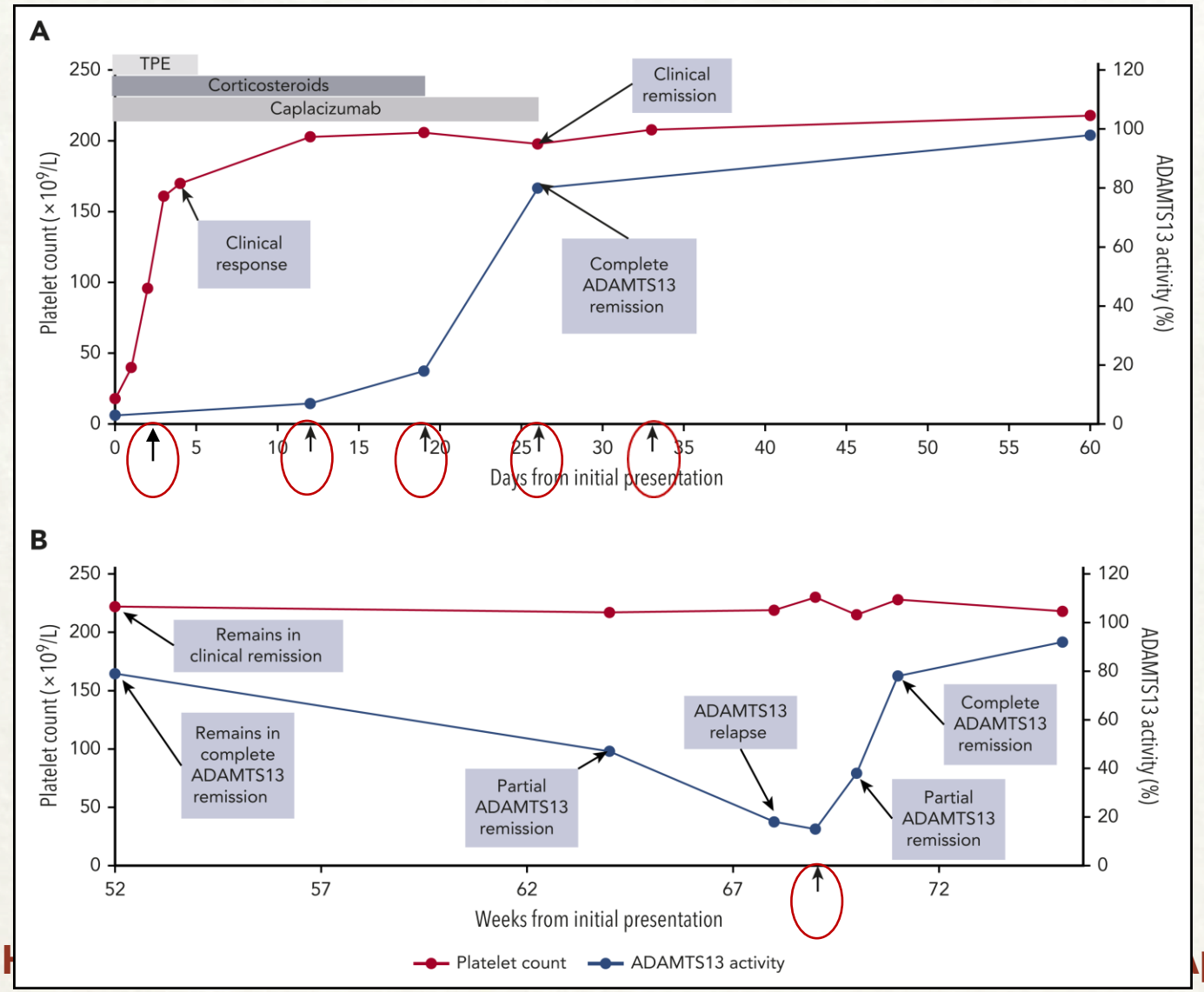
Numbers at risk										
Rituximab	30	30	24	15	13	12	7	3	2	1
No rituximab	18	17	11	9	9	8	8	5	5	3



Jestin *et al*,
Blood 2018

Rituximab in iTTP

Early rituximab in acute episode



Elective rituximab for ADAMTS13 relapse

↑ Rituximab

Goal of iTTP therapy = ongoing ADAMTS13 CR

Adapted from Cuker *et al* 2021

Immune TTP – treatment

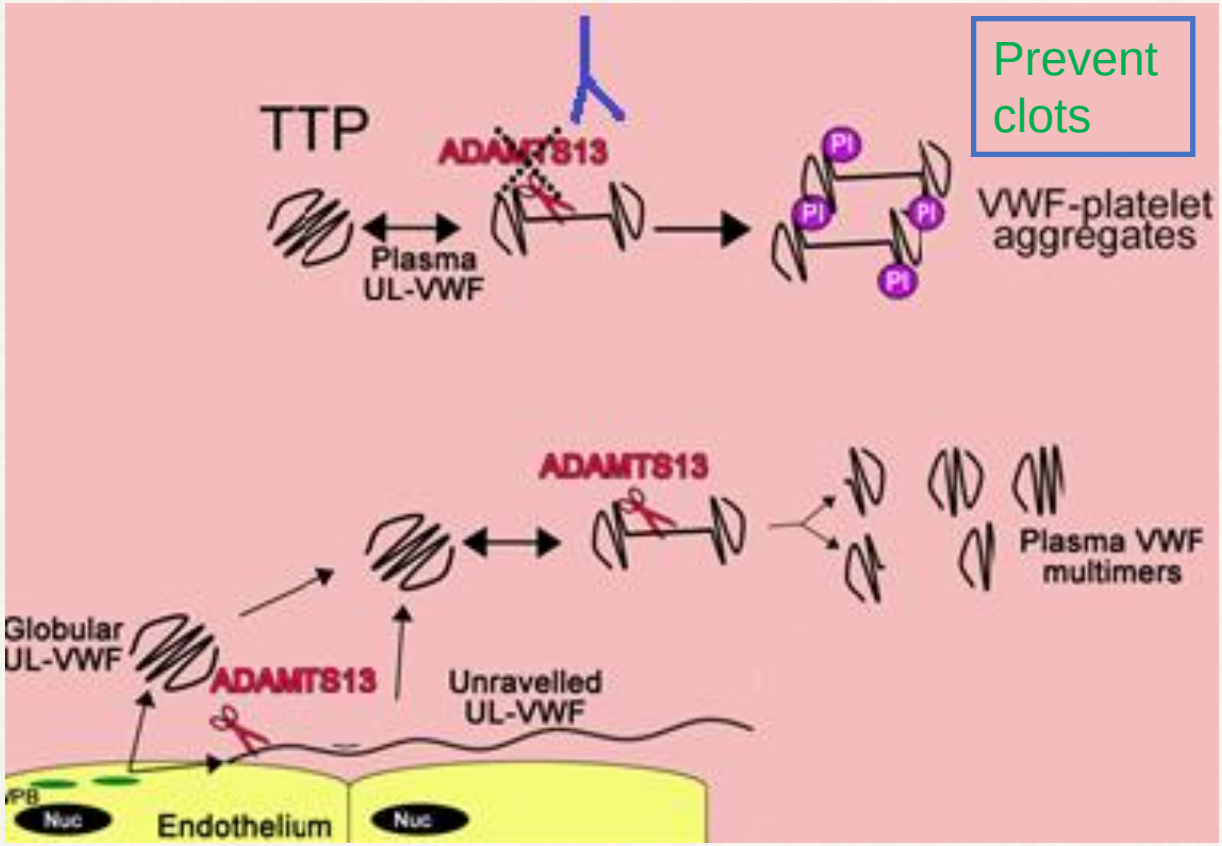
Current therapy

Daily plasma exchange (PEX)	Immunosuppression (corticosteroids and/or rituximab)
• removes ULvWF • removes autoantibodies • replenishes ADAMTS13	inhibits autoantibody formation

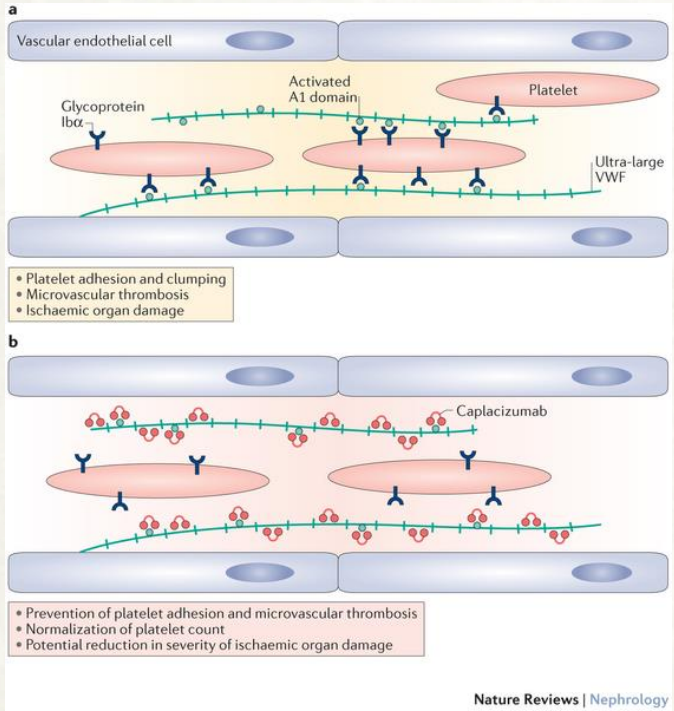
Issues:

- Mortality of 10-20%
- Refractoriness to treatment (assoc with poor outcomes)
- Disease exacerbations

How drugs work in TTP



Caplacizumab – anti VWF nanobody



A single-domain antibody fragment
- single monomeric variable antibody domain able to bind selectively to a specific antigen

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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†

