Plasma Exchange in Thrombotic Microangiopathies

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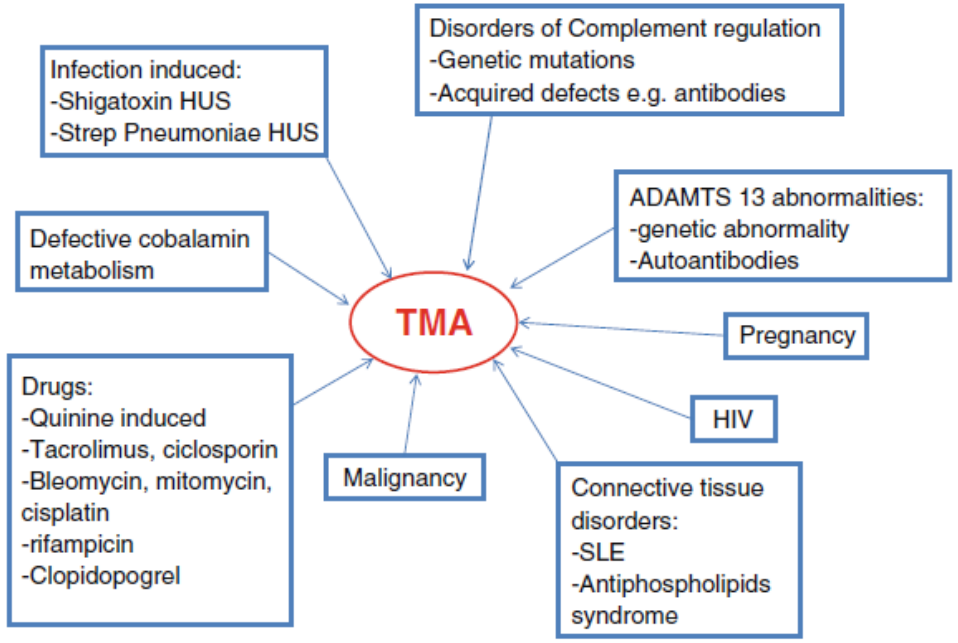
Objectives

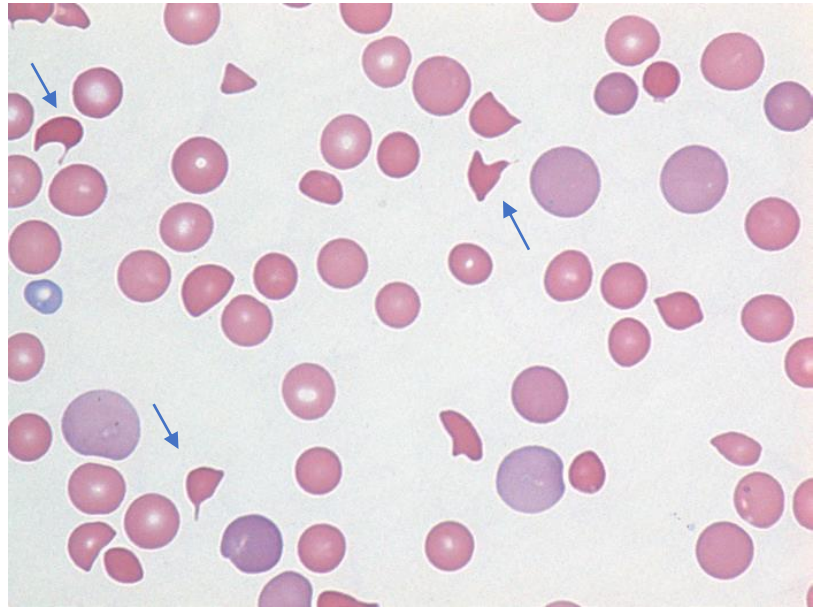
- Primary Thrombotic Microangiopathies (TMA): Definition/Classification
- Acquired Thrombotic Thrombocytopenic Purpura: Etiology/Diagnosis
- Plasma Exchange in Acquired TTP
- Acquired TTP: New Therapy
- Plasma Exchange and Other Therapy in Complement-Mediated TMA

Thrombotic Microangiopathies

- Microvascular (arterioles, capillaries) thrombosis

- Microangiopathic hemolytic anemia (MAHA) and thrombocytopenia





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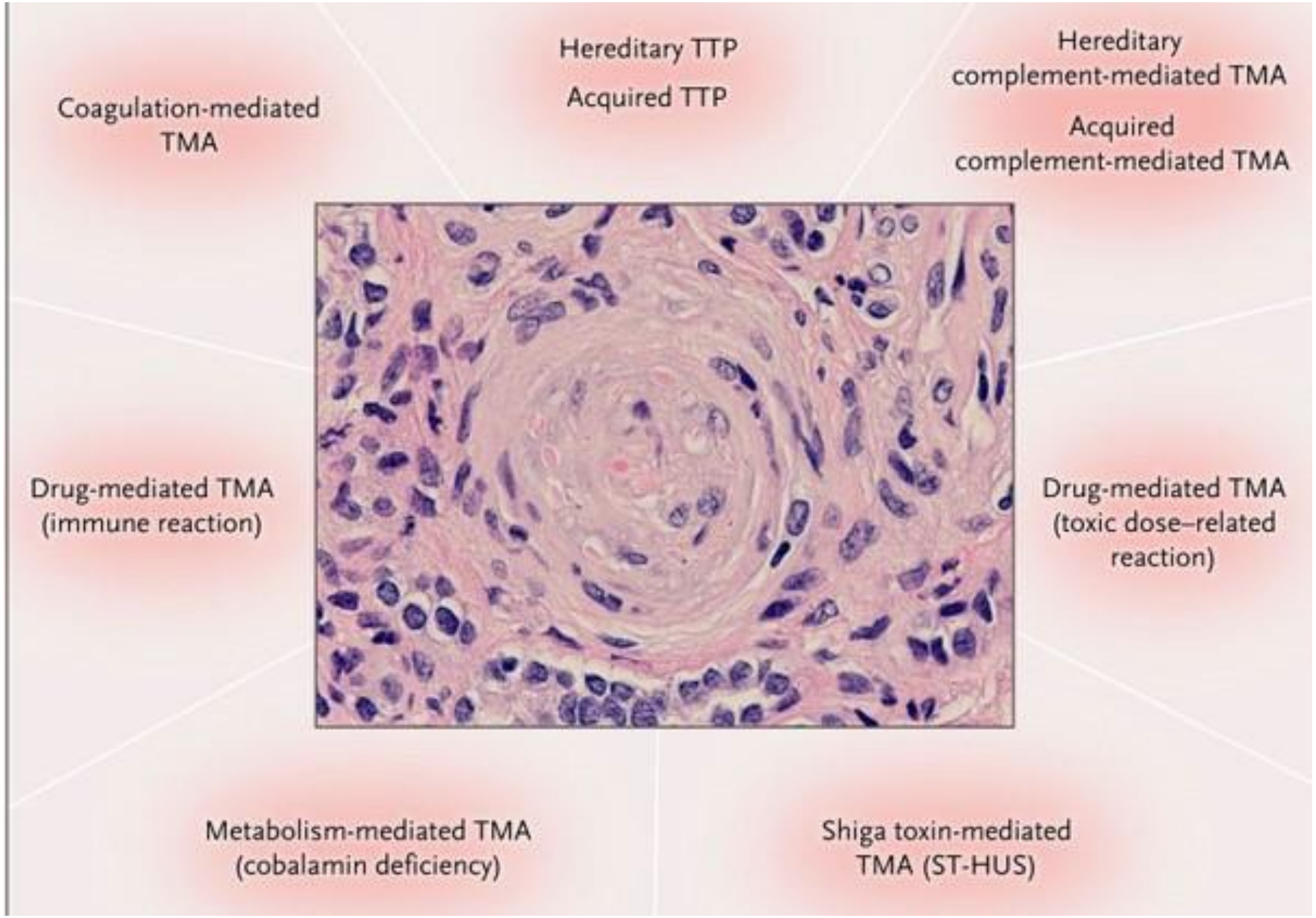
Primary Thrombotic Microangiopathy (TMA) Syndromes



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George JN, Nester CM. N Engl J Med 2014

Table 2. Common Disorders Associated with Microangiopathic Hemolytic Anemia and Thrombocytopenia.*

Systemic infection
Systemic cancer
Severe preeclampsia, eclampsia, HELLP syndrome
Severe hypertension
Autoimmune disorders (e.g., systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome)
Hematopoietic stem-cell or organ transplantation

