aTTP/iTTP: Clinical Approach and recent updates

Maissaa Janbain, MD, MSCR
Tulane School of Medicine

Disclosures

- Advisory Committee: Takeda
- Honoraria: Takeda, Bayer, Genentech, Biomarin, CSL Behring, Spark Therapeutics, Octapharma, Sanofi, Sobi
- Speaker Bureau: Takeda, Biomarin, Spark therapeutics, CSL Behring, Sanofi
- Research support: Genentech

Agenda

- Epidemiology of TTP
- Pathophysiology of TTP
- PLASMIC Score
- 2017 and 2021 IWG TTP Outcomes Definitions
- ISTH Guidelines for diagnosis
- ISTH Guidelines for management of iTTP
- Caplacizumab: indication, HERCULES, dosing
- Summary

TTP: Thrombotic thrombocytopenic purpura, ISTH international society of thrombosis and hemostasis, IWG intenational working group

TTP is a rare, life-threatening thrombotic disorder[1]

Defined by severe ADAMTS13 deficiency

Accumulation of ultra-large VW multimers[2,3]

Increased platelet aggregation, leading to dissemination of micro vascular platelet-rich microthrombi

ADAMTS13, a disintegrin and metaloproteinase with a thrombospondin type 1 motif 13, VWF von willebrand factor

1.Joly BS et al. *Expert Rev Hematol.*2019;12(6):383-395. 2.Joly BS et al. *Blood.*2017;129(21):2836-2846. 3.Gearge Jet al. *South Med J.*2007;100(5):512-514. 4.Scully M et al.. *Br J haematolo.* 2012;158(3):323-335

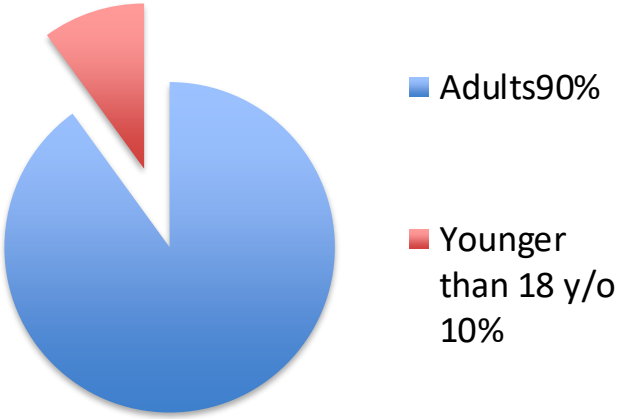
The epidemiology of TTP

- ~4 cases per 1 million people is the estimated US annual incidence rate[1]
  - 18 cases per 1 million people reported in the Oklahoma registry[2]
- 2.5x to 3.5x more common in women than men[2]
- Median age of onset:30-39 y/o[2]
- African Americans have a 7-fold higher incidence than non-African Americans[3]

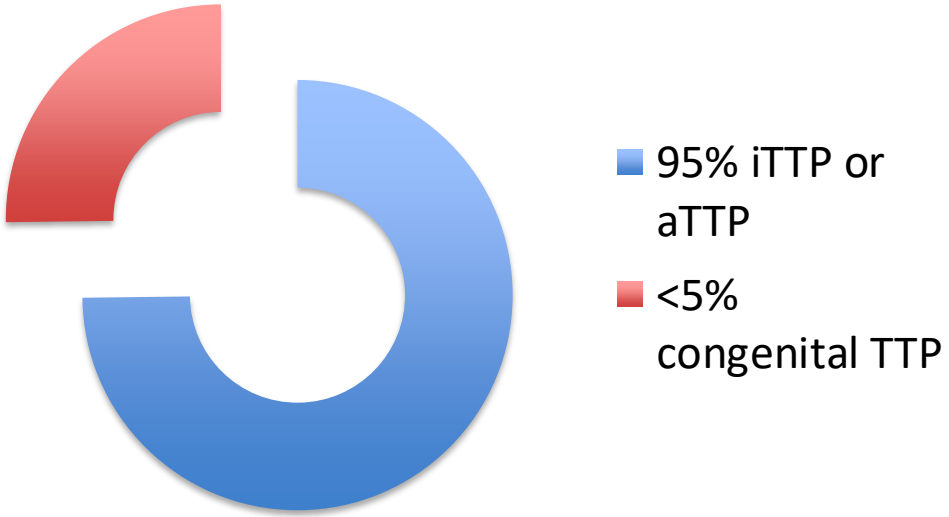
1.Miller DP et al. *Epidemiology* 2004;15(2)208-215. 2. Hovinga JA et al. *Nat Rev Dis Primers.* 2017;3:17020. 3.Chiasakul T et al.. *Hematology.* 2018(1):530-538