N Engl J Med 2016; 374:511-522 | February 11, 2016 | DOI: 10.1056/NEJMoa1505533

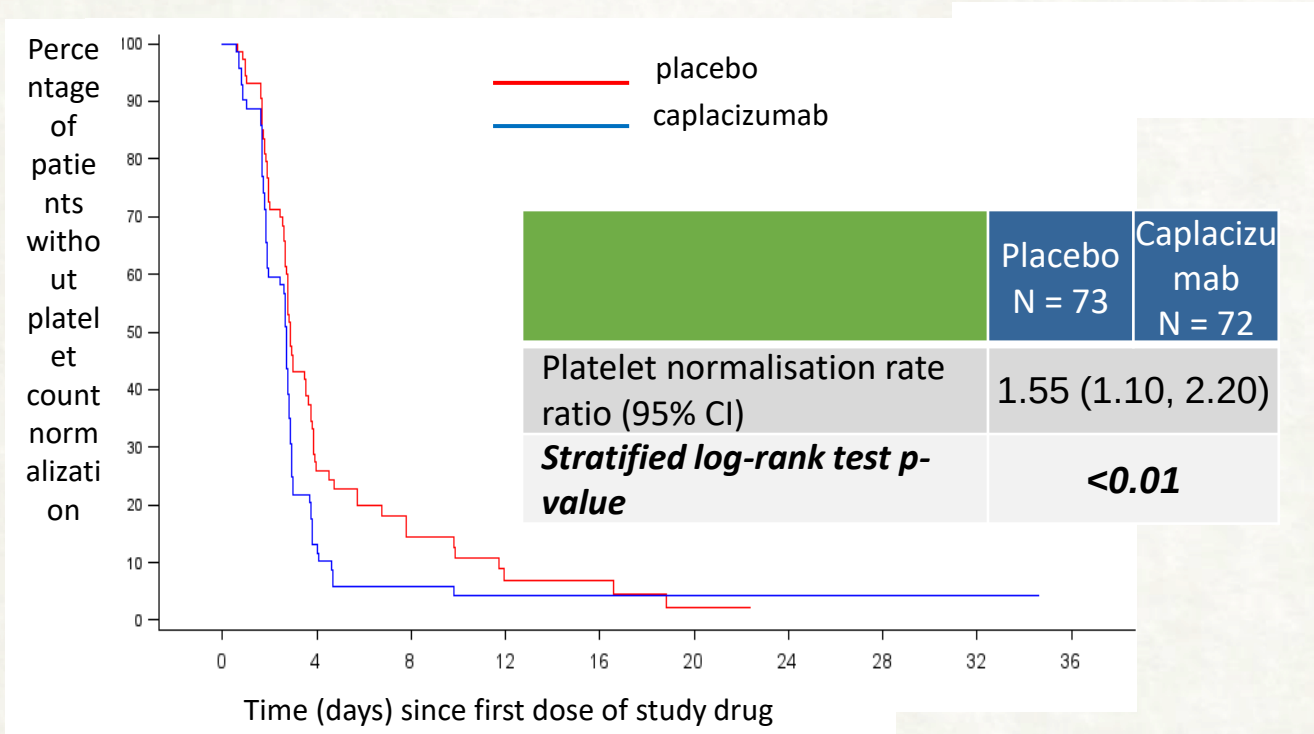
The NEW ENGLAND JOURNAL of MEDICINE

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, B. Biswas, H. De Winter, and R.K. Zeldin, for the HERCULES Investigators*

Hercules: Phase III Trial



	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***	

Platelet count response was defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

Scully *et al*, *NEJM 2019*

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
aTTP-related death[2]	3 (4.1)	0
recurrence (exacerbation) of aTTP[3]	28 (38.4)	3 (4.2)
Recurrence during follow-up period (relapses)	0	6 (9.1)[2]

Capla 500 project

10 worldwide countries - 942 patients
Unprecedented, international academic effort on rare disease

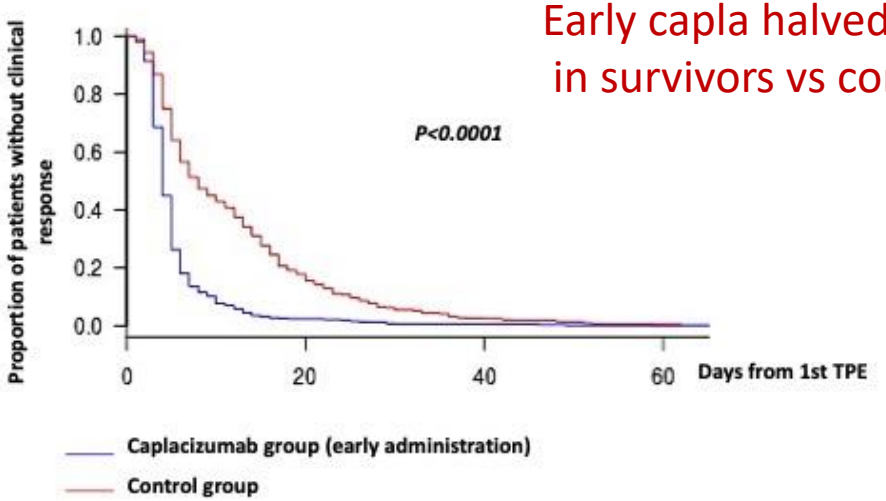
Capla started <3d n=715
≥4 d n=218

Table. Clinical presentation at diagnosis and main outcomes according to therapeutic groups.

	Caplacizumab group (N=942)	Historic control group (N=495)	p-value
Clinical presentation			
Age (years)	46 (33-58)	43 (33-56)	0.32
Females	67%	68%	0.82
Number of previous iTTP episodes			
None	82%	82.6%	0.80
1	13%	16.4%	
≥2	5%	1%	
Neurologic involvement	64%	61%	0.25
Headache	37%	31.5%	0.60
Confusion	26.1%	19.6%	0.01
Seizure	8.4%	9.2%	0.67
Coma (Glasgow Coma Scale ≤8)	3.7%	2.8%	0.59
Focal deficiency	38.7%	23.4%	<0.0001
Troponin > upper normal value	71.2%	69.1%	0.50
Hemoglobin level (g/dL)	8.4 (7-10)	8.6 (7.3-10.4)	0.05
Platelet count (x10^9/L)	12 (8-21)	13 (9-25)	0.05
Serum creatinine (µmol/L)	92.8 (72-124)	88 (71-118)	0.12
Estimated glomerular filtration rate (ml/min/1.73m²)	74 (52-97)	76 (56-100)	0.14
LDH level (x upper normal value)	3.9 (2.3-5.7)	3.74 (2.3-6)	0.61
French severity score*			0.7
0	15.1%	20%	
1	35.1%	35.2%	
2	34.8%	29.2%	
3	14.8%	14.5%	
4	0.20%	1.1%	
ADAMTS13 activity	<5% (<5%-<5%)	<5% (<5%-<5%)	0.45
Detectable free anti-ADAMTS13 antibodies	91.3%	85.1%	0.001
Outcome			
3-month survival	98.6%	93.3%	<0.0001
Clinical response	99.2%	94.7%	<0.0001
Exacerbation rate	4.8%	35%	<0.0001
Refractoriness	2.5%	12.7%	<0.0001
Number of TPE to achieve clinical response	5 (4-7)	8 (5-15)	<0.0001
Time to ADAMTS13 activity ≥20% (days)	29 (18-50)	33 (18-74)	0.001

Abbreviations: iTTP: immune-mediated thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; ADAMTS13: A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs; member 13. *Based on age, cerebral involvement, and LDH level. Continuous variables are provided as median [IQR]; qualitative variables are provided as percentage of patients in the respective treatment group. P-value was considered significant when < 0.05.

Figure. Cumulative daily rate of event (clinical response)-free survival after first therapeutic plasma exchange within 3 months in patients of the caplacizumab group who received early caplacizumab administration (within 3 days following first therapeutic plasma exchange [TPE]) versus patients of the control group.



Early capla halved time to clinical response in survivors vs controls

Failure to achieve clinical response 5x less likely with capla
↓refractoriness + exacerbations
↓PEX to clinical remission regardless of rituximab use.
46 pt exacerbations following capla interruption while A13 activity <10%
Time to ADAMTS13 ≥20% shorter in capla group - ritux more used.

Capla 500 project

Unfavorable outcomes very low with early caplacizumab initiation

- death 1%
- refractoriness 1.1%
- exacerbations 5.3%

Capla-related AE in 220 pt (23%)

- major bleeding (N=19, 2.2%) including GI bleeding (N=8)
  ICH, severe CVC insertion bleeding, PV bleeding (N=2 each)
- clinically relevant non-major bleeding (N=34, 3.7%)
- non-clinically relevant non-major bleeding (N=114, 14%)
- injection site reaction (N=35, 4.5%)

Coppo *et al*, ASH 2023

Capla 500 project

Caplacizumab added to PEX and immunosuppression
↓unfavorable outcomes during acute iTTP including mortality
↓alleviates burden of care
at the potential expense of rare, major bleeding events

Coppo *et al*, ASH 2023

PEX-free management of iTTP: the Austrian-German experience

43 patients (33F) with 45 acute iTTP episodes 2018 -22. Median 38y (20-83)
TMA with organ dysfunction, severe ADAMTS13 deficiency and anti-A13 Ab

- Robust increase in platelet count in majority of patients
- Median time to initial platelet count normalisation 4 days (IQR 3-4 days, n = 23).

- 3 patients did not improve with platelet counts after the first capla dose and received additional PEX. Underlying conditions - CMV viremia, HIV, ITP.
- One patient with recurrent TTP was first treated with PI due to ?cTTP , later switched to capla once antibodies were detected.
- 4 patients had exacerbations managed with capla alone, after initial SOC treatment.

PEX is not mandatory for acute iTTP management
- clinical remission with capla + immunosuppression alone in majority of cohort.

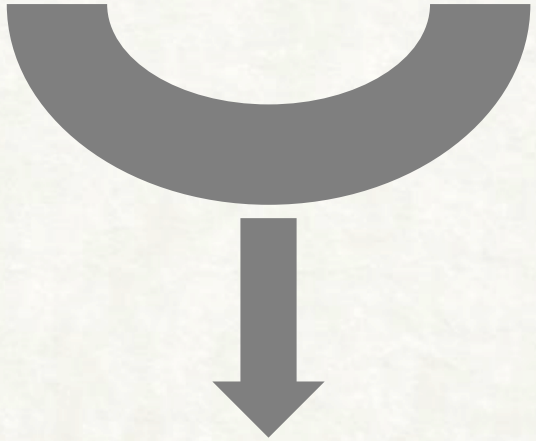
Knoebl *et al,* ISTH 2023

The Current…

PEX:
ADAMTS13 replacement

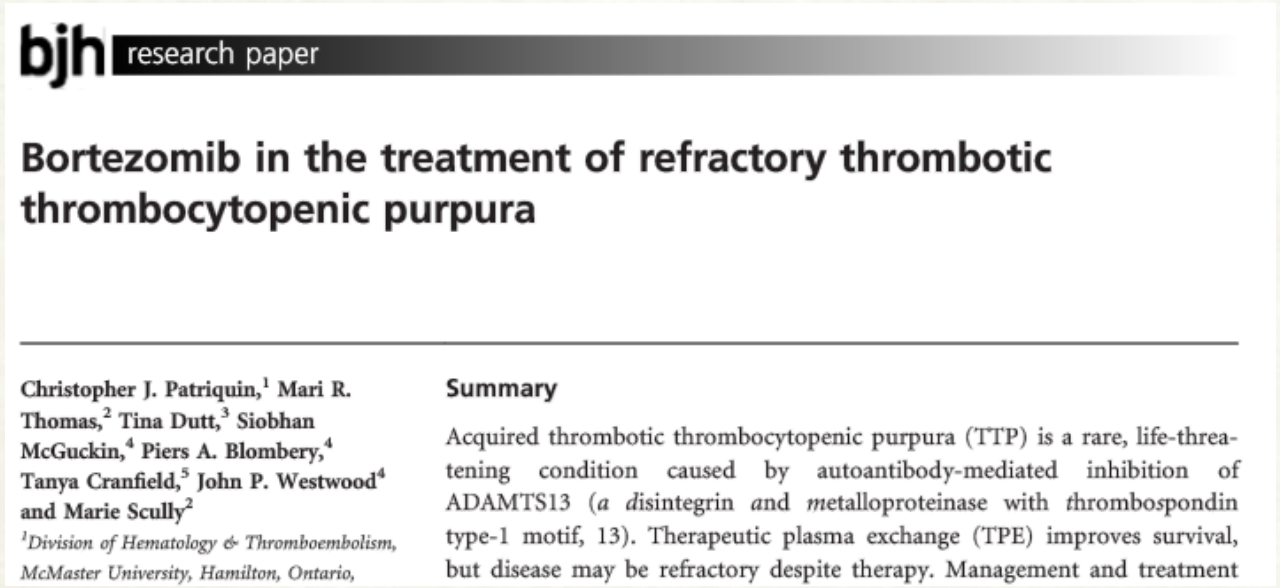
Caplacizumab
To reduce microthrombi

Immunosuppression
To remove antibodies



Normal platelet count
Normal ADAMTS13 activity
Reduced time to remission and mortality