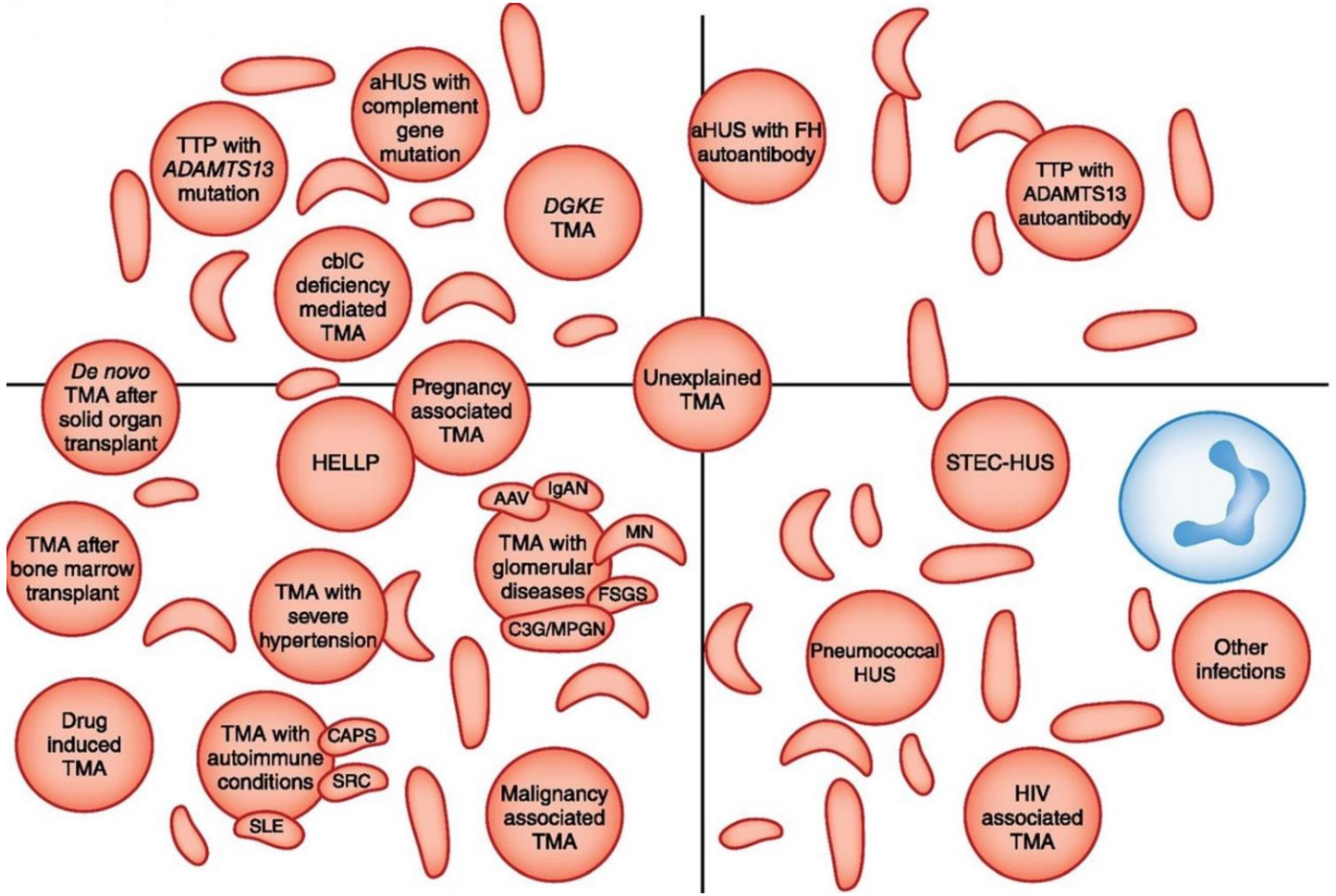
George JN, Nester CM. N Engl J Med 2014

More Renal involvement

More Neurologic involvement

Primary TMA: Hereditary

Primary TMA: Acquired



Secondary TMA/ Drugs

Infection associated TMA

More Renal involvement

More Renal involvement

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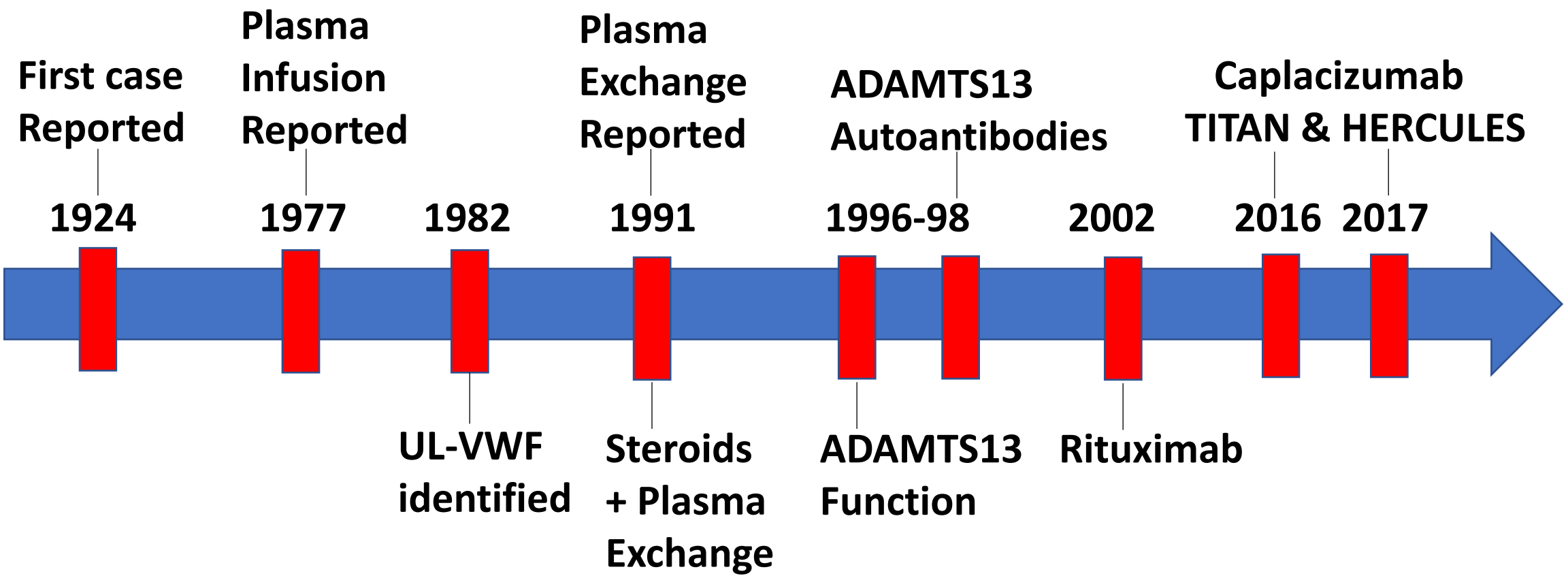
Modified from Brocklebank V: Clin J Am Soc Nephrol 2018

Acquired TTP: Important dates



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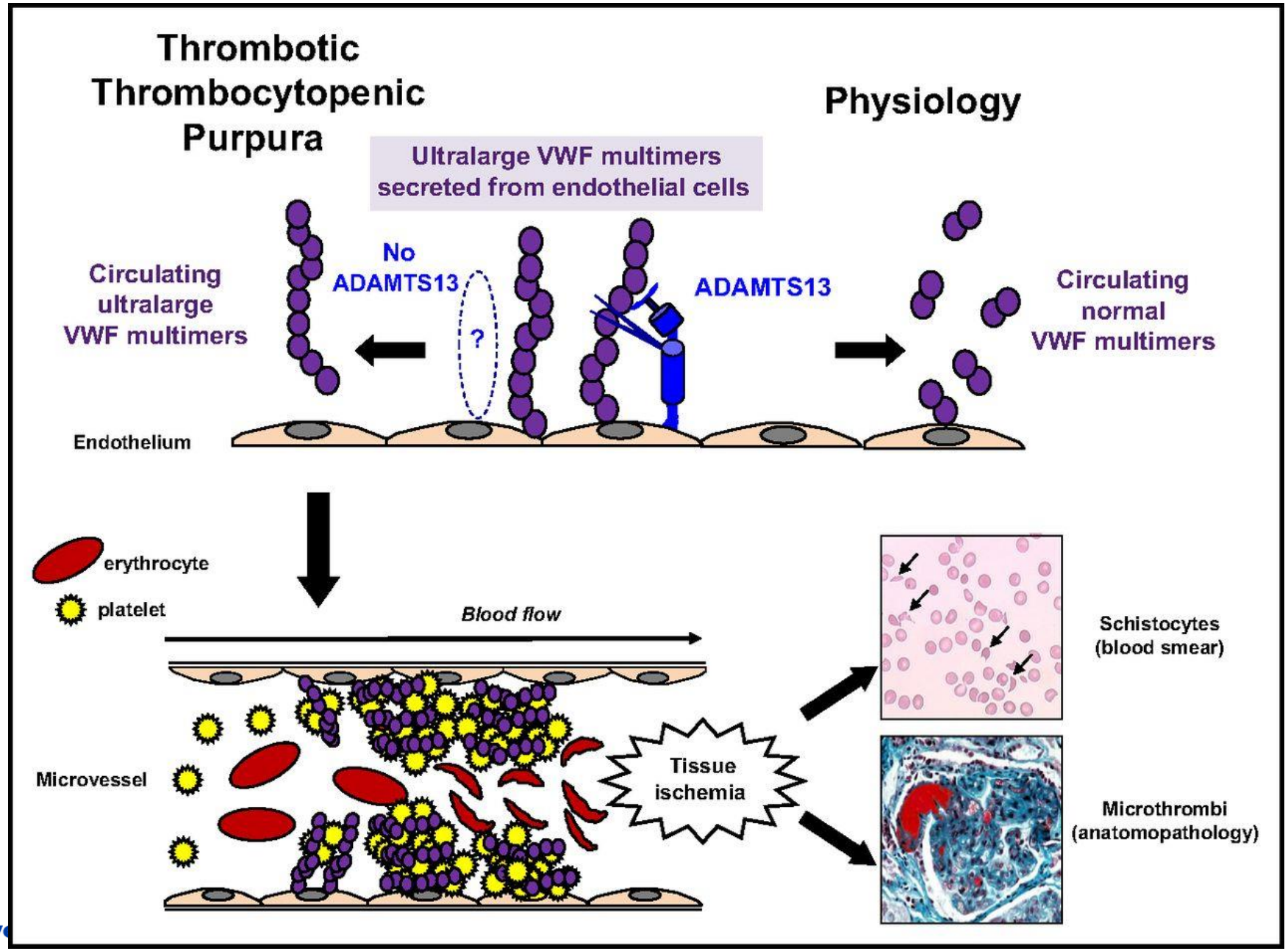
Dane K. Hematology Am Soc Hematol Educ Program, 2018



Bérangère S.
Blood, 2017

Acquired TTP

- Deficiency of ADAMTS 13 (A disintegrin and metalloprotease with thrombospondin type I motif member 13)
  - Cleaves large multimers of vWF
  - Autoantibody formation against ADAMTS13 (inhibitory vs non-inhibitory)
- Severe ADAMTS deficiency (<10% activity): majority of patients
    - Not 100% specific for TTP
    - TTP remains a clinical Diagnosis
- Low activity (10-60%) can be commonly seen in other conditions (e.g., complement mediated-thrombotic microangiopathy, malignancy, sepsis)
- Classic pentad not needed

Laboratory Findings Suggestive of Acquired TTP

Laboratory data	Results
Platelet Count x 103/uL	<30
Hemoglobin g/dL	<10
LDH	Elevated
Haptoglobin	Decreased
Reticulocyte count	Increased
Indirect bilirubin	Increased
Peripheral blood smear	Increased schistocytes, nucleated RBCs
Creatinine	Mildly elevated (<1.5 mg/dL)
Troponin T	May be increased
PT, INR, aPTT, fibrinogen	Normal
Direct antiglobulin test	Negative

PLASMIC Score for Estimating the Likelihood of Severe ADAMTS13 Deficiency in Adults with Suspected Acquired TTP

Variables	Points
Platelet Count <30,000/uL	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

PLASMIC score (points)	Risk of severe ADAMTS13 deficiency <10%
0-4	Low
5	Intermediate
6-7	High

INR: International normalized ratio. MCV: Mean corpuscular volume.