The epidemiology of TTP

By Age[1]

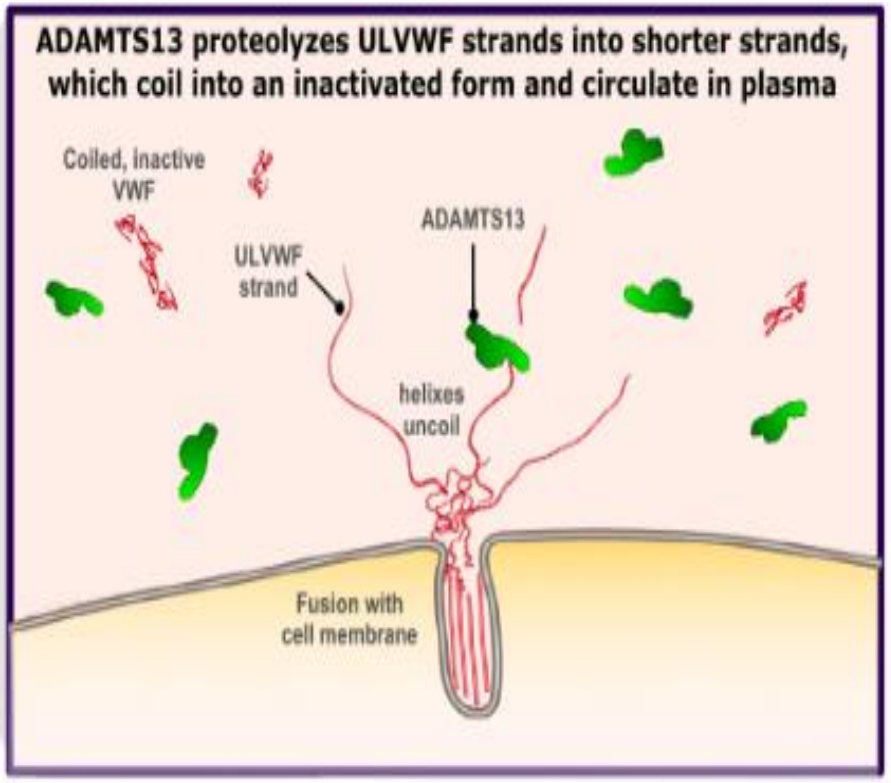


By Type[2]