Additional immunosuppression- Bortezomib



bjh research paper

Bortezomib in the treatment of refractory thrombotic thrombocytopenic purpura

Christopher J. Patriquin,[1] Mari R. Thomas,[2] Tina Dutt,[3] Siobhan McGuckin,[4] Piers A. Blombery,[4] Tanya Cranfield,[5] John P. Westwood[4] and Marie Scully[2]

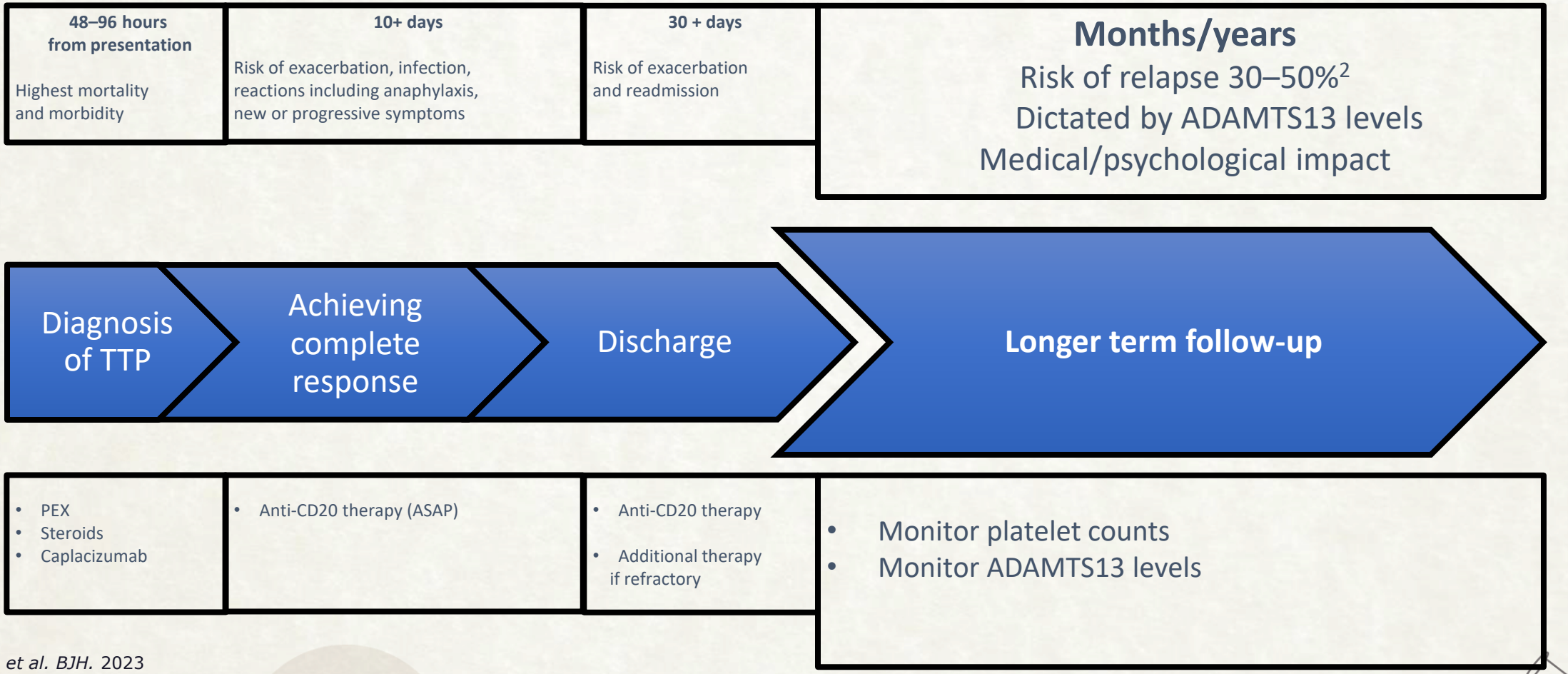
[1]*Division of Hematology & Thromboembolism, McMaster University, Hamilton, Ontario,*

Summary

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening condition caused by autoantibody-mediated inhibition of ADAMTS13 (*a disintegrin and metalloproteinase with thrombospondin* type-1 motif, 13). Therapeutic plasma exchange (TPE) improves survival, but disease may be refractory despite therapy. Management and treatment

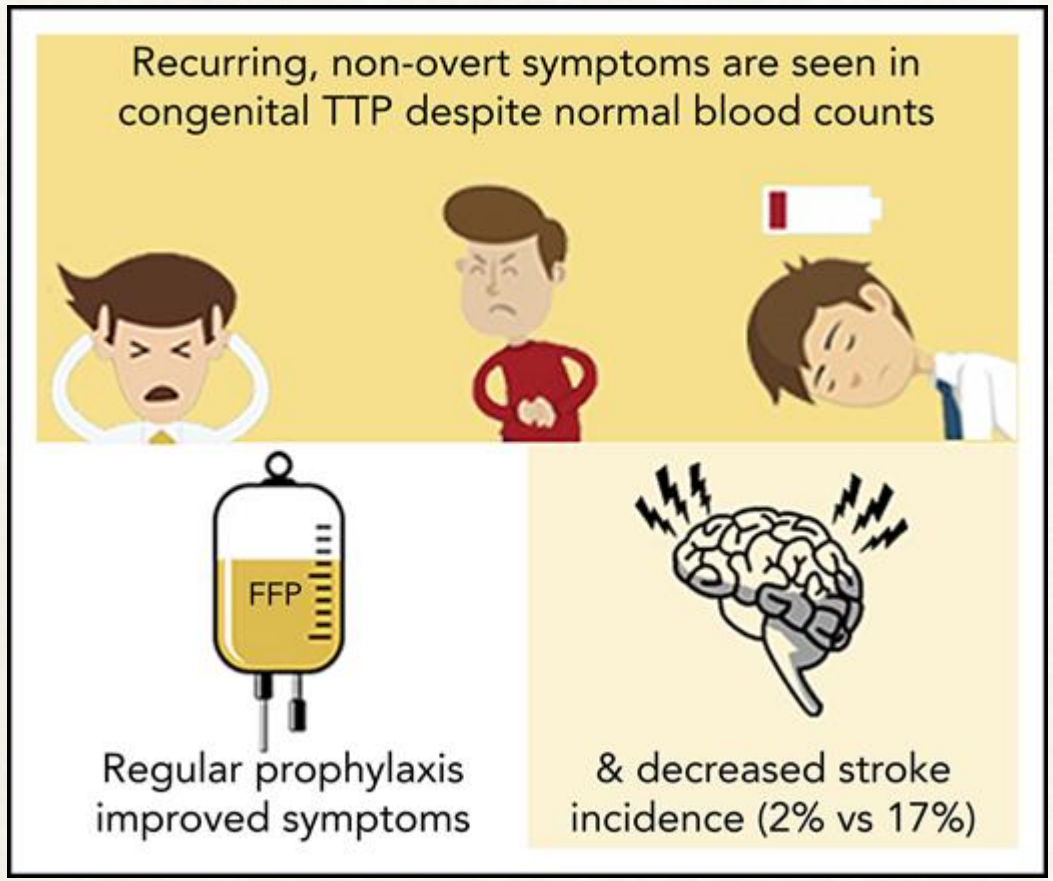
- Case reports/small series of bortezomib use as additional immunosuppression in refractory cases
- Rapid clearance of anti ADAMTS13 IgG
- Difficult to assess contribution of single agent in heavily treated patients

TTP Pathway – Lifelong Care

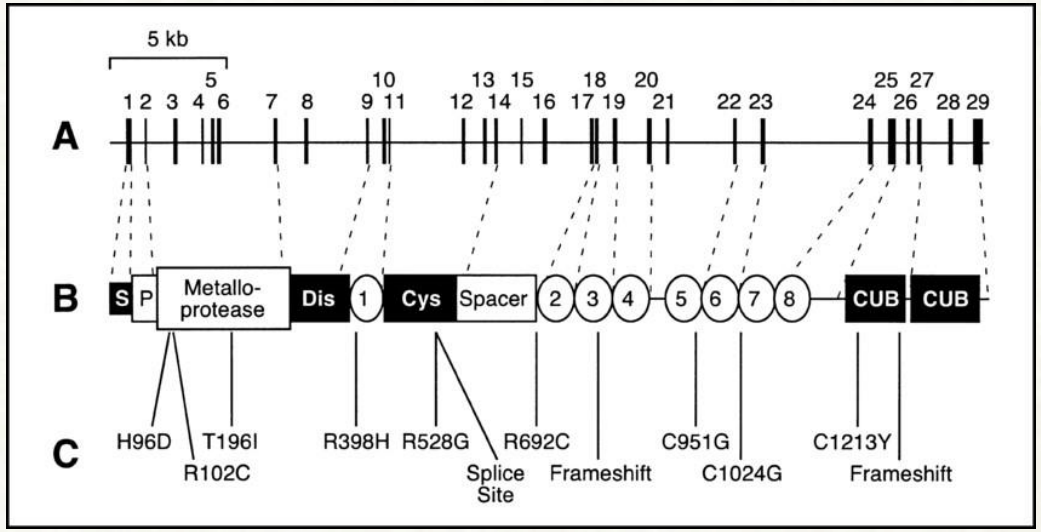


Scully *et al. BJH.* 2023

Congenital TTP



Alwan *et al* 2020



Zheng *et al* 2002

Natural history of congenital TTP: International Hereditary TTP Registry

182 hTTP pt from 20 countries. Median F/U 3.6y (0-18.5) 54% F
61% Caucasian 27.5% Asian 1.1% Black 10.4% other ethnicities

TTP history
46% first symptoms in perinatal period (0-3m)
Median age at diagnosis 19.1y (0-69.9)
Prior to enrollment, 86%≥ one acute TTP episode with mean (SD) 4.3 (4.5) events/patient.

Burden of disease
TIA/strokes 31%
↑BP 20%
CKD 12%
Migraines/severe headache 8.2%
Seizures 7.7%

Schraner *et al* ASH 2023

Natural history of congenital TTP: International Hereditary TTP Registry

Prospective follow up 82/182 pt (45%) had 265 acute TTP episodes
Overall event rate of 297/1000 person-years.

n=8 died during FU, 5/8 on regular PI.
- n=3 acute TTP; age 33, 44, 52y
- n=3 cardiac; age 39, 49, 56 y
- n=2 unknown; age 75, 79 y

Significant clinical burden

Recurrent acute TTP episodes → neuro, CV, renal sequelae + early mortality
Delayed diagnosis & insufficient treatment likely contributed

Awareness, timely diagnosis and sufficient ADAMTS13 replacement therapy (for acute episodes and prophylactically) crucial for improving short- and long-term clinical outcomes

Schraner *et al* ASH 2023

Estimating the population-based prevalence of congenital TTP using large-scale sequencing data

Table 1. Estimated prevalence of cTTP using pathogenic reported variants only.