†Reticulocyte count >2.5%, or haptoglobin undetectable, or indirect bilirubin >2.0 mg/dL

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Modified from Bendapudi PK Lancet 2017

Diagnostic Accuracy of PLASMIC Score in Patients with Suspected TTP
A Systematic Review and Meta-analysis

Compared PLASMIC score vs reference ADAMTS13
13 Studies with 970 assessed patient's vs 330 true TTP

High Probability PLASMIC SCORE (≥ 6)
Sensitivity: 85% (67-94%)
Specificity 89% (81-94%)

↓

Author conclusion:
15% of patients with TTP have a score <6
Not acceptable for screening

High Probability PLASMIC SCORE (≥ 5)
Sensitivity: 99% (91-100%)
Specificity 57% (41-72%)

↓

Author conclusion:
1% of patients with TTP have a score <5
Acceptable for screening

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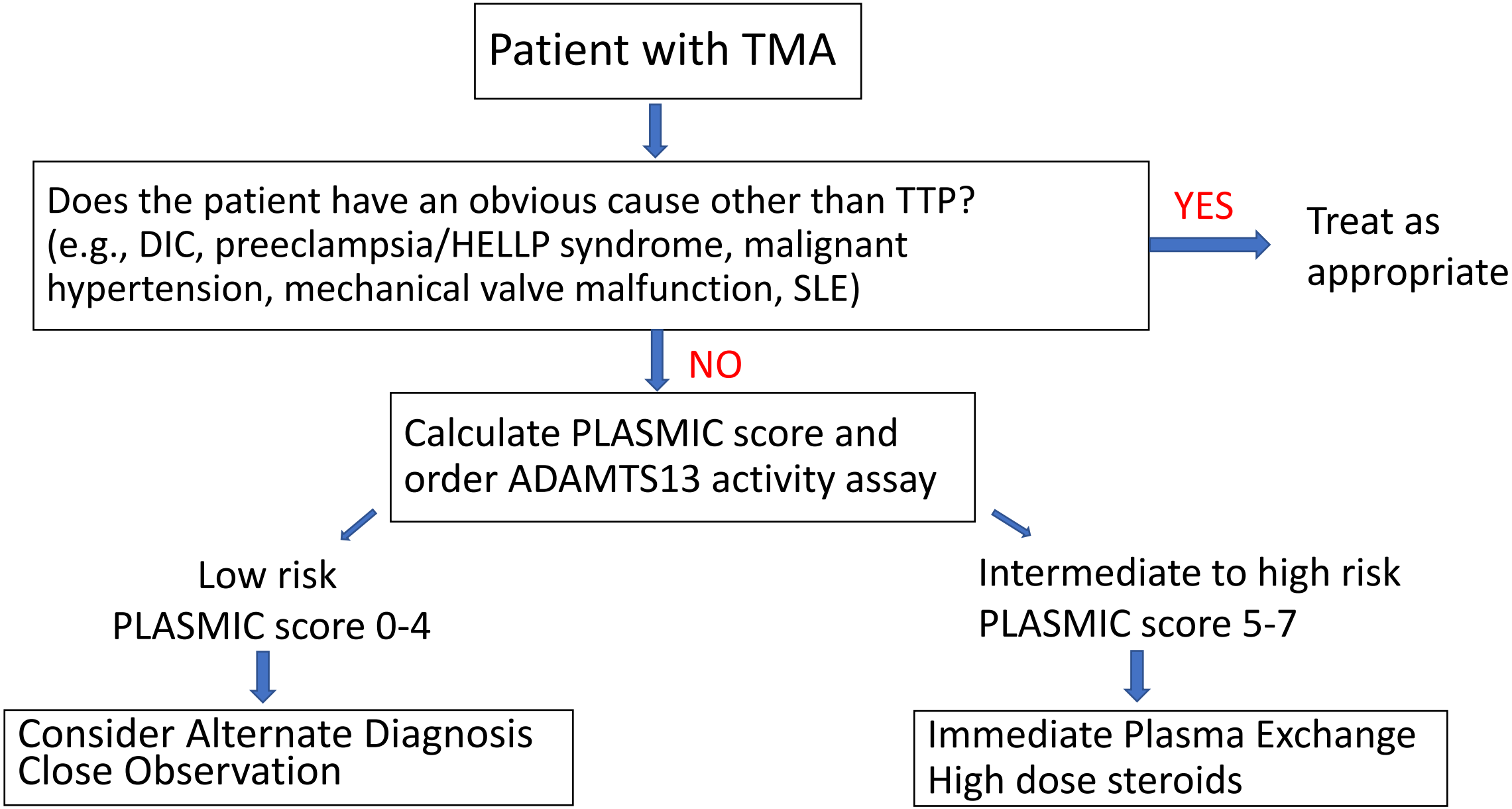
Paydary K. Transfusion, 2020



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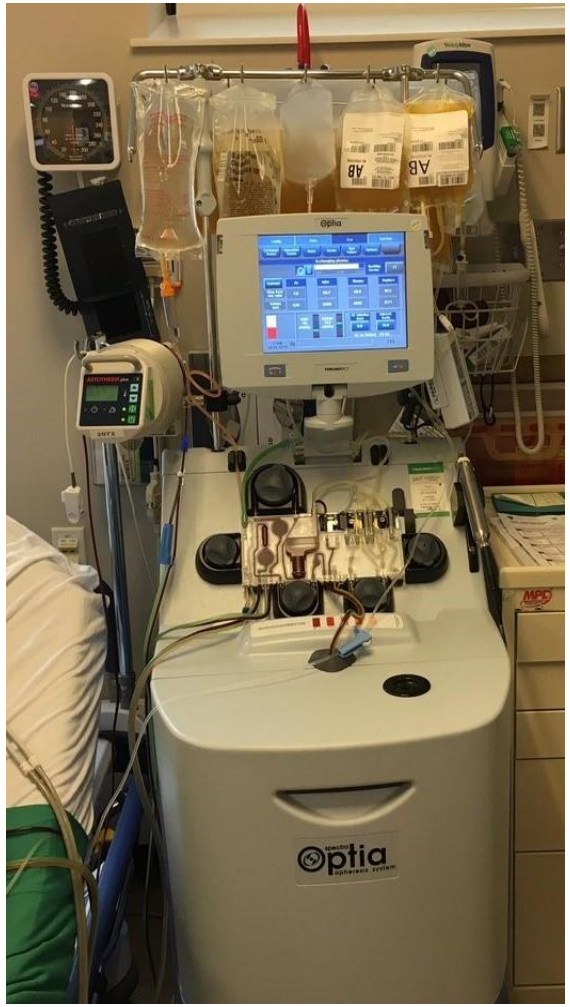
Chiasakul T. Am Soc Hematol Educ program 2018

Why Therapeutic Plasma Exchange Works in Acquired TTP

- Removes the ADAMTS13 inhibitor
- Removes ultra-large VWF multimers
- Replaces the ADAMTS13



American Society for Apheresis (ASFA) Categories

ASFA category	Definition
I	Primary treatment, either stand-alone or in conjunction with other therapies
II	Secondary treatment, either stand-alone or in conjunction with other therapies
III	Role of apheresis is uncertain, and decision-making should be individualized
IV	Evidence demonstrates apheresis to be ineffective or harmful

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Padmanabhan A. J Clin Apher, 2019

TABLE 3 Grading Recommendations, Strength and Quality of Evidence

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT = Randomized controlled trial

Adopted from Guyatt, 2006; 2008.

Plasma Exchange (PLEX) in Acquired TTP

- Proven first line therapy (ASFA category I, Grade 1A)
- Start as soon as possible following diagnosis
  - Needs excellent peripheral veins or a vascular catheter for access
- If delay in initiating PLEX (i.e., awaiting transfer to a PLEX Center), start plasma infusions at 25-30ml/kg per day as rescue treatment if patient can tolerate
- Draw sample for ADAMTS13 activity before plasma infusions/PLEX
  - Test still valuable if performed afterwards (Wu N, Transfusion 2015)

Plasma Exchange in Acquired TTP

Plasma Exchange, 1 to 1.5 plasma volume (40-60ml/kg)

- Replacement fluid:
  - Plasma (FFP, FP24)
  - Cryo-poor plasma – No definitive proof of improved outcomes
  - Solvent detergent treated plasma (e.g., Octaplas)
  - Plasma/5% albumin – less common

UP Front:

- **Corticosteroids**
  - Standard risk- Prednisone 1 mg/kg/day
  - High dose Methylprednisolone 1 g x 3 days (switch to prednisone once platelets rise).
- **Rituximab**
  - 375 mg/m2 intravenously once a week for 4 consecutive weeks
  - Give Post PLEX - Wait 18-24 hours to perform next PLEX

Plasma Exchange in Acquired TTP

- Daily procedure until:
  - Platelet count >150,000/uL for 2 consecutive days
  - LDH approaching normal
- Most patients respond within 7-10 days
  - 75% response rate after 7 exchanges (Rock et al 1996)
- Then withdraw PLEX and close monitoring
  - ? Value of tapering PLEX

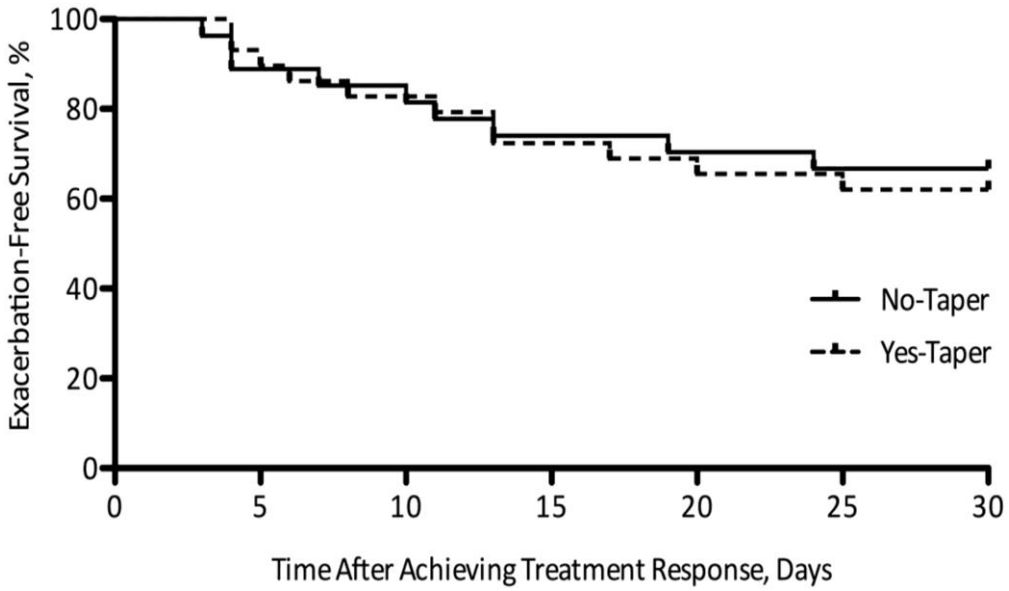
Therapeutic plasma exchange taper does not decrease exacerbations in immune thrombotic thrombocytopenic purpura patients

- Prospective observational study over 4 yrs.