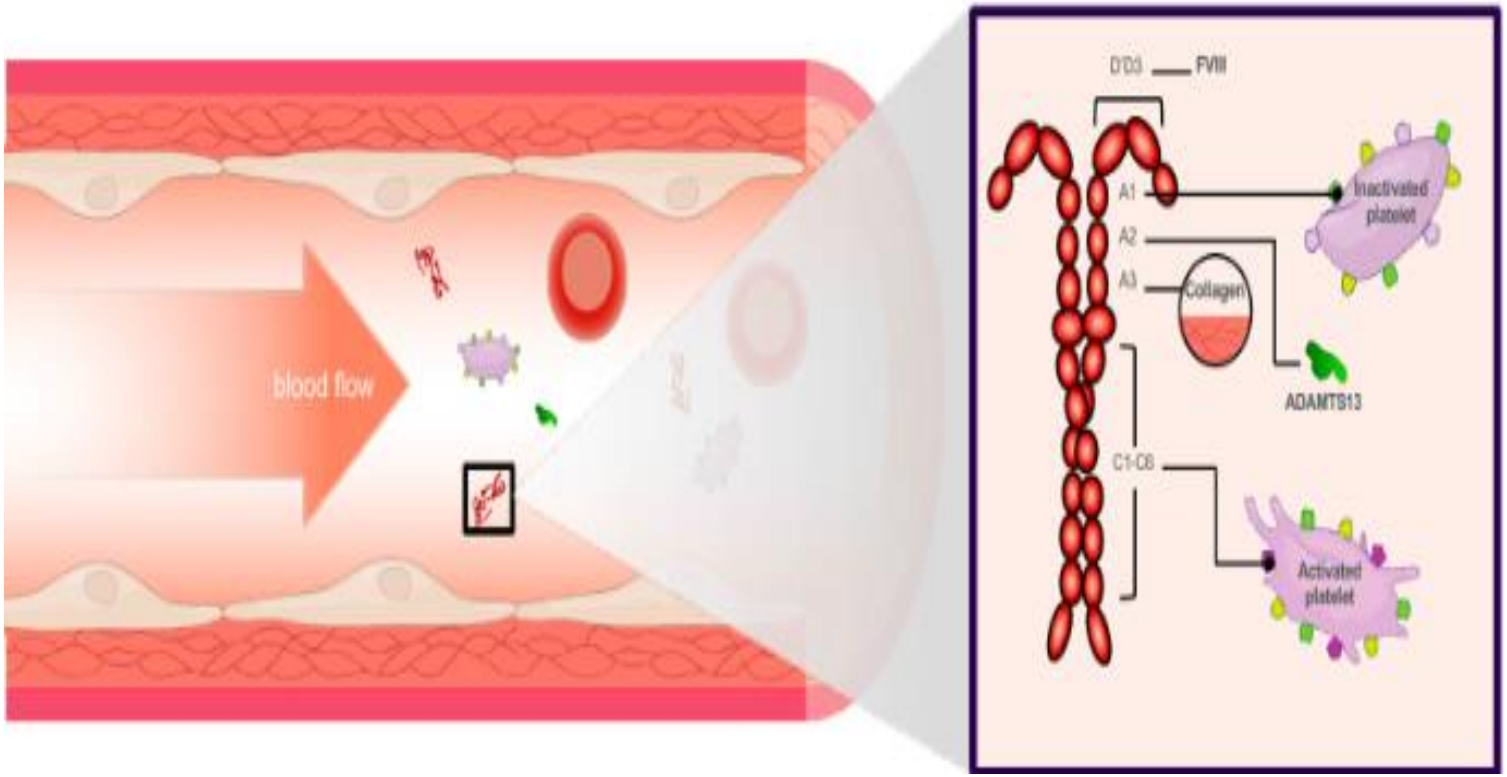
1. Hovinga JA et al. *Nat Rev Dis Primers.* 2017;3:17020
2. Joly BS et al. *Expert Rev Hematol.* 2019;12(6):383-395.

Endothelial cells, VWF and ADAMTS-13 (In all Blood Vessels)



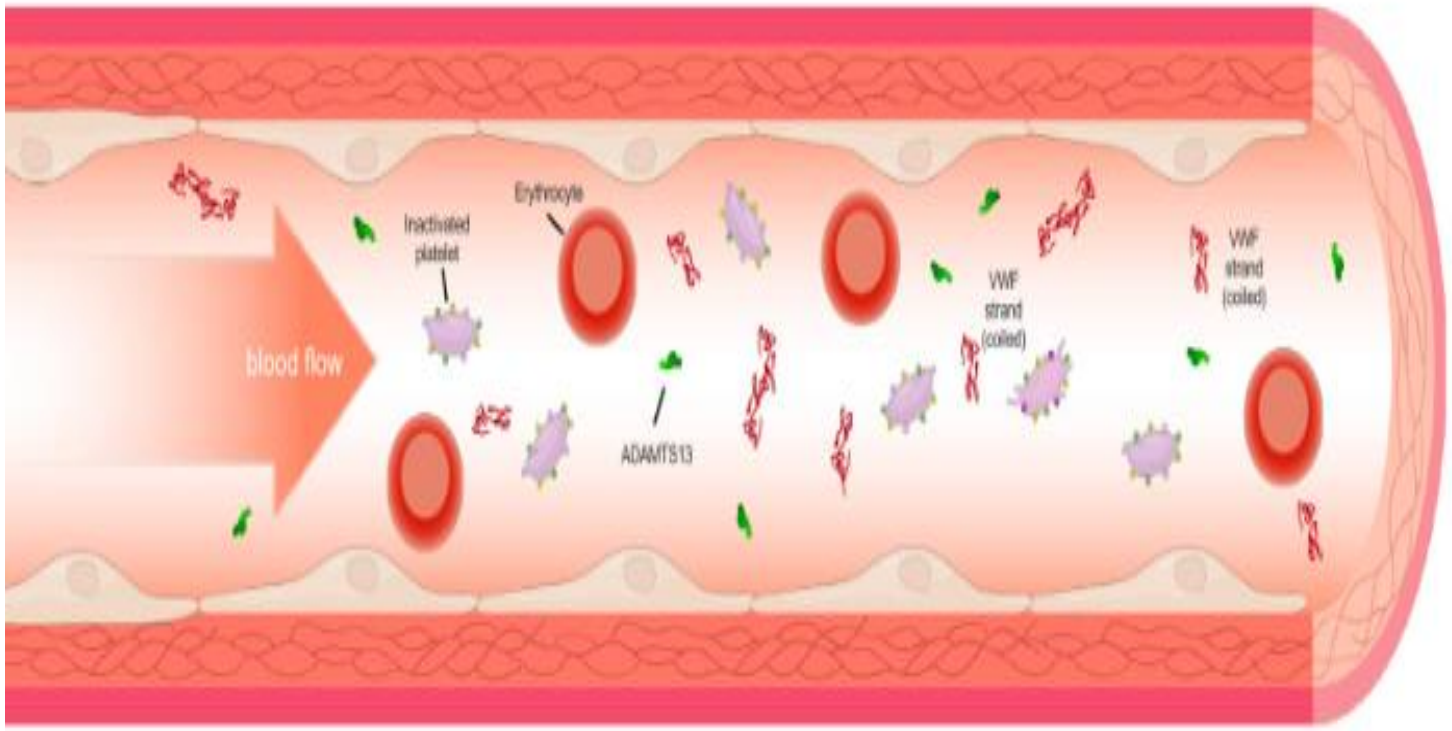
Leebeek FW et al. N Engl J Med. 2016 Nov 24;375(21):2067-2080.