Population	Total Number Of Alleles	Total Number Of affected alleles	Collettive Frequency Of Variants	Prevalence in 10^6 Individuals (recessively-inherited)	Prevalence in 100 Individuals (Carrier)
All	282912	1159	0.004	17	0.8
Africans and African Americans	24974	62	0.002	6	0.5
Latinos/Admixed Americans	35440	134	0.004	14	0.7
Ashkenazi Jewish	10370	8	0.001	0.6	0.2
East Asians	19954	42	0.002	4	0.4
Finnish	25124	129	0.005	26	1.0
Europeans (not Finnish)	129206	710	0.005	30	1.1
South Asians	30616	49	0.002	3	0.3
Other ethnicities	7228	25	0.003	12	0.7

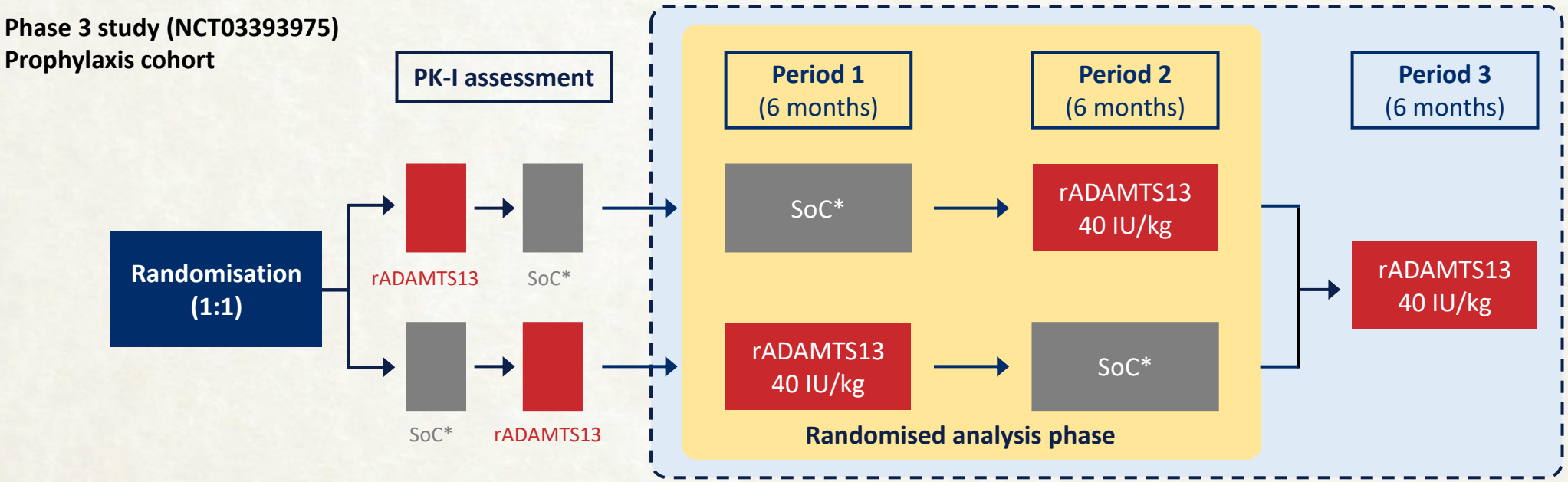
gnomAD + ClinVar +literature

True cTTP prevalence >10 x previously reported
- suggests that many patients might be undiagnosed

Mutational burden of ADAMTS13 higher
- 167 novel variants (302 previously reported).

Peyvandi *et al* ASH 2023

Phase 3 RCT open-label, multicenter, crossover rADAMTS13 in patients with congenital TTP



Pre-planned interim analysis of prophylaxis treatment cohort
(after 30 adolescents/adults had completed study; data cutoff: August 12, 2022)

Scully *et al*, 2023 ISTH

Phase 3 RCT open-label, multicenter, crossover rADAMTS13 in patients with congenital TTP

Age 12-58 years 61% F

Primary outcome

No acute TTP events occurred during rADAMTS13 prophylaxis

Mean rADAMTS13 exposure: 13.2 months

One event occurred during SoC.

Secondary outcomes

TTP manifestations eg thrombocytopenia - lower with rADAMTS13

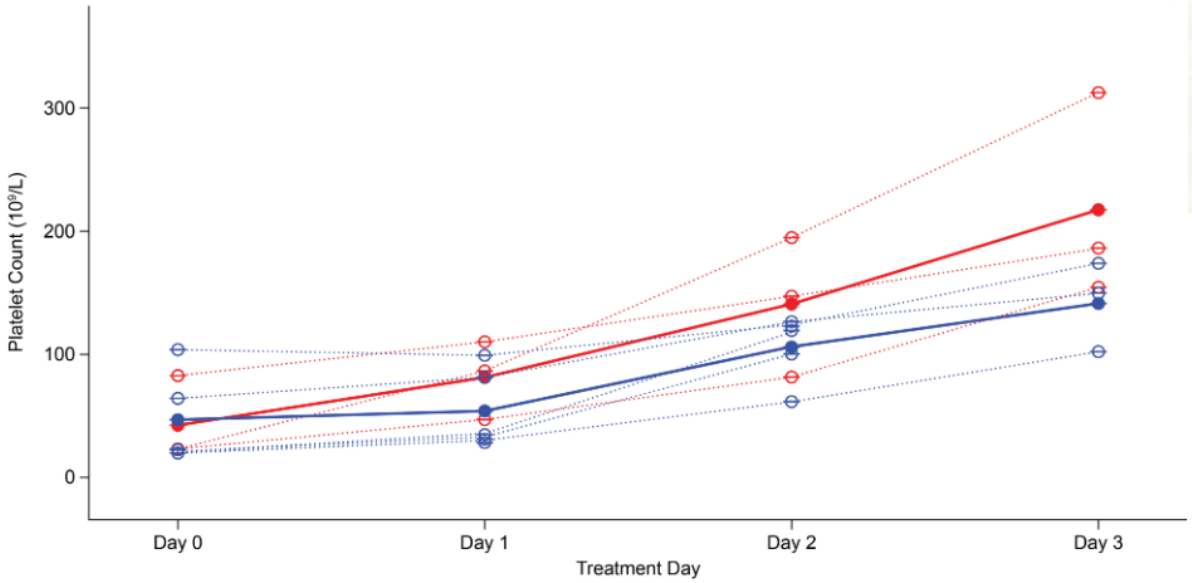
No rADAMTS13-related SAEs were reported.

No neutralising antibodies developed during rADAMTS13 prophylaxis

Scully *et al*, 2023 ISTH

rADAMTS13 for treatment of acute TTP events in congenital TTP: Phase 3 Crossover RCT & 3b Continuation

Figure. Platelet counts during the first 3 days of treatment for an acute TTP event in patients with cTTP enrolled in either the phase 3 study or the phase 3b continuation study



- 8 suspected acute TTP events were treated in 7 patients
- No acute events occurred while patients were receiving rADAMTS13 prophylaxis

Table. Summary of acute TTP events reported in patients with cTTP enrolled in either the phase 3 study or the phase 3b continuation study

	Treatment	Platelet count, 10^9/L		LDH, U/L	
		Event Start	Event End	Event Start	Event End
Phase 3 (NCT03393975)					
Patient 1	SoC (FFP)	104 (56.5% decrease from baseline [239])	279	454 (2.41× baseline)	194 (1.03× baseline)
Patient 2	rADAMTS13	84	270	236 (1.10×ULN)	205 (0.96×ULN)
Patient 3	rADAMTS13	24	155	598 (2.43×ULN)	278 (1.13×ULN)
Patient 4, event 1	SoC (FFP)	23	62	685 (2.78×ULN)	320 (1.30×ULN)
Patient 4, event 2	SoC (FFP)	23	101	652 (2.65×ULN)	323 (1.31×ULN)
Patient 5	SoC (S/D-treated plasma)	20	276	458 (2.04×ULN)	263 (1.17×ULN)
Patient 6	SoC (S/D-treated plasma)	65	150	211 (1.06×ULN)	187 (0.94×ULN)
Phase 3b (NCT04683003)					
Patient 7	rADAMTS13	20	546	1027.4	282.4

cTTP, congenital thrombotic thrombocytopenic purpura; FFP, fresh frozen plasma; LDH, lactate dehydrogenase; rADAMTS13, recombinant ADAMTS13; S/D, solvent/detergent; SoC, standard of care; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal.

- **All 3 acute TTP events treated with rADAMTS13 resolved promptly with the treatment protocol**
- **No serious TEAEs related to rADAMTS13** and **no neutralising antibodies** against ADAMTS13

Scully *et al*, 2023 ASH

Takeda's ADZYNMA (ADAMTS13, recombinant-krhn) Approved by U.S. FDA as the First and Only Recombinant ADAMTS13 Enzyme Replacement Therapy for the Treatment of Congenital Thrombotic Thrombocytopenic Purpura (cTTP)

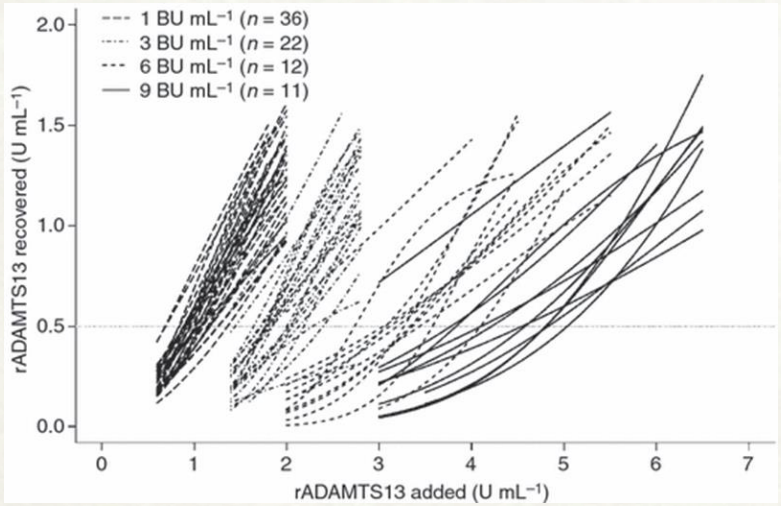
November 9, 2023

Share

FDA approved for the prophylactic and on-demand treatment of adult and pediatric patients with cTTP

Phase 2 studies rADAMTS13 for iTTP

- Phase 2a RCT of supplementing PEX with rADAMTS13
- Planned phase 2b RCT without PEX