- Yes-taper cohort: N:26 (29 consecutive episodes)
- No-taper cohort: N:24 (27 consecutive episodes)

- Daily PLEX, 1 PV (plasma replacement) Prednisone 1 mg/kg/d at PLEX initiation
- Rituximab 375mg/m2 IV weekly x 4 weeks-all patients in Yes-Cohort within 2 weeks of TTP diagnosis (only 25% of No-taper group received Rituximab)

- Exacerbation: 37.9% Yes-Taper vs 33.3% No-taper



Treatment related complications (blood components, or central venous catheters) significantly greater in the Yes-Taper group

Raval JS. Transfusion, 2020

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TABLE 2. Major complications of PEX treatment in patients with their initial episode of clinically diagnosed TTP, HUS, or TMA*

Complication	2011-2014 (n = 40)	1996-2014 (n = 342)
Catheter-related major complications		
Death	0	7
Pulmonary hemorrhage and pneumothorax	0	4
Systemic infection	0	3
Nonfatal complications	8	75
Systemic infection	3	37
Documented bacteremia	2	31
Suspected bacteremia†	1	4
Fungemia	0	2
Localized infection at catheter insertion site‡	1	3
Thrombosis	2	24
Catheter obstruction§	0	17
Venous thrombosis requiring systemic anticoagulation	2	7
Pulmonary hemorrhage	0	2
Retroperitoneal hemorrhage	0	1
Catheter insertion site hemorrhage‖	2	4
Pericardial tamponade	0	1
Pneumothorax¶	0	2
Insertion of incorrect catheter§	0	1

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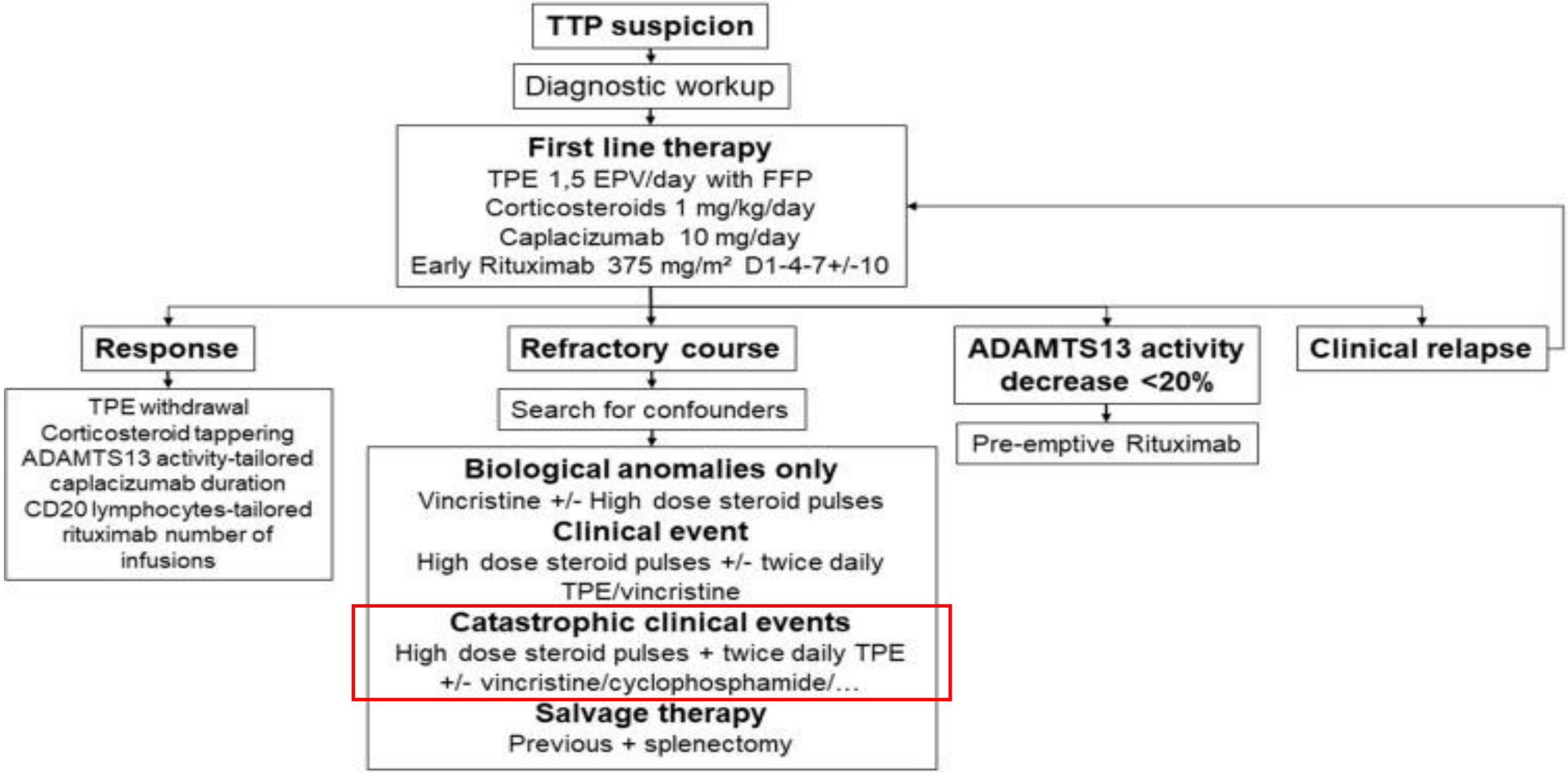
McClain RS. Transfusion 2014

TABLE 2. Major complications of PEX treatment in patients with their initial episode of clinically diagnosed TTP, HUS, or TMA*

Complication	2011-2014 (n = 40)	1996-2014 (n = 342)
Plasma-related complications (no deaths have occurred)		
Hypotension requiring treatment	2	9
With syncope**	1	1
Anaphylaxis with cardiac arrest	0	1
Serum sickness	0	2
Hypoxia**	1	9
With chest pain	1	1
Vomiting**	0	1
Fluid overload††	0	1
Hypocalcemia, arrhythmia**	1	1

* The definition of major complications and the classification of complications as central venous catheter related or plasma related have been previously described.[1]
† Negative blood cultures but treatment with parenteral antibiotics for presumed sepsis.
‡ Required hospitalization and systemic antibiotics.
§ Required removal of the catheter and placement of a new catheter.
‖ Required RBC transfusion.
¶ Required placement of a chest tube.
** Required stopping PEX.
†† Required stopping PEX, intubation, and ventilation therapy.



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Lemiale V. Therap Clin Risk Mgmt 2021

Benefits of Frontline Rituximab in Acquired TTP

Study Arm	Treatment	Median Response time	Median LOS	Exacerbation	Relapse (Months)
Rituximab 375mg/m2 weekly x4 (N:40)	PLEX + Steroid + Rituximab within 3 days of admission	12 days	16.5	0%	0% at 12 mo. 3% at 24 mo. 10% at 27 mo.
Historical Control N:40	PLEX + steroid	Not reported	20	Not reported	16% at 12 mo. 24% at 24 mo. 57% at 27 mo.

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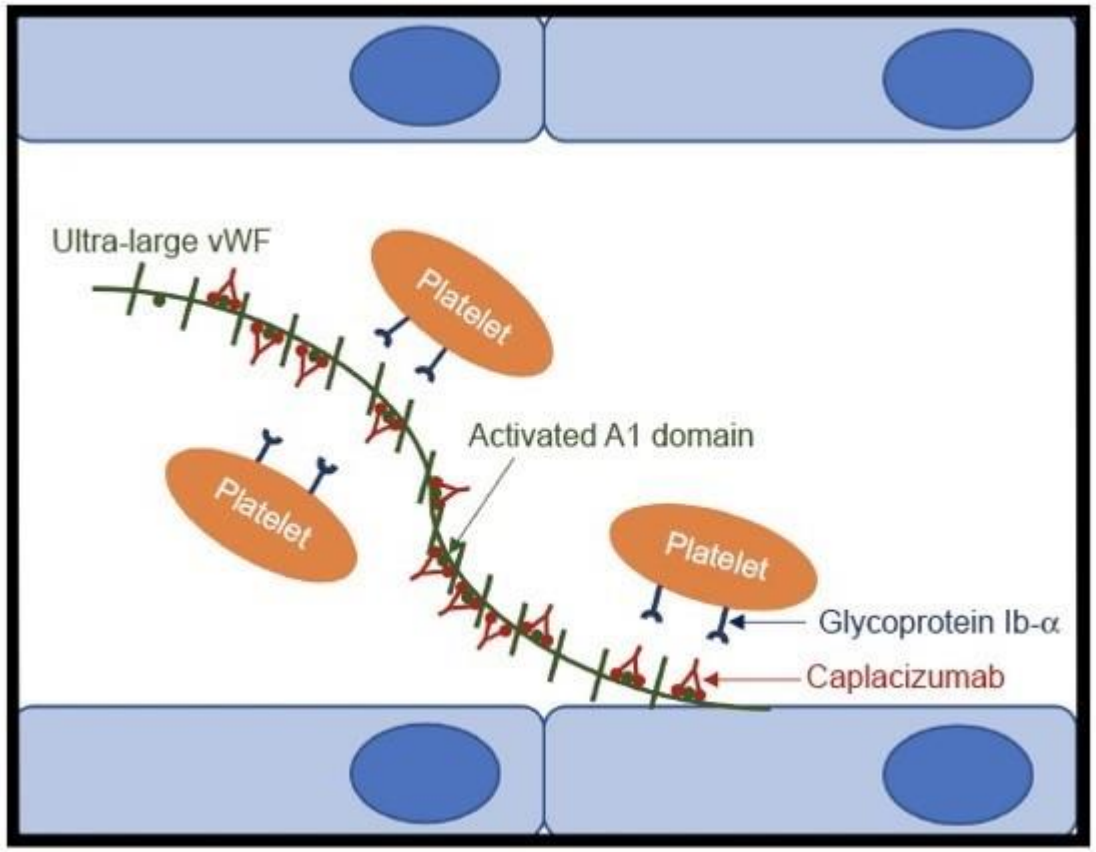
Scully M, Blood 2011

Caplacizumab

- A humanized immunoglobulin nanobody directed towards the A1 domain of vWF
- Specifically inhibits interaction of vWF with the platelet GPIb receptor complex
  - Phase II TITAN Trial- Peyvandi NEJM 2016
  - Phase III HERCULES Trial – Scully NEJM 2019
  - Approved by EMA in September 2018
  - Approved by US FDA in February 2019



$270.000 (30-day course)