Binding Domains of VWF (In all Blood Vessels)



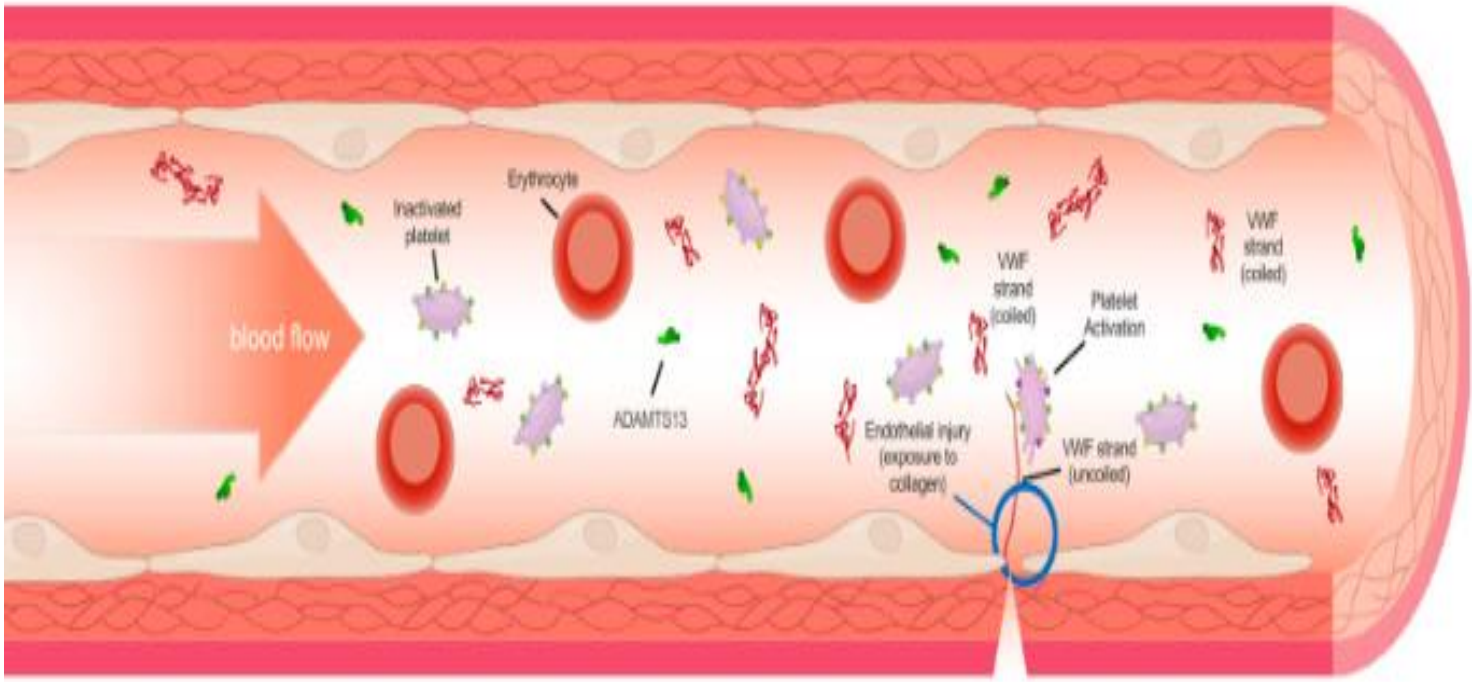
Kremer et al. *Nature Reviews* 2017;3:1-17