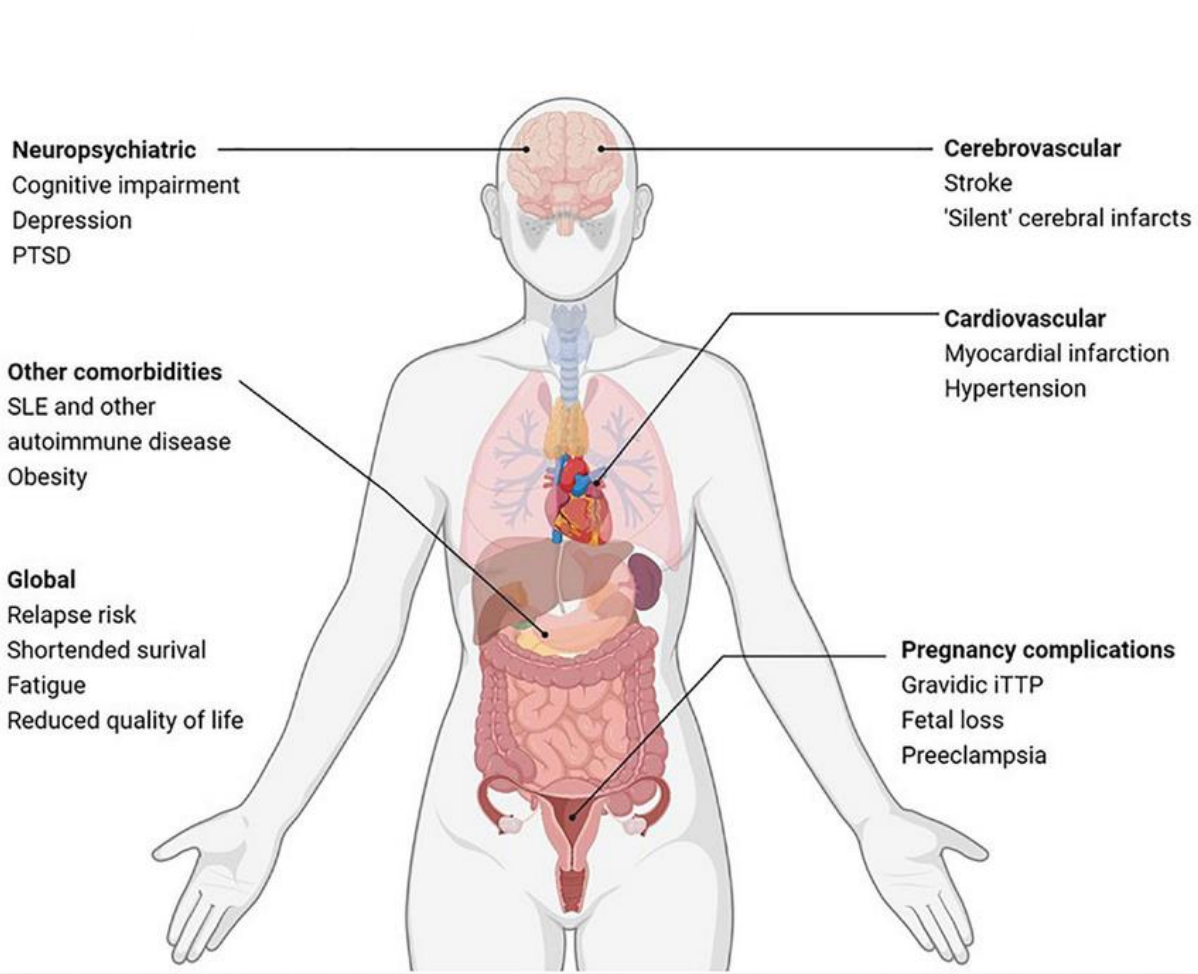


Plasma samples from 36 different TTP patients with neutralizing anti-ADAMTS13 antibodies adjusted to 1, 3, 6 and 9 BU / mL.

Effective concentration to restore 0.5 U/mL ADAMTS13 activity (EC50) shown by horizontal line.

Plaimauer *et al,* JTH 2011

TTP - Long term effects and monitoring



Selvakumar *et al* 2023

What is the impact of acute TTP ?

J Clin Psychiatry. **1984** Nov;45(11):477-9.
The cost of surviving thrombotic thrombocytopenic purpura: case report.
Greenberg DB, Carey RW.
The **neuropsychiatric sequelae of thrombotic thrombocytopenic purpura (TTP) have not been discussed previously since most patients did not survive. The affective disorder, personality change, and cognitive deficits which resulted from TTP ….**The **neurologic and psychiatric residua did not indicate a chronic form of the disease.**

Am J Hematol. **2011** Jan;86(1):87-9
Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura Cataland et al
….evaluation of neurologic injury that included a magnetic resonance imaging (MRI), a neurocognitive testing, and health-related quality of life. Twenty-seven patients with a history of idiopathic TTP functioning normally in their activities of daily living. **39% of the MRI studies were abnormal; 63% patients demonstrated neurocognitive impairment**, particularly in **visual learning and memory**. Health-related quality of life scores were also significantly lower than age- and gender-matched US norms for both the composite mental component score and physical component score.
…….the prevalence of neurologic findings in TTP patients in remission is quite high and is largely undetected by routine clinical evaluations.

TTP survivors exhibit impaired stress perfusion on cardiac MRI

Characteristics	TTP Survivors (n = 10)	Control (n = 13)	p-value
Age (years, IQR)	44.5 (40.8 – 49.5)	53 (37 – 61.5)	.232
Sex (%)	Male 20% Female 80%	Male 31% Female 69%	.66
Race (%)	White 70% Black 30%	White 92% Black 8%	.281
BMI (mg/m^2, IQR)	34.5 (29.3 – 41.6)	26.5 (21.5 – 31.4)	**.012**
Hypertension	70%	46%	.402
Systolic BP (mmHg, IQR)	144 (136 – 157)	132 (129 – 152)	.313
Diastolic BP (mmHg, IQR)	94 (90 – 97)	82 (72 – 87)	**.003**
Diabetes	20%	0%	.178
Known Cardiac Disease	10%	85%	**<.001**

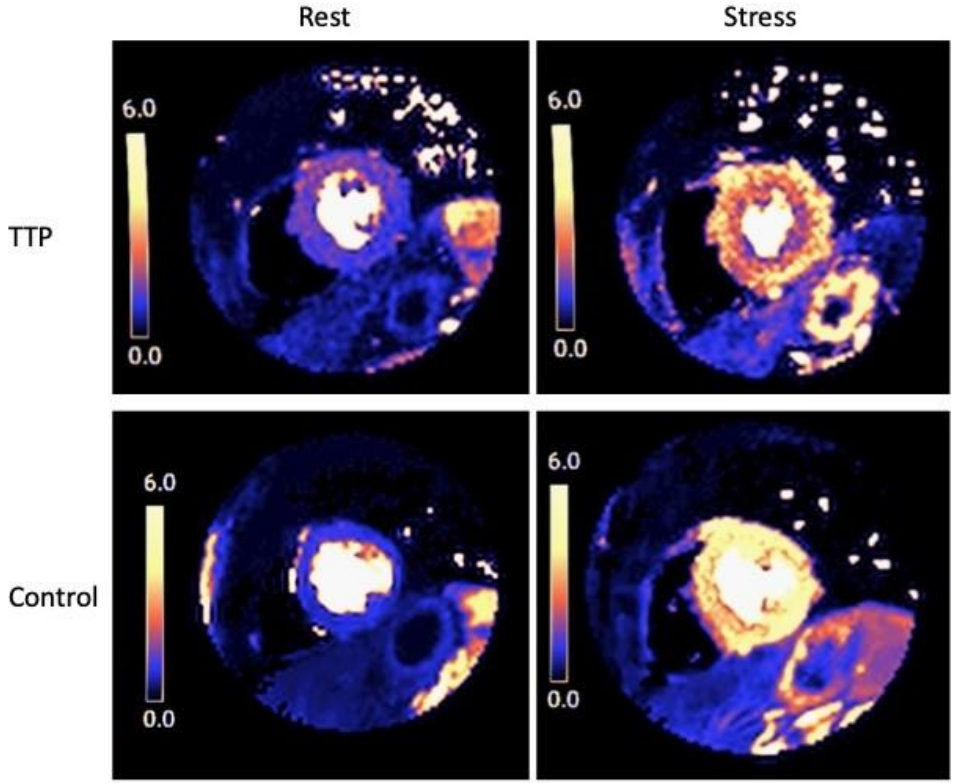


Figure 1. Quantitative perfusion maps of a TTP (top row) and a control subject (bottom row). Rest images are on the left and stress images are on the right.

The color maps shows perfusion in ml/min/g with brighter colors indicating higher perfusion. Stress imaging of the iTTP patient shows decreased flow in the subendocardium.

Asymptomatic structural changes +
↓perfusion common in TTP survivors
?clinical significance
Subclinical myocardial damage
↑CV morbidity & mortality

Sukumar *et al*, ASH 2023

So what ADAMTS13 level should we be aiming for?

Journal of Thrombosis and Haemostasis, **14**: 2114–2120 DOI: 10.1111/jth.13479

ORIGINAL ARTICLE

Low ADAMTS-13 activity and the risk of coronary heart disease – a prospective cohort study: the Rotterdam Study

Regular Article

THROMBOSIS AND HEMOSTASIS

Low ADAMTS13 activity is associated with an increased risk of ischemic stroke

Arterioscler Thromb Vasc Biol. 2016 Dec;36(12):2446-2451. Epub 2016 Oct 13.

Von Willebrand Factor, ADAMTS13, and the Risk of Mortality: The Rotterdam Study.

CM-HUS

Haemolytic Uraemic Syndrome (HUS)

HUS and TTP are Thrombotic Microangiopathies with similar features

Microangiopathic haemolytic anaemia
Thrombocytopaenia
Organ dysfunction

- acute renal failure in HUS
- CNS, cardiac complications in TTP

due to thrombi forming in arterioles and capillaries

but *different* pathogenesis

D+ HUS

- Commonest form
- Accounts for 90-95% cases in children
- Abrupt onset following diarrhoea (e.g. E.Coli) in preceding weeks
- Supportive treatment alone
- Good prognosis
- 5% die or ESRF
- Recurrence rare post transplant

CM-HUS

- Rare
- 5-10% cases in children
- Majority of adult cases
- Diarrhoeal prodrome less frequent
- Poorer prognosis
- Mortality, ESRF in 25%
- Long-term 50% evolve to ESRF
- High disease recurrence post transplant

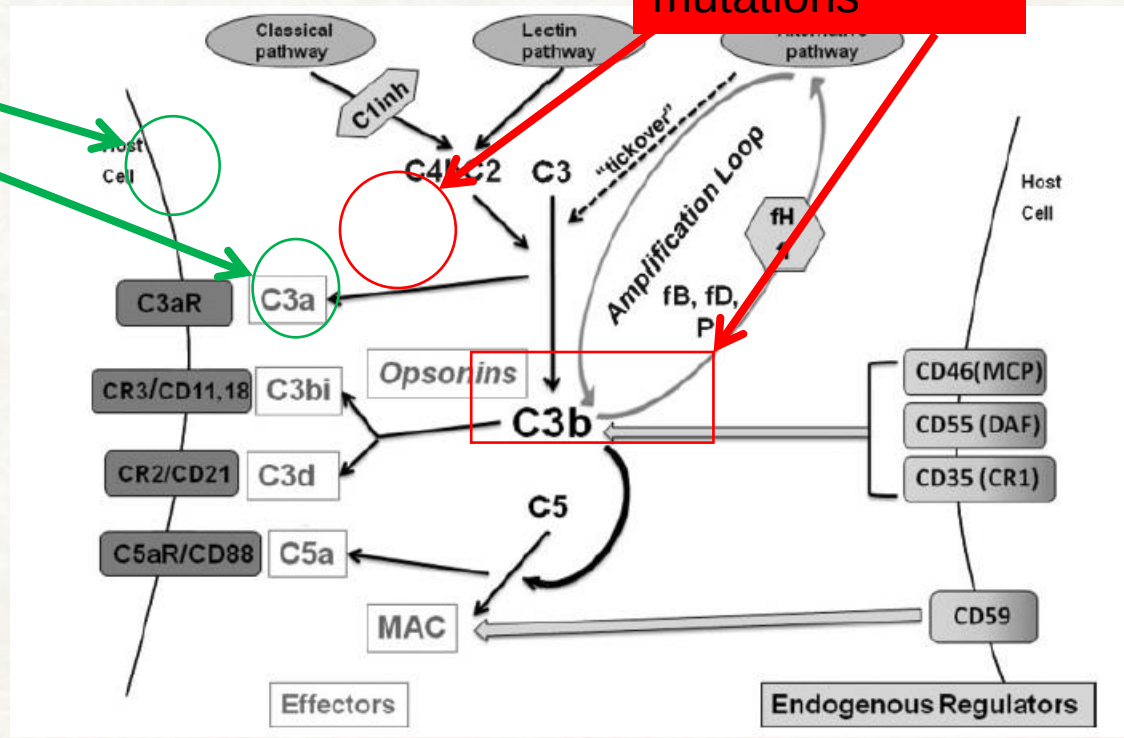
Aetiology of CM-HUS (aHUS)