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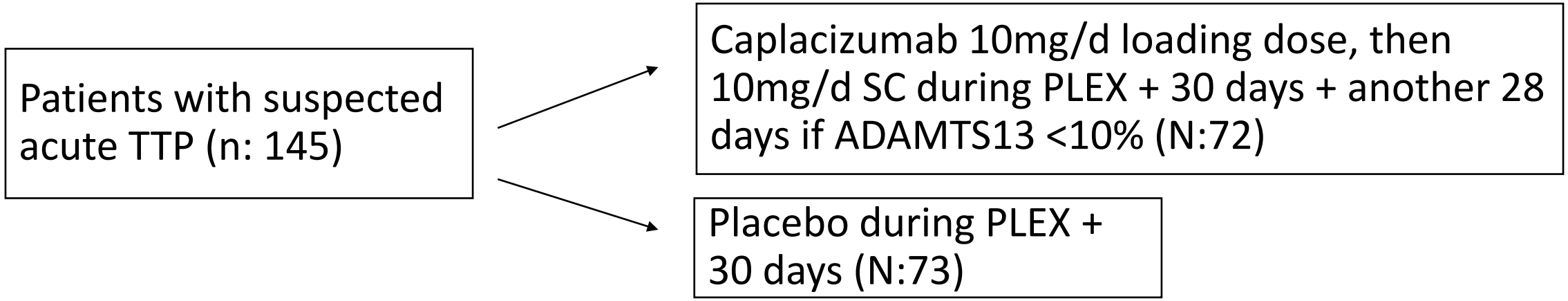
HERCULES Trial (Phase III RCT of Caplucizumab vs Placebo in TTP)



	Median days to Platelet Response	Exacerbation within 30 days of stopping PLEX	1-2 month relapse after 30 days of stopping PLEX	Mortality
Caplacizumab	2.7 days	9 (12%)	6 (8%)	1 (1%)
Placebo	2.9 days	28 (38%)	3 (0%)	3 (4%)

- Median PLEX 5 days in Caplacizumab group vs 7 days in Placebo
- All patients with relapse had persistent ADAMTS-13 deficiency <10% after drug Cessation

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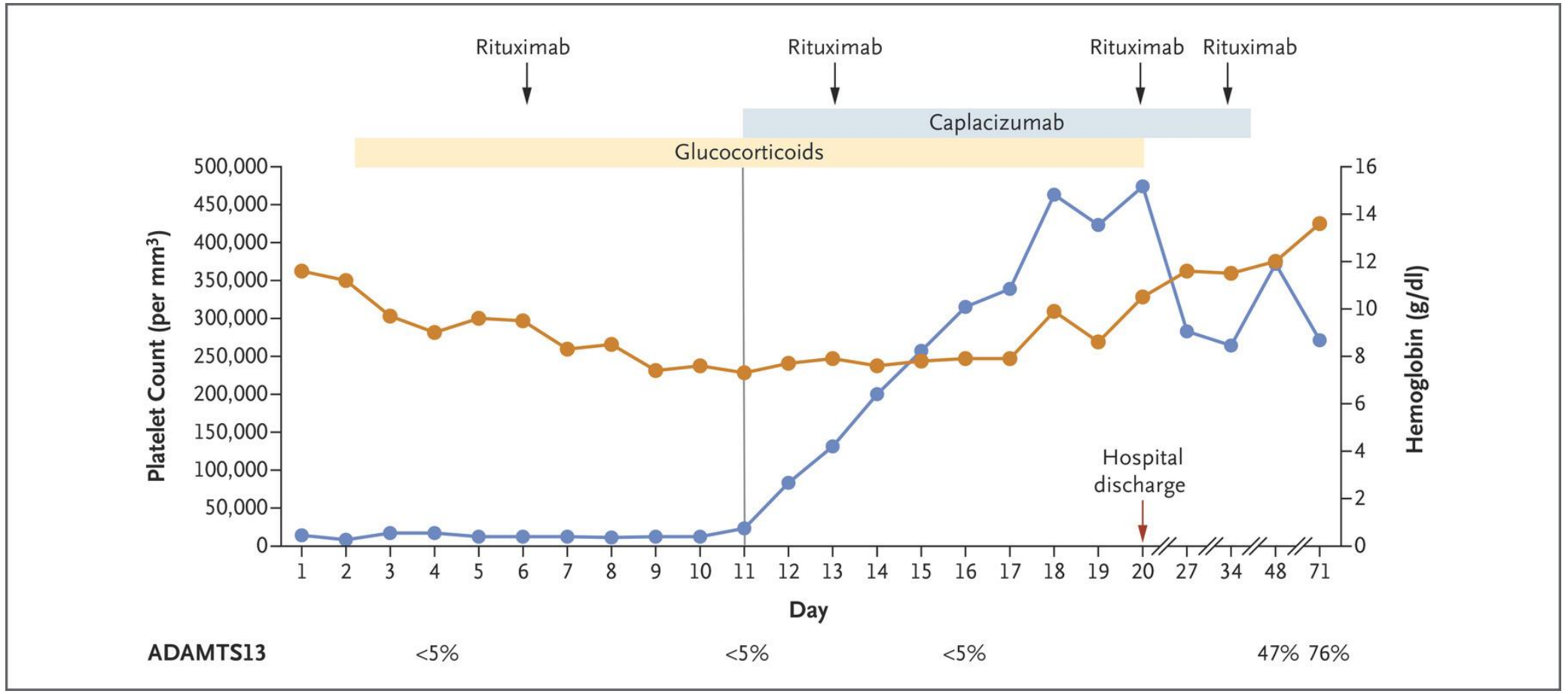
Scully M. N Engl J Med 2019

Phase III HERCULES trial- Other Secondary Outcomes

Outcome during treatment period	Caplacizumab (n:72)	Placebo (n:73)
Major thromboembolic events	6 (8%)	6 (8%)
Bleeding (mostly mucocutaneous)	46 (65%)	35 (48%)
Severe Bleeding	3 (4%)	1 (1%)
Serious Bleeding	8 (11%)	1 (1%)
Refractory disease	0	3 (4%)
Time to normalization of LDH, creatinine, troponin	2.9 (1.9-3.9) days	3.4 (1.9-7.7) days

Scully M. N Engl J Med 2019

Caplacizumab Therapy without Plasma Exchange for Acquired TTP



Chander DP. NEJM 2019

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Evolution of Acquired TTP Treatment

The past (1924-1975): No effective treatment (10% Survival)

The beginning (1976-1990): Effective treatment

- Whole blood exchange transfusion (1976)
- Plasma Infusion (1977)

The present (1991-2021): Increasingly effective treatment

- Plasma exchange (1991, 78% survival)
- Corticosteroids (1991)
- Plasma exchange, corticosteroids, rituximab (2002)
- Plasma exchange, corticosteroids, rituximab, caplacizumab (2020, 94*-99% survival)

The future: (2022-): Simpler, safer treatment

- Caplacizumab, rituximab

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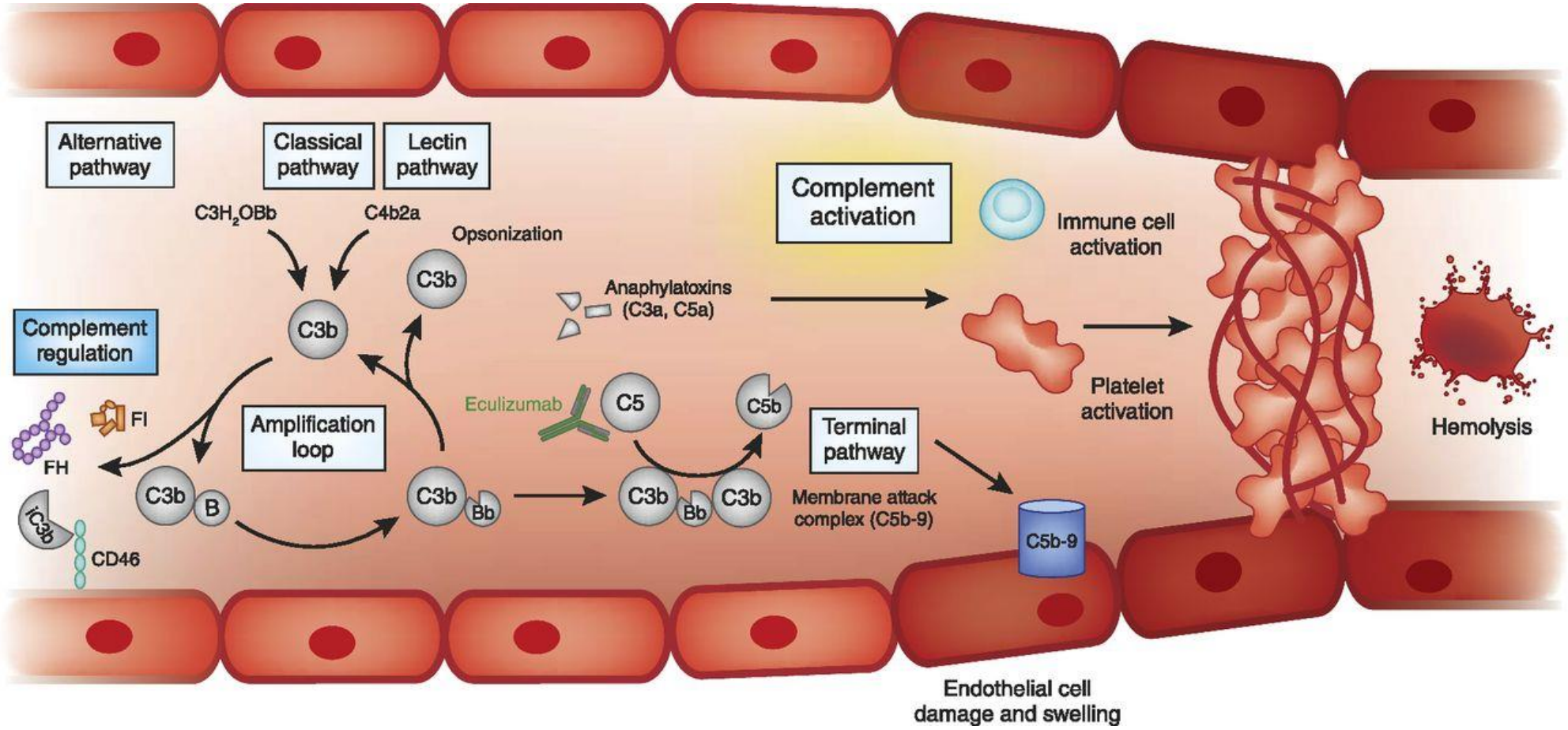
Modified from George JN. NEJM 2019
*Dutt T, Blood 2021

Complement-Mediated TMA

"Unfettered complement activation ultimately results in thrombus formation, platelet consumption, vascular occlusion and mechanical hemolysis"



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Brocklebank V: Clin J Am Soc Nephrol 2018

Complement-mediated TMA

- ESRD or death occurs in ~33 to 40% of patients during the first clinical manifestation of CM-TMA
- Severe AKI, less severe thrombocytopenia, ADAMTS13 >10%
- Complement studies, genetic studies, kidney biopsy

PLEX in Complement-mediated TMA

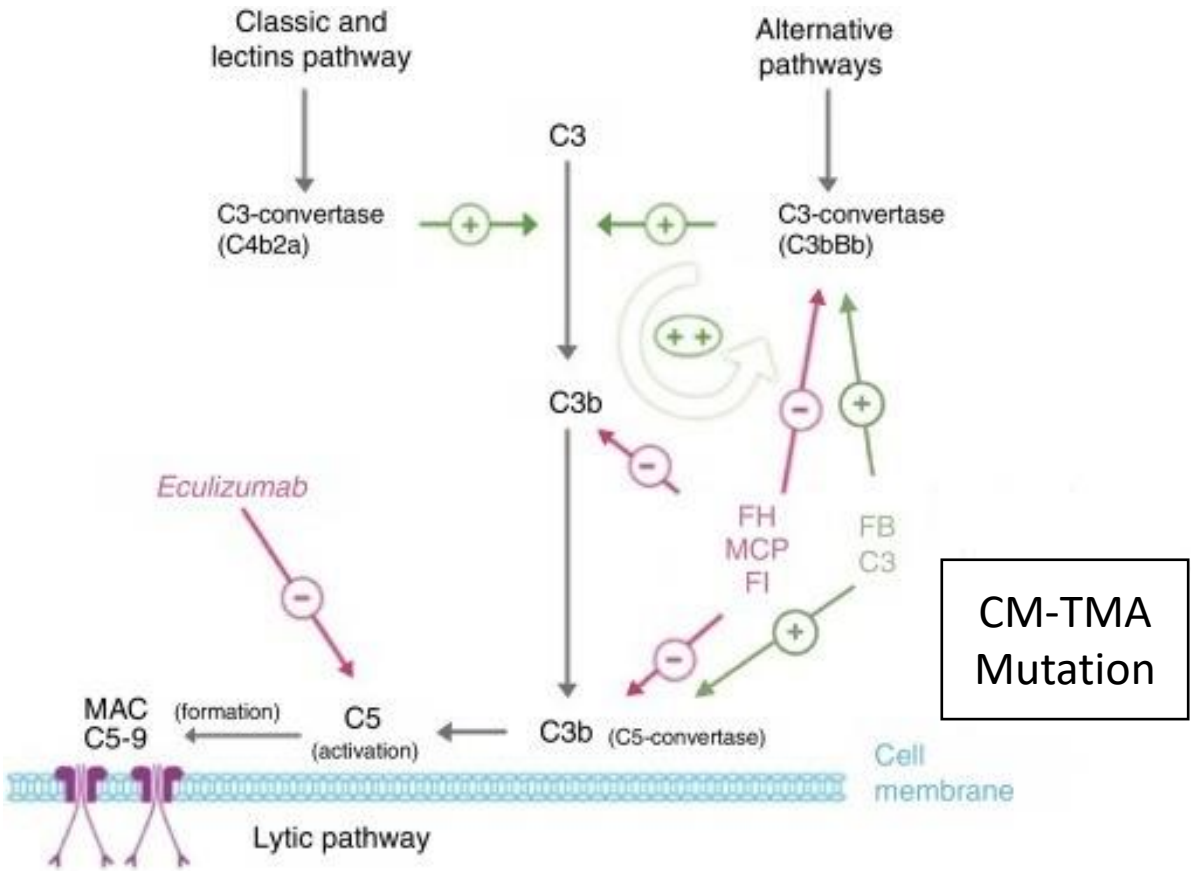
- Rationale: PLEX replaces nonfunctioning complement regulators, removes autoantibodies and hyper-functional complement proteins
- Evidence for efficacy is limited for complement factor gene mutations
  - + impact on hematologic recovery, not renal recovery
  - Within 1 year of diagnosis, up to 65% of patients treated with PLEX or plasma infusion sustain permanent renal damage, have progression to ESRD, or die
- ASFA recommendations:
  - Complement factor gene mutation (except MCP): Category III, Grade IIC
  - Factor H Antiantibodies: ASFA Category 1, Grade IIC

Eculizumab

- A recombinant humanized monoclonal antibody that binds C5 and blocks its subsequent cleavage into C5a and C5b

- Early initiation of Eculizumab has been shown to lead to better outcomes in CM-TMA (Improves TMA and renal function)

- Susceptibility to infection with encapsulated gram-negative organisms, particularly Neisseria infections, is the most serious side effect
  - Need for vaccination/antibiotic prophylaxis



CM-TMA Mutation

$500.000 per year

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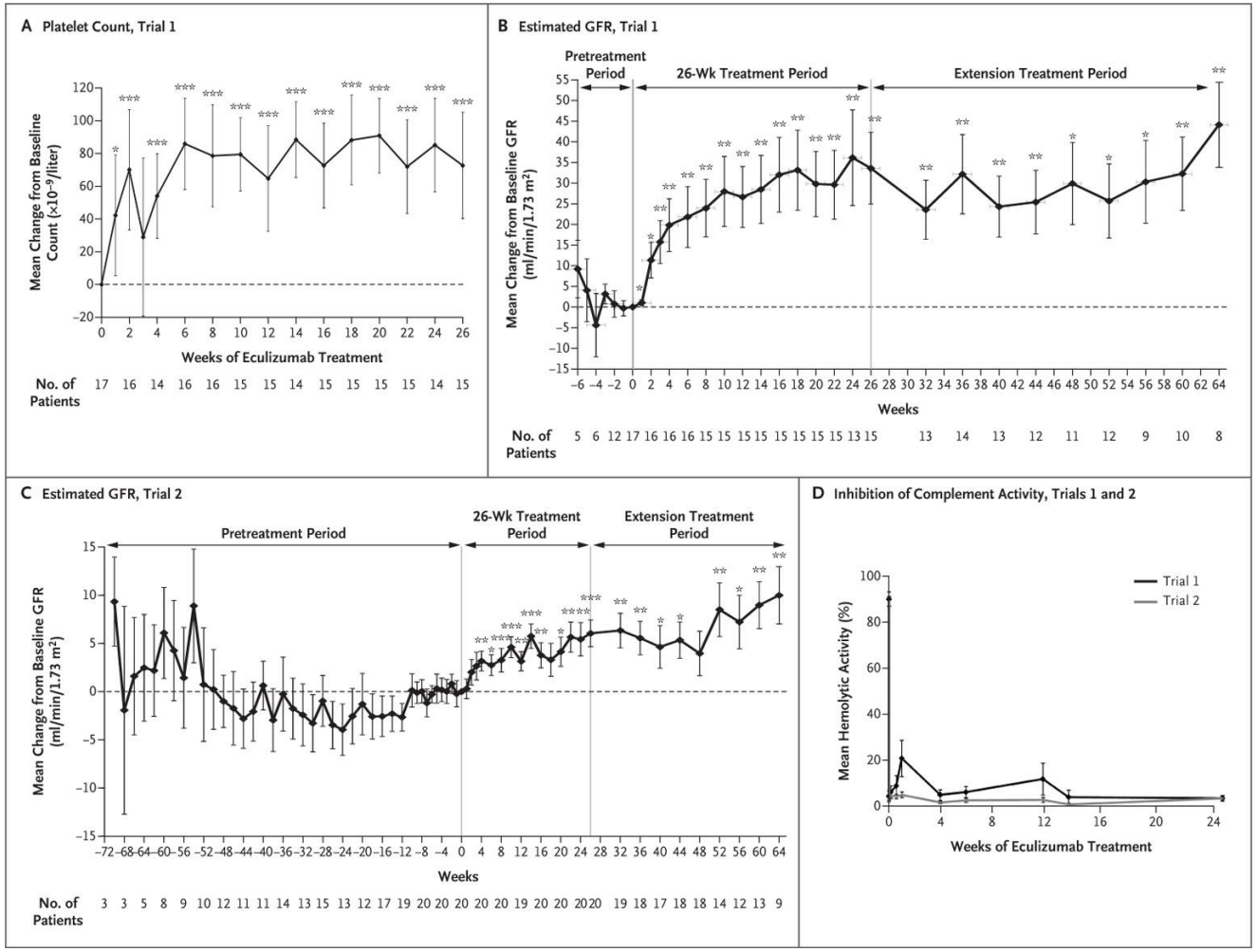
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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



- Two prospective phase 2 trials in aHUS; age >12
- Trial 1: Persistent low platelets and AKI while on PLEX treatment
- Trial 2: AKI, stable platelets on PLEX for at least 8 weeks
- Treated for 26 weeks with Eculizumab and during long term extension phase
- Significant improvement in hematologic recovery and renal function in both trials