- Can be familial and sporadic
- Mutations or polymorphisms (or both) in genes for **Complement proteins**
- ? Triggered by infection, pregnancy
- Likely multifactorial

CM-HUS & Complement

Gain of function mutations

Loss of function mutations



Emlen et al, 2010

CM-HUS prognosis correlated with genetic defect

Table 3 Main clinical characteristics of patients with atypical hemolytic uremic syndrome according to complement abnormality

Gene or subgroup	Frequency in aHUS	Minimal age at onset		Risk of death or ESRD at 1st episode or within < 1 y	Risk of relapses	Risk of recurrence after renal transplantation	Plasma therapy indicated
		Children	Adults				
CFH	20-30%	Birth	any age	50-70%	50%	75-90%	Yes
CFI	4 -10%	Birth	any age	50%	10-30%	45-80%	Yes
MCP	5 -15%	> 1 y	any age	0-6%	70-90%	< 20%	Questionable
C3	2 -10%	7 m	any age	60%	50%	40-70%	Yes
CFB	1-4%	1 m	any age	50%	3/3 not in ESRD	100%	Yes
THBD	3 -5%	6 m	rare	50%	30%	1 patient	Yes
Anti-CFH Ab	6%	Mostly 7-11 y		30-40%	40-60%	Yes if high Ab titer	Yes (+ IS)

CFH: factor H; CFI: factor I; MCP: membrane cofactor protein; CFB: factor B; THBD: thrombomodulin; Ab, antibodies; ESRD: end stage renal disease; IS: immunosuppressive treatment.

- CFH mutations have worst outcome
- Within 1 year, up to 70% with CFH mutations die or have ESRF
- High rate of recurrence in patients post transplant with mutations in CFH and CFI as these are synthesised in liver

Kavanagh & Goodship, 2010

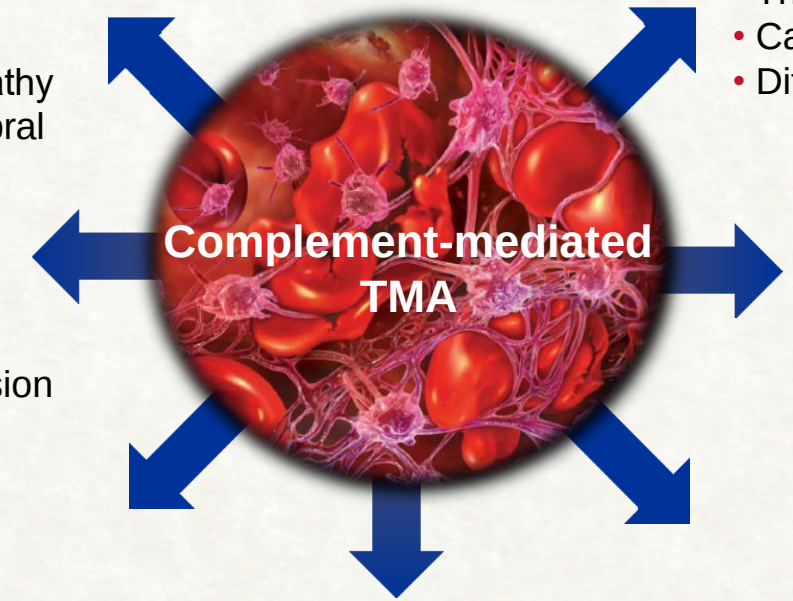
Clinical presentation alone does not fully differentiate CM-HUS from TTP

CM-HUS	TTP
Well-recognised CM-HUS signs: • Decreased platelet count • Microangiopathic haemolysis • Renal insufficiency	**Well-recognised TTP signs:** • Decreased platelet count • Microangiopathic haemolysis • Neurological dysfunction
Under-recognised CM-HUS signs: • Neurological dysfunction (up to 48%) • Cardiac symptoms (up to 43%)	**Under-recognised TTP signs:** • Renal pathology (96%) • Renal insufficiency (47%)

CM-HUS is a multisystem disorder

CNS
- Confusion
- Seizures
- Stroke
- Encephalopathy
- Diffuse cerebral dysfunction

Cardiovascular
- Myocardial infarction
- Thromboembolism
- Cardiomyopathy
- Diffuse vasculopathy



Renal
- Elevated creatinine
- Oedema
- Malignant hypertension
- Renal failure
- Dialysis
- Transplant

Gastrointestinal
- Liver necrosis
- Pancreatitis
- Diabetes mellitus
- Colitis
- Diarrhoea
- Nausea and vomiting
- Abdominal pain

Pulmonary
- Dyspnoea
- Pulmonary haemorrhage
- Pulmonary oedema

Blood[1,]
- Haemolysis
- Decreased platelets
- Fatigue
- Transfusions

Impaired quality of life
- Fatigue
- Pain and anxiety
- Reduced mobility

Complement analysis does not support diagnosis of CM-HUS

- Levels of complement proteins and inhibitors are sometimes measured to look for evidence of complement activation or dysfunction

eg low C3 indicates C3 consumption by activation

eg low FH could indicate a FH mutation

In CM-HUS these tests do not reliably support the diagnosis

- Most CM-HUS patients (including patients with identifiable mutations) have normal C3 and C4 levels
- Factor H levels – normal in up to 87% of CM-HUS patients with identified CFH mutation

Diagnosis of CM-HUS does not require identification of a genetic mutation

- Genetic mutation cannot be identified in 30–50% of patients with CM-HUS
- Absence of identifiable genetic mutations does not exclude CM-HUS
- Genetic analysis generally takes weeks to months
- Prognosis comparable (patients with identifiable mutations vs no identifiable mutation)

Identification of genetic mutation is not required for initial CM-HUS management decisions

CM-HUS treatment

Plasma exchange/infusion forms mainstay of initial treatment:

- Removes factor H autoantibodies and hyper functional complement components
- Replaces non-functioning complement regulators

CM-HUS treatment

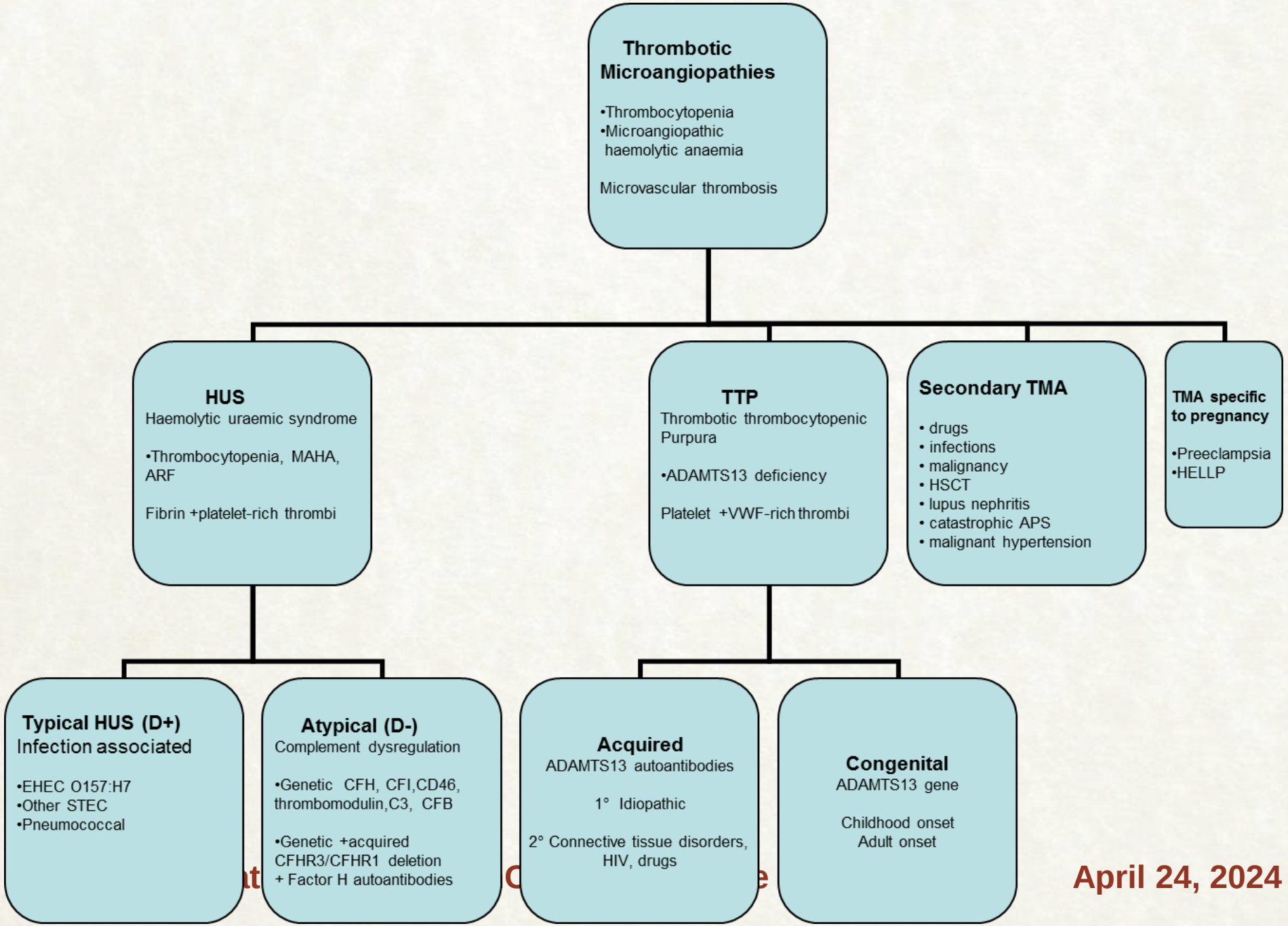
Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

Legendre et al, NEJM 2012

Vaccinate against meningococcus
Prophylactic antibiotics

Secondary TMAs


Thrombotic Microangiopathies
•Thrombocytopenia
•Microangiopathic haemolytic anaemia
Microvascular thrombosis
HUS
Haemolytic uraemic syndrome
•Thrombocytopenia, MAHA, ARF
Fibrin +platelet-rich thrombi
TTP
Thrombotic thrombocytopenic Purpura
•ADAMTS13 deficiency
Platelet +VWF-rich thrombi
Secondary TMA
• drugs
• infections
• malignancy
• HSCT
• lupus nephritis
• catastrophic APS
• malignant hypertension
TMA specific to pregnancy
•Preeclampsia
•HELLP
Typical HUS (D+)
Infection associated
•EHEC O157:H7
•Other STEC
•Pneumococcal
Atypical (D-)
Complement dysregulation
•Genetic CFH, CFI,CD46, thrombomodulin,C3, CFB
•Genetic +acquired CFHR3/CFHR1 deletion + Factor H autoantibodies
Acquired
ADAMTS13 autoantibodies
1° Idiopathic
2° Connective tissue disorders, HIV, drugs
Congenital
ADAMTS13 gene
Childhood onset
Adult onset

Transplant-associated TMA

- MAHAT, renal dysfunction, ↑BP, neurological features eg seizures
- High mortality, no definitive diagnostic criteria

No beneficial role for PEX
- ↓immunosuppression
- Treat coexisting infections
- Meticulous BP control
- General supportive therapy
- ??use of eculizumab

Drug-Induced TMA

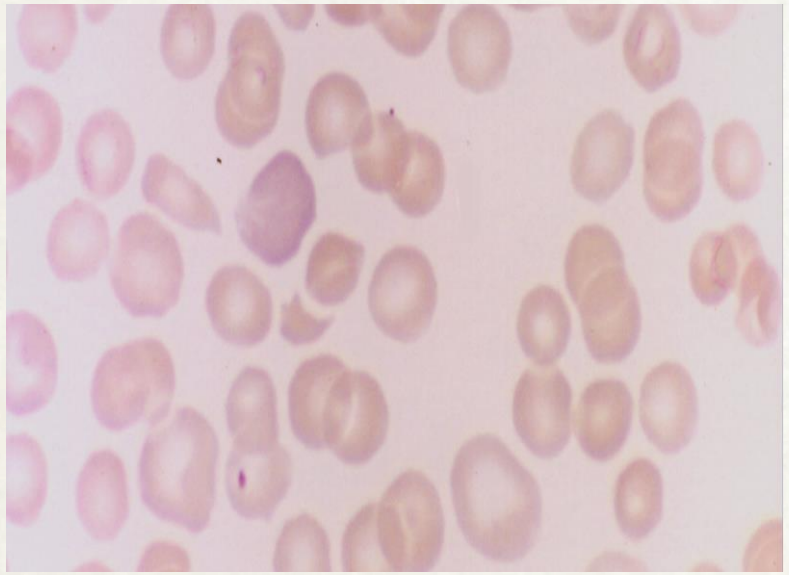
Primarily renal impairment + MAHAT

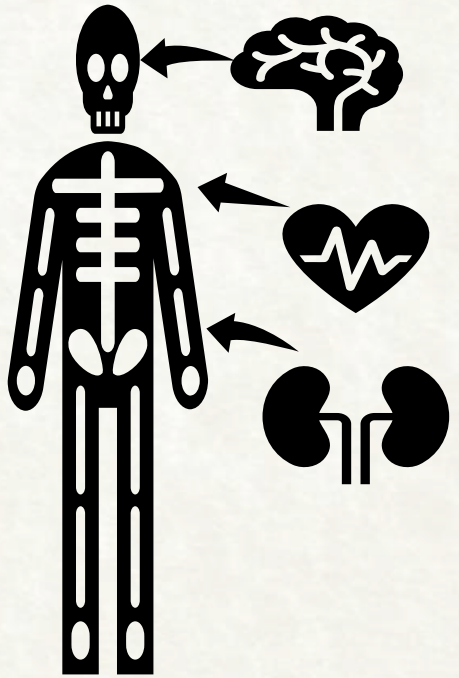
- Drug-dependent antibody - sudden onset of symptoms that recur with repeated administration of drug e.g oxaliplatin
- Dose-dependent toxicity - slowly progressive kidney injury with MAHAT e.g. gemcitabine, mitomycin C

Stop drug
Generally no role for PEX
?complement inhibition eg gemcitabine

Diagnosis of TMA in pregnancy

Platelet count <100 x10^9/L
Hb <100 g/L
LDH >1.5 ULN





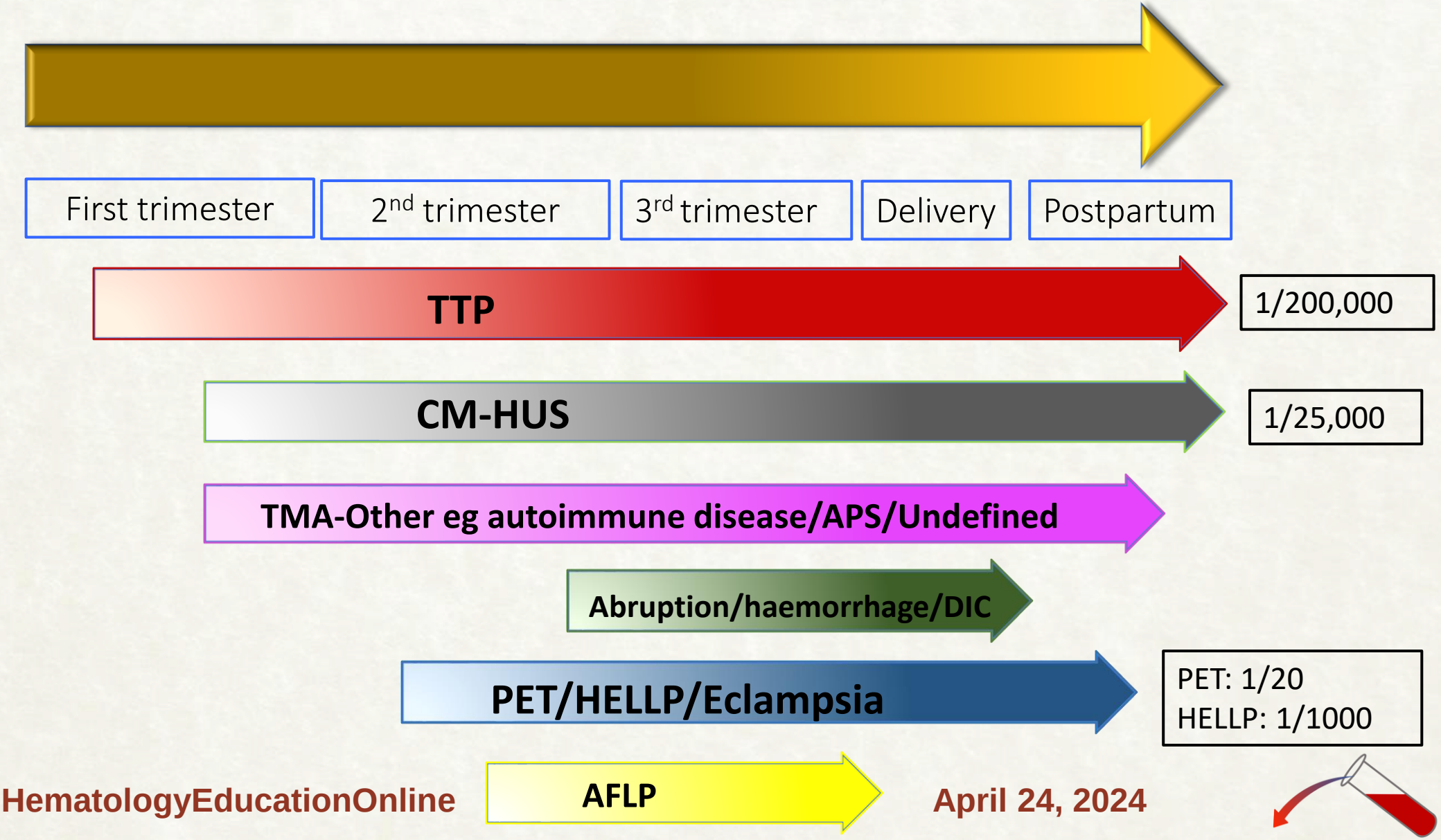
Fakhouri & IWG, Blood 2020

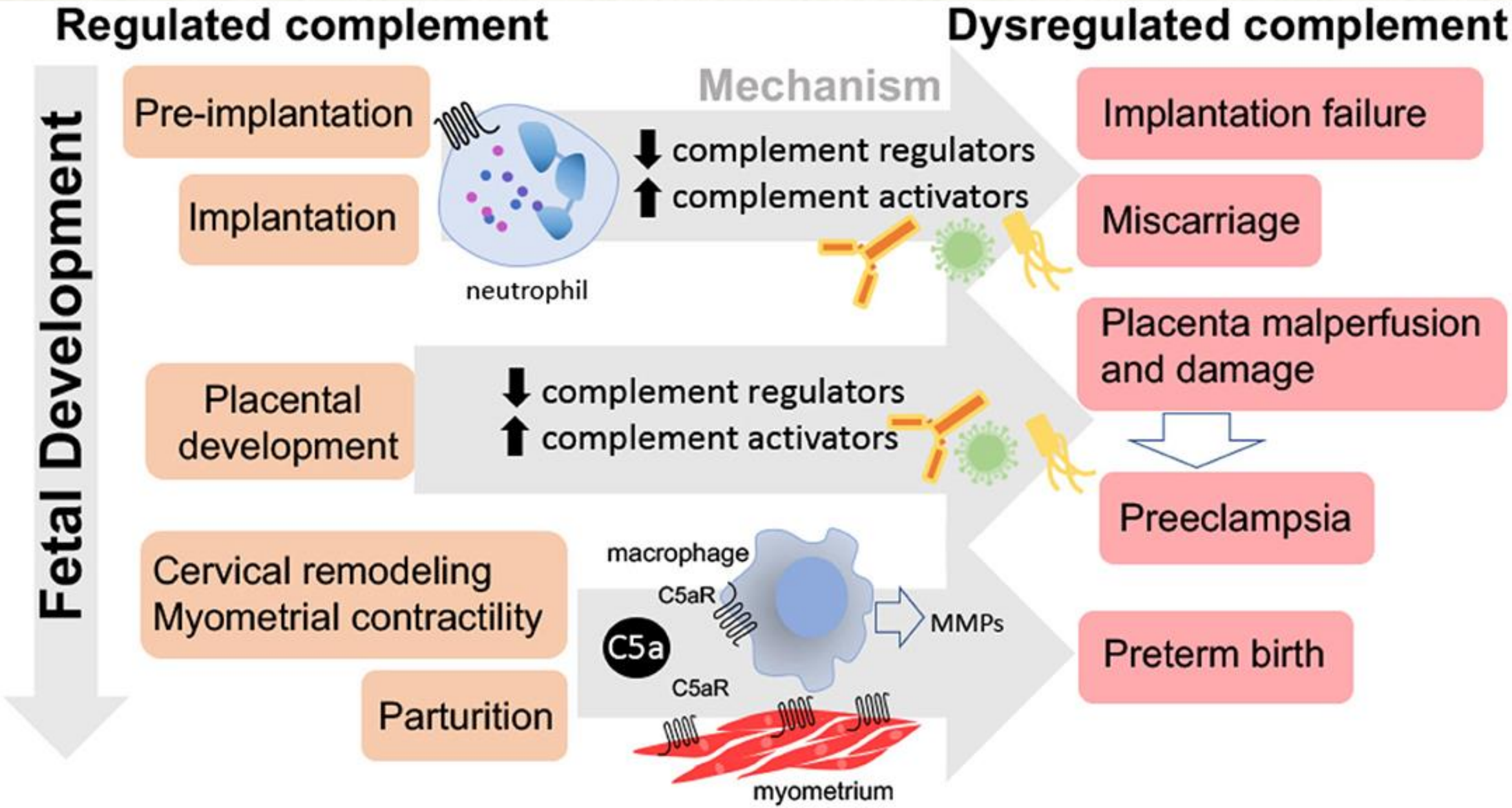
DDx pregnancy TMAs

	MAHA	Thrombocytopenia	Coagulopathy	HBP	Abdominal symptoms	Renal impairment	Neurological symptoms
PET	+	+	±	+++	±	±	++
HELLP	+	+	±	+	+++	+	±
TTP	++	+++	–	±	+	++	+++
HUS	+	++	±	++	+	+++	±
AFLP	±	+	++	+	++	+	±
SLE	+	+	±	+	±	++	+
APS	+	++	±	++	–	++	++

PET: pre-eclampsia, HELLP: hemolysis, elevated liver enzymes and low platelets, TTP: thrombotic thrombocytopenia HUS: hemolytic uraemic syndrome AFLP: acute fatty liver of pregnancy SLE: systemic lupus erythematosis APS:
±: possibly occurs.
+++: definitive feature. HBP: high blood pressure.