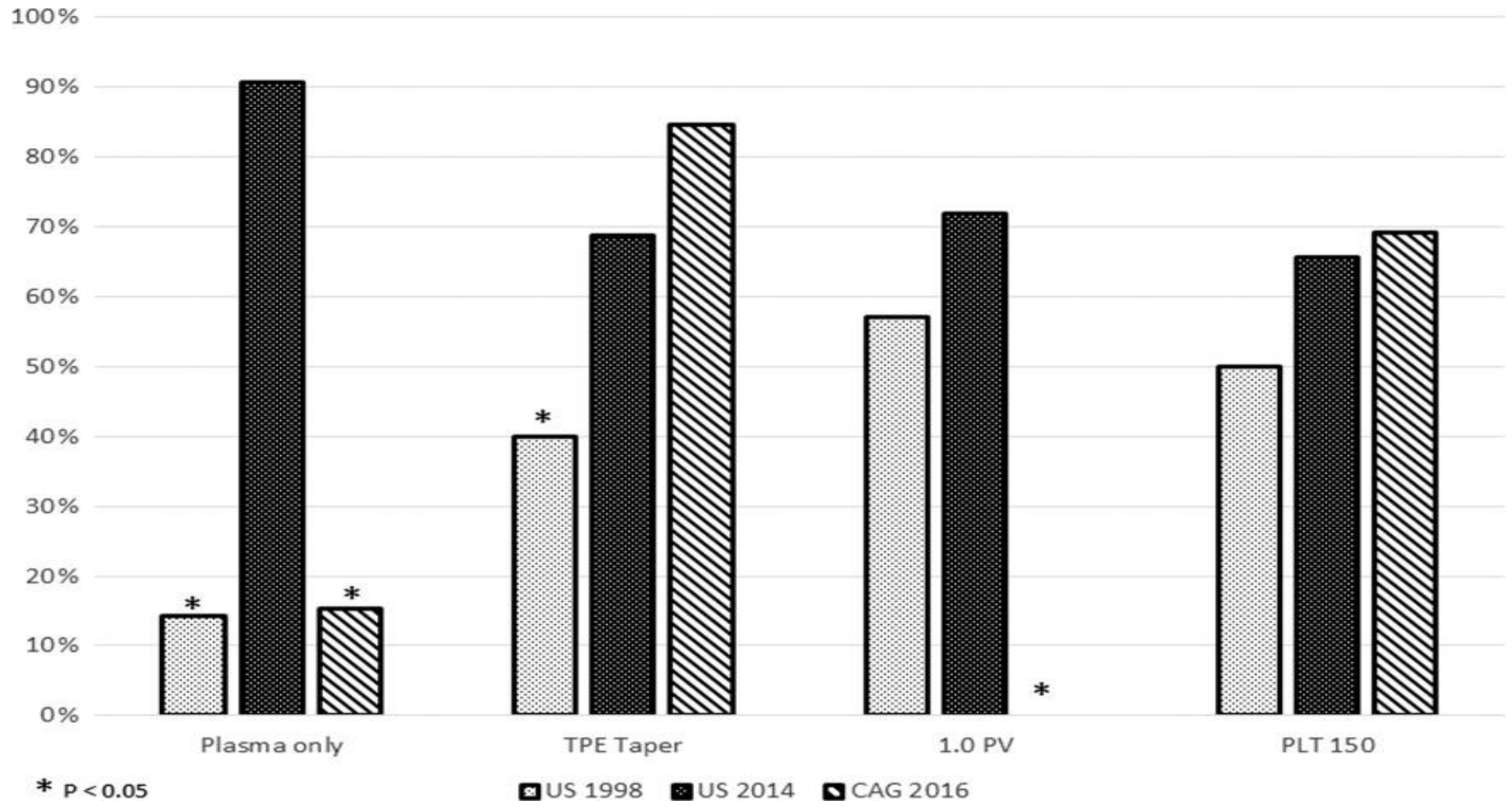
Legendre CM. NEJM 2013

Summary

- Primary TMA syndromes are a group of disorders with distinct pathologic mechanisms that help guide approach to their treatment
- Plasmic score, when applied correctly, is useful to triage plasma exchange decisions in suspected acquired TTP while awaiting ADAMTS13 levels
- Initial treatment of acquired TTP remains daily plasma exchange with corticosteroids. Addition of rituximab to frontline therapy may reduce inpatient hospital stay and reduces relapse in a time dependent manner
- Tapering of plasma exchange in acquired TTP does not reduce exacerbations and may increase treatment related complications
- Addition of caplacizumab to initial treatment reduces time to response, number of plasma exchanges, hospital length of stay, exacerbation and mortality after plasma exchange. It increases relapse long-term, bleeding and health care cost
- Efficacy of plasma exchange is uncertain in CM-TMA associated with mutations of complement regulatory genes. Eculizumab is the treatment of choice in this setting

- Thank You!

Treatment of acquired Thrombotic Thrombocytopenic Purpura in the U.S. remains heterogeneous: Current and future points of clinical equipoise



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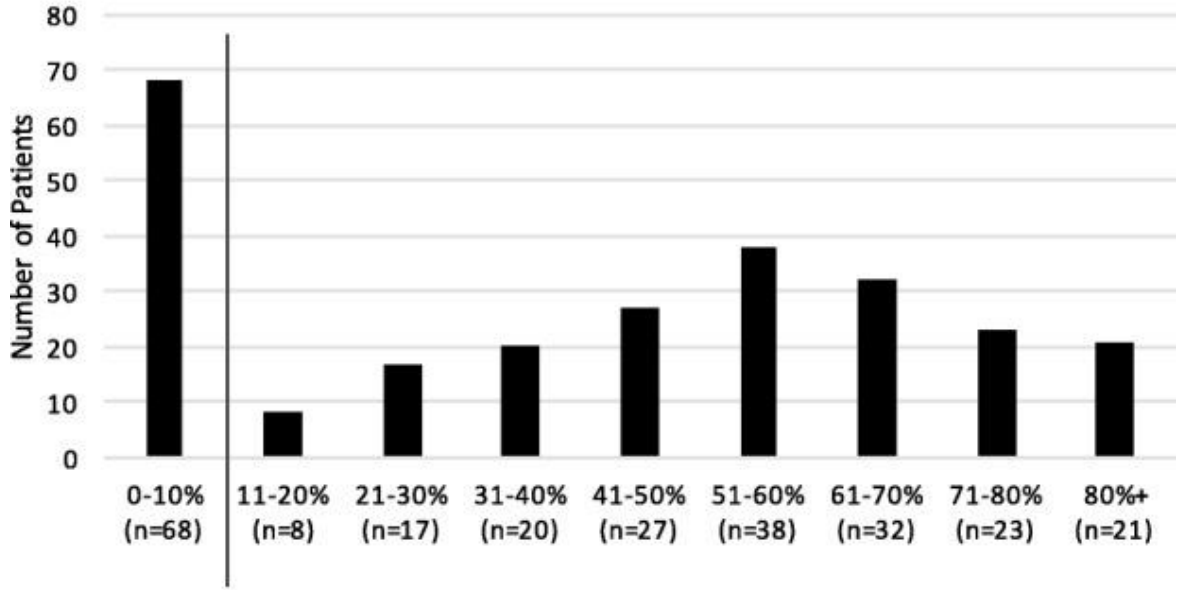
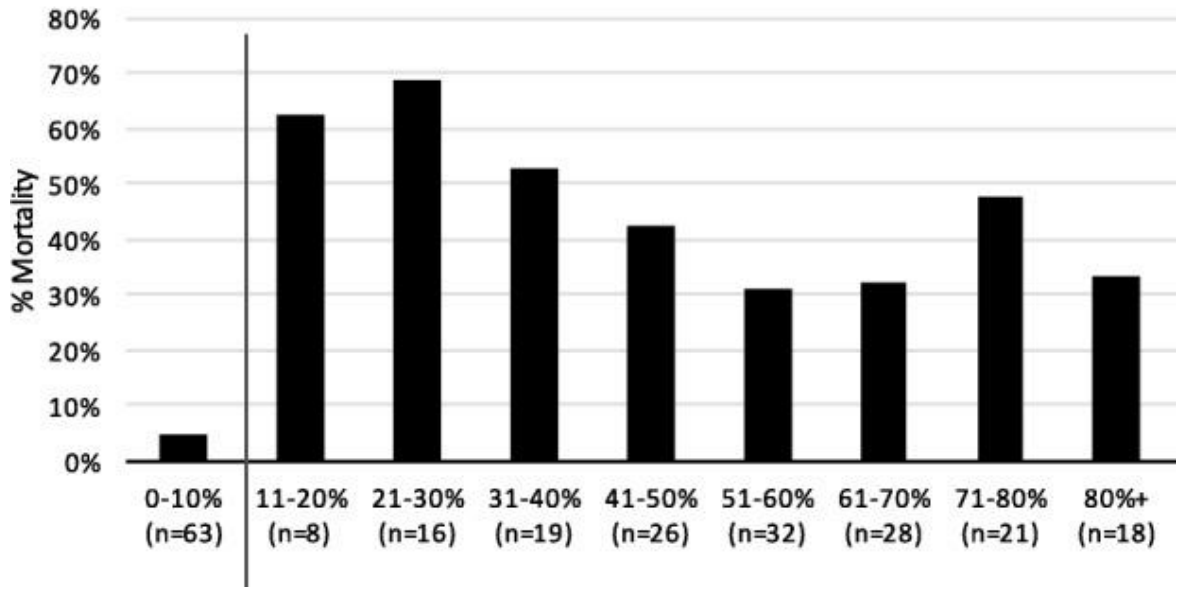
Mazepa. J Clin Apher. 2018

Distribution of TMA Patients by ADAMTS13 Activity



90 Day Mortality by ADAMTS13 Activity



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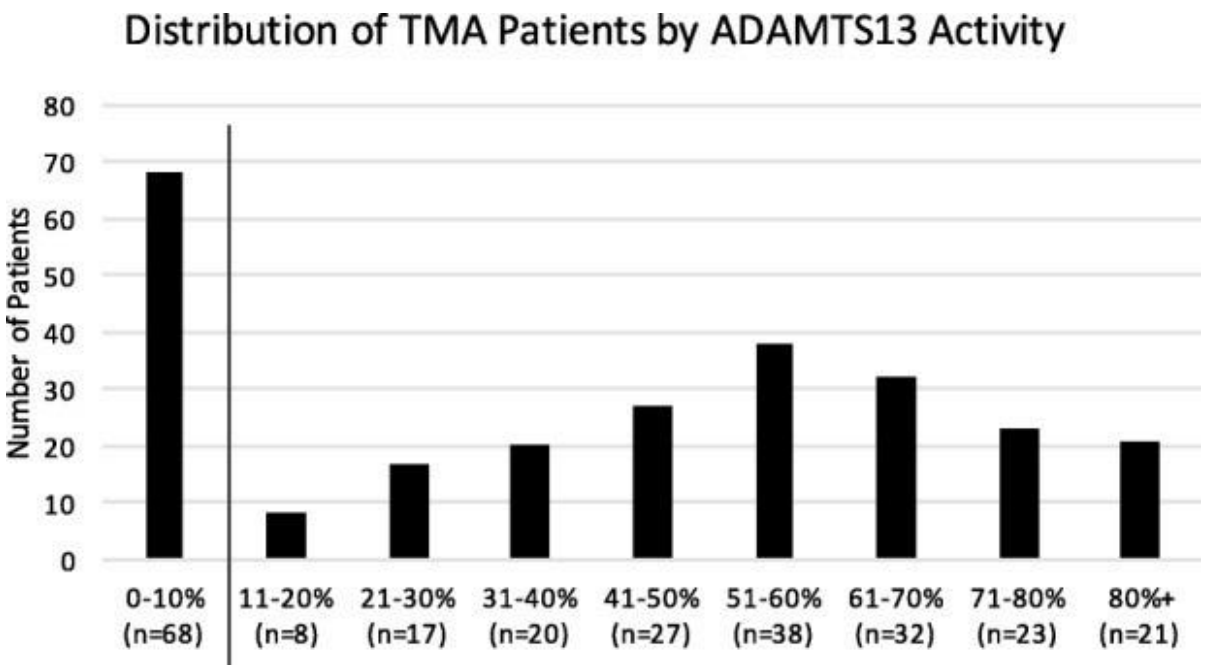

Variable %[a]	Moderate deficiency: 11-40%, N = 45	Mild deficiency: 41-70%, N = 97	No deficiency: ≥70%, N = 44	p value
DIC/sepsis/MOF	53	19	11	< 0.01[b]
Transplant associated	7	14	20	0.16
Disseminated cancer	11	18	7	0.22
Drug associated	7	7	11	0.68
Autoimmune	4	8	7	0.75
Malignant hypertension	0	7	7	0.18
HUS/aHUS	0	8	9	0.08
Idiopathic TTP	2	0	2	0.23
Multifactorial	9	5	11	0.38
Other TMA[c]	7	13	14	0.52