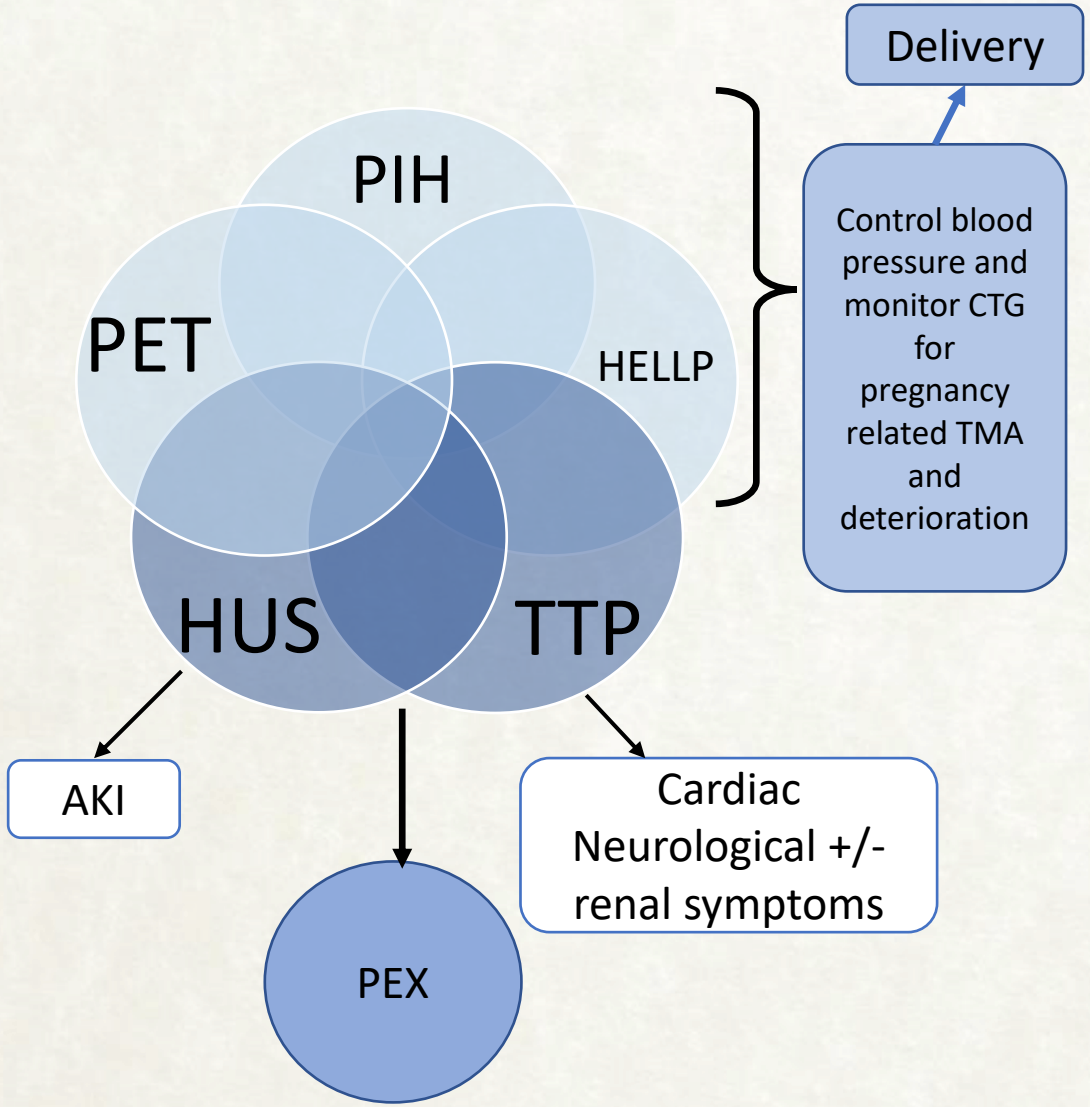
Pregnancy-associated TMAs





Girardi et al, Front Immunol 2020

Management of pregnancy-related and pregnancy-associated TMAs



TTP & HUS:

- May have features of PET/HELLP/PIH

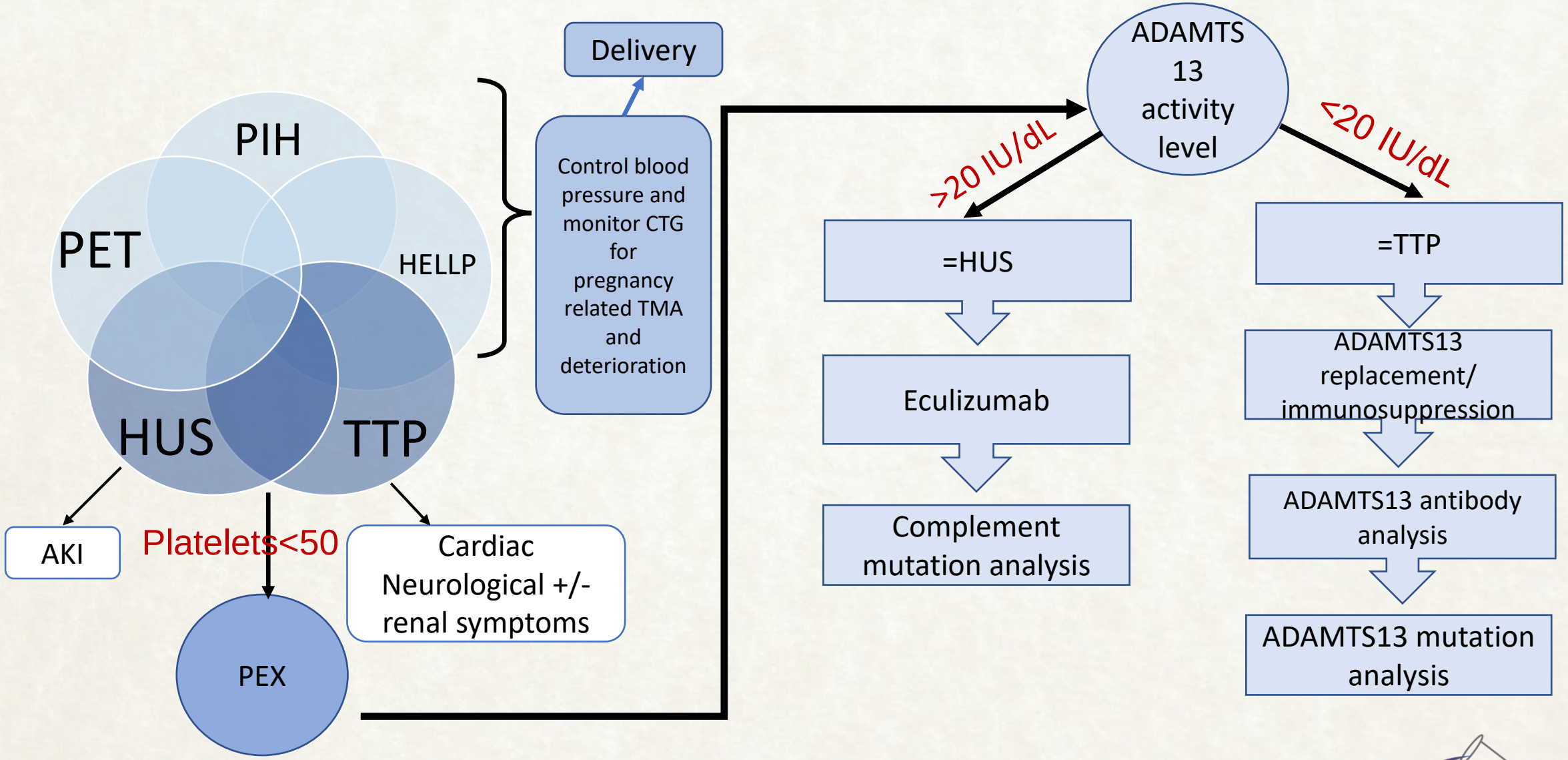
TTP & HUS:

- Medical emergencies
- Thrombocytopenia-may not be severe
- TMA remains active after delivery

PET/HELLP:

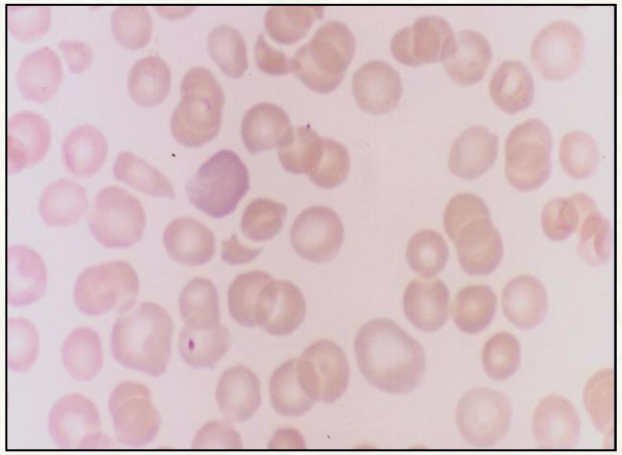
- Resolution with delivery
- BUT: Needs monitoring 48-72 hours post delivery

Management of pregnancy-related and pregnancy-associated TMAs



Differential diagnosis of TMAs: summary

- MAHA
- Thrombocytopenia
- Absence of underlying cause



Assume TTP
Commence PEX urgently

Haematological emergency

Differential diagnosis of TMAs: summary

Early differential diagnosis critical to improve patient outcomes

- ADAMTS13 <10% = TTP
- Clinical presentation alone does not fully differentiate CM-HUS from TTP or STEC-HUS
- CM-HUS ADAMTS13 activity >10%
  STEC test negative

TTP conclusion

TTP = acute life threatening illness with severe ADAMTS13 activity

Treatment:

- ADAMTS13 replacement
- Immunosuppression
- Caplacizumab

Chronic condition:

- Long term follow up to prevent relapse
- Longer term impact of acute disease/chronically reduced ADAMTS13 levels

- Prof Marie Scully
- Dr JP Westwood
- Dr Matt Stubbs
- Dr Nithya Prasannan
- TTP CNS Team
- Apheresis Team - UCLH
- TTP clinical trials team - UCLH
- Collaborators & Investigators of the UK TTP registry
- National and International Collaborators

The future?