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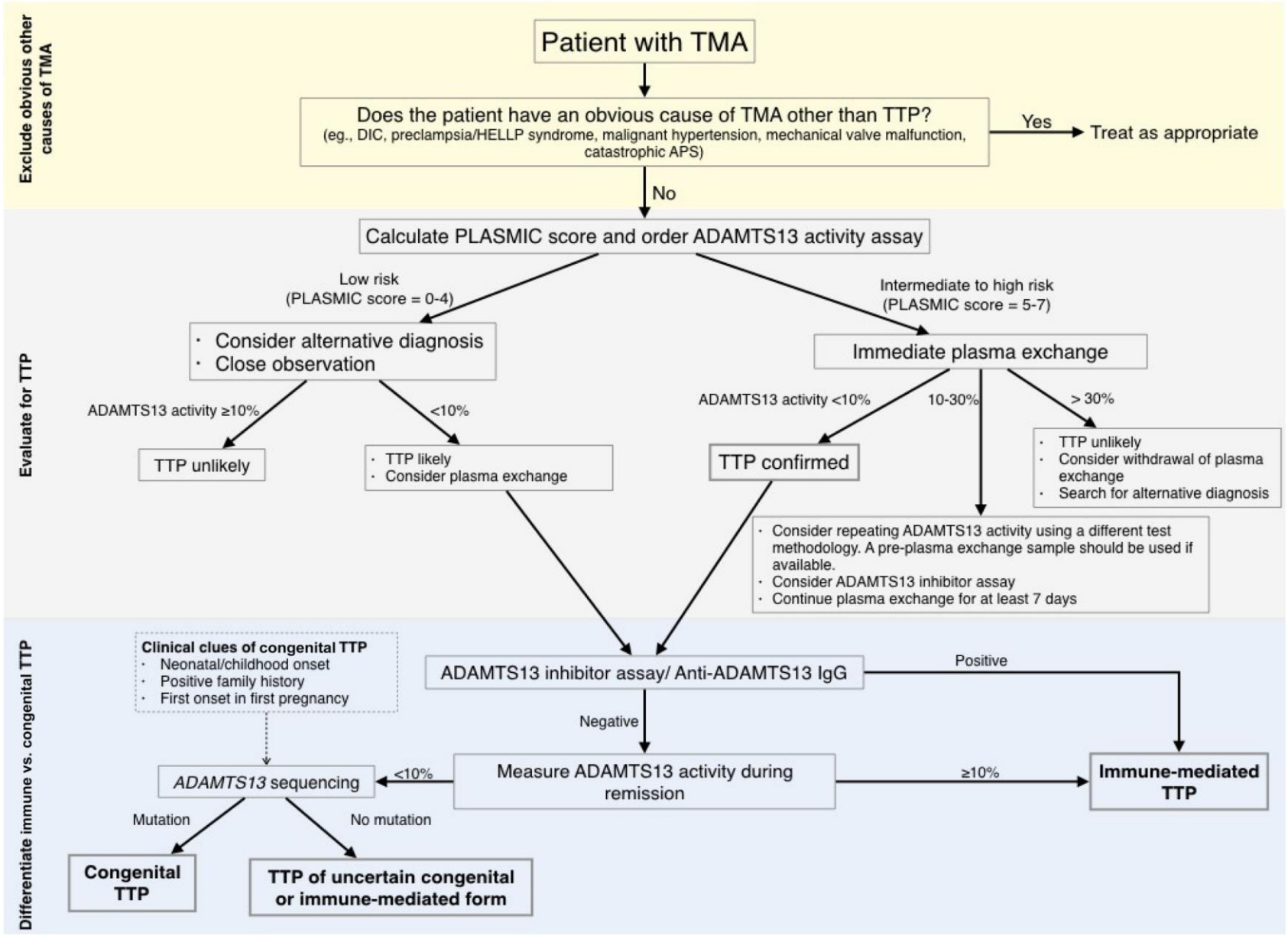

Chiasakul T, Hematology Am Soc hematol edu program 2018

TITAN Trial (Phase II RCT of Caplacizumab vs Placebo in acute TTP)

Patients (N:75) with suspected acute TTP (ADAMTS13 deficiency not an inclusion criteria

Caplacizumab
- IV flat dose before PLEX
- 10mg/d SC after each PLEX + 30d (N:36)

Placebo during PLEX + 30 d (N:39)

	Median time to platelet Response	Exacerbation within 30 days of stopping PLEX	12 month relapse after 30 days of stopping PLEX	Mortality
Caplacizumab	3.0 days	3 (8%)	11 (31%)	0/36
Placebo	4.9 days	11 (28%)	3 (8%)	2/39

Complete Remission Caplucizumab: 29/36 (81%), Placebo: 18/39 (46%)

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Peyvandi F. N Engl J Med 2016

Caplacizumab in a TTP

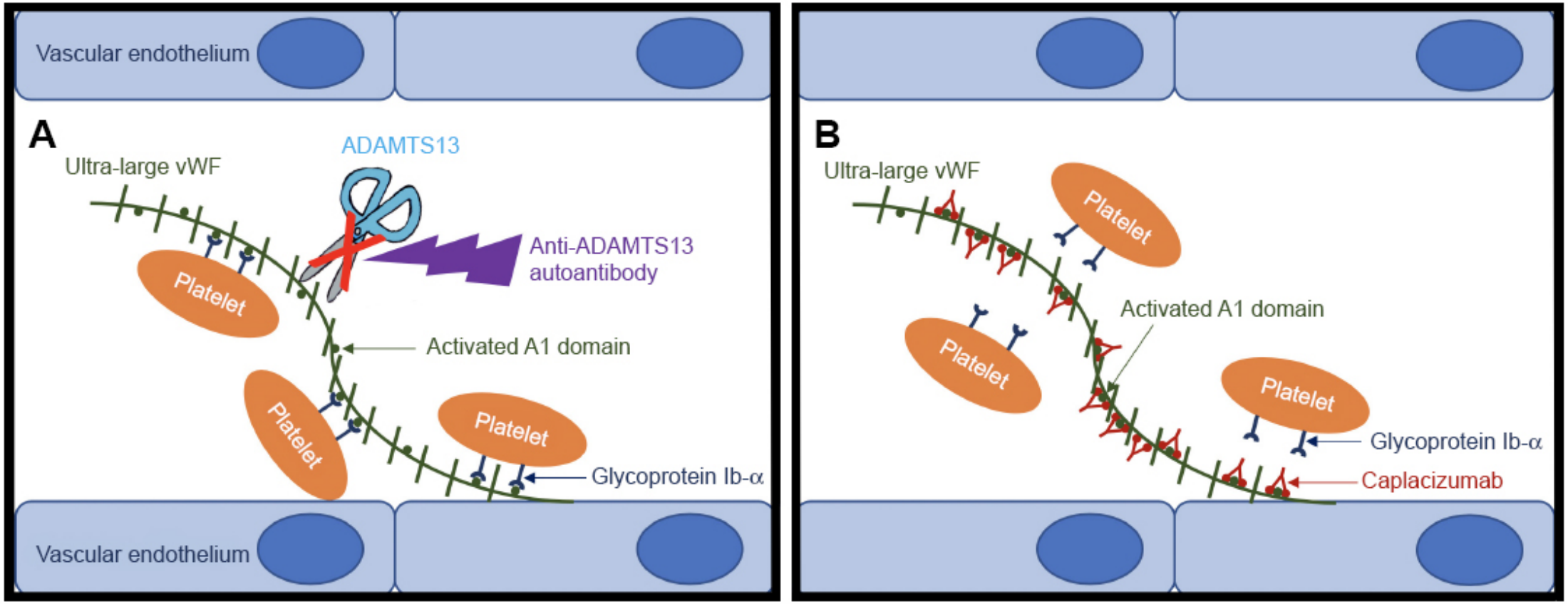

Figure 1 The mechanism of action of caplacizumab.
Notes: (**A**) The pathogenesis of aTTP; the presence of anti-ADAMTS13 autoantibodies inhibits the proteolytic cleavage of ultra-large vWF multimers by ADAMTS13, which results in the aggregation of platelets through GP1b-α receptors and the activated A1 domain of the vWF causing microvascular thrombosis and ischemic organ damage. (**B**) Caplacizumab blocks the platelet and ultra-large vWF interaction by binding to A1 domain of vWF.
Abbreviations: aTPP, acquired thrombotic thrombocytopenic purpura; GP1b-α, glycoprotein 1b-alpha; vWF, von Willebrand factor.

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Twice-daily Plasma Exchange in aTTP with Severe Disease Activity

French TMA Reference Center

- 19 TTP patients with undetectable ADAMTS13 activity
- Twice-daily PLEX in patients with short-term life-threatening disease due to worsening condition
  - Failure of daily PLEX to improve platelet count or worsening thrombocytopenia, plus either
  - Neurologic involvement -or- increase in cardiac troponin I
- Most patients received 1+ doses of rituximab when twice-daily PLEX initiated
- Twice-daily PLEX stopped when platelets >100,000/µL x 2 days

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Soucemarianadin M. Eur J Haematol 2016

Twice-daily Plasma Exchange in aTTP with Severe Disease Activity

Median duration of twice-daily PLEX was 3 days (range 2-22 days)

- 12/19 patients (63%) responded to twice-daily PLEX without requiring new therapies
- 6/19 patients (32%) did not response to twice-daily PLEX
  - 4 with persistently refractory disease
  - 2 with disease exacerbations
- 1 patient expired after 2 days of twice-daily PLEX

Patients with severe TTP and short-term high-risk findings may benefit from twice-daily PLEX

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PLEX in Other Primary TMA

Disorder	Pathophysiology	ASFA Category
TMA-Shiga Toxin Mediated	Direct endothelial damage with apoptosis from shiga toxin effect	III-Severe neurologic symptoms IV-No neurologic symptoms
TMA-Drug Induced	Variable Mechanism – Direct endothelial damage –or- from ADAMTS 13 Autoantibodies	I- Ticlopidine (no longer available in US) III- Clopidogrel IV- Gemcitabine/Quinine
TMA-Coagulation Mediated	Mutations in DGKE, Plasminogen, thrombomodulin --> thrombosis and complement Activation	III
TMA-Metabolism mediated	Homozygous mutations in MMACHC (encoding methyl-malonic and homocysteinuria type C protein)	NC

PLEX in Other TMA

Disorder	Pathophysiology	ASFA Category
TMA Hematopoietic Stem Cell Transplant	Endothelial damage due to infection, chemo/radiation therapy, or GVHD. Complement regulatory pathway mutations	III
TMA Malignancy	Activation of coagulation by tumor tissue factor expression-?Complement regulatory Pathway mutations	NC
HELLP Syndrome	Mutations in alternate complement pathway regulatory elements	III- Postpartum IV- Antepartum