Binding and Activation of Platelets (In all Blood Vessels)



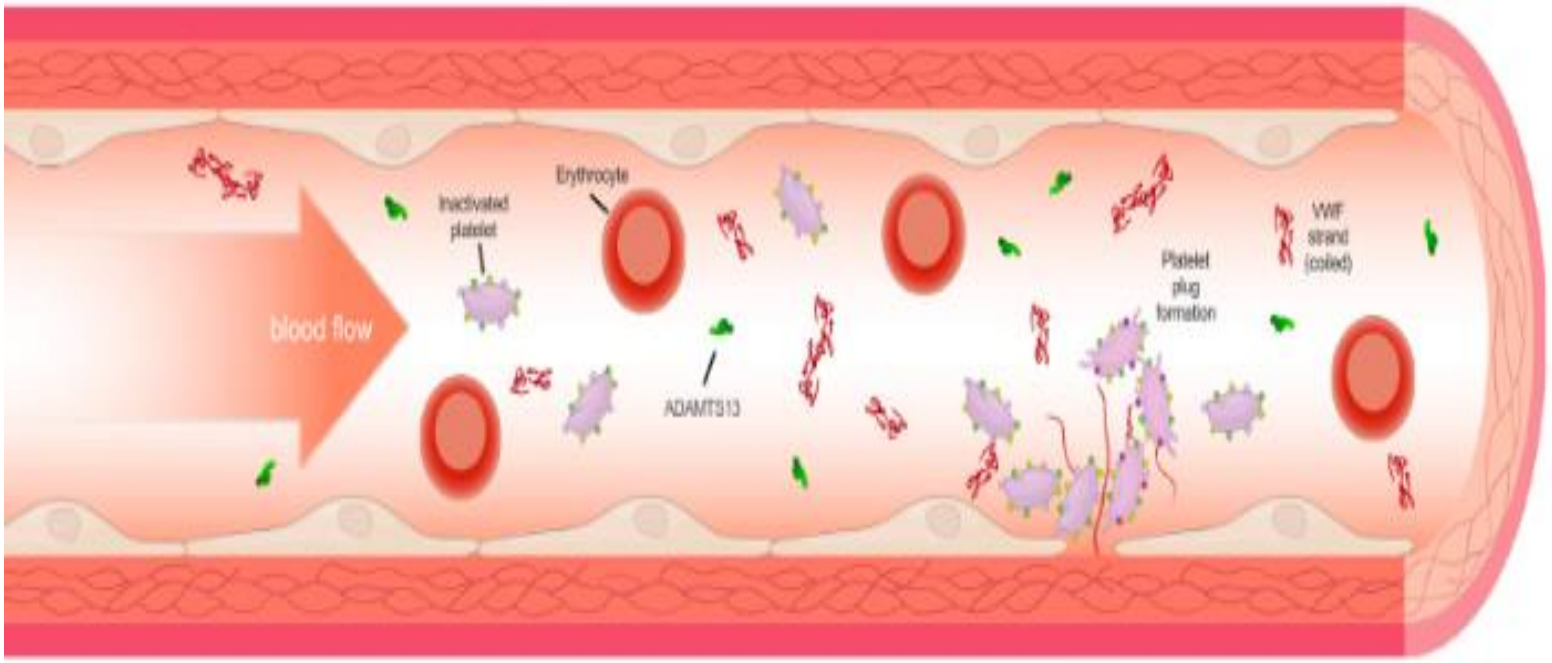
Kremer et al. *Nature Reviews* 2017;3:1-17

Binding and Activation of Platelets (In all Blood Vessels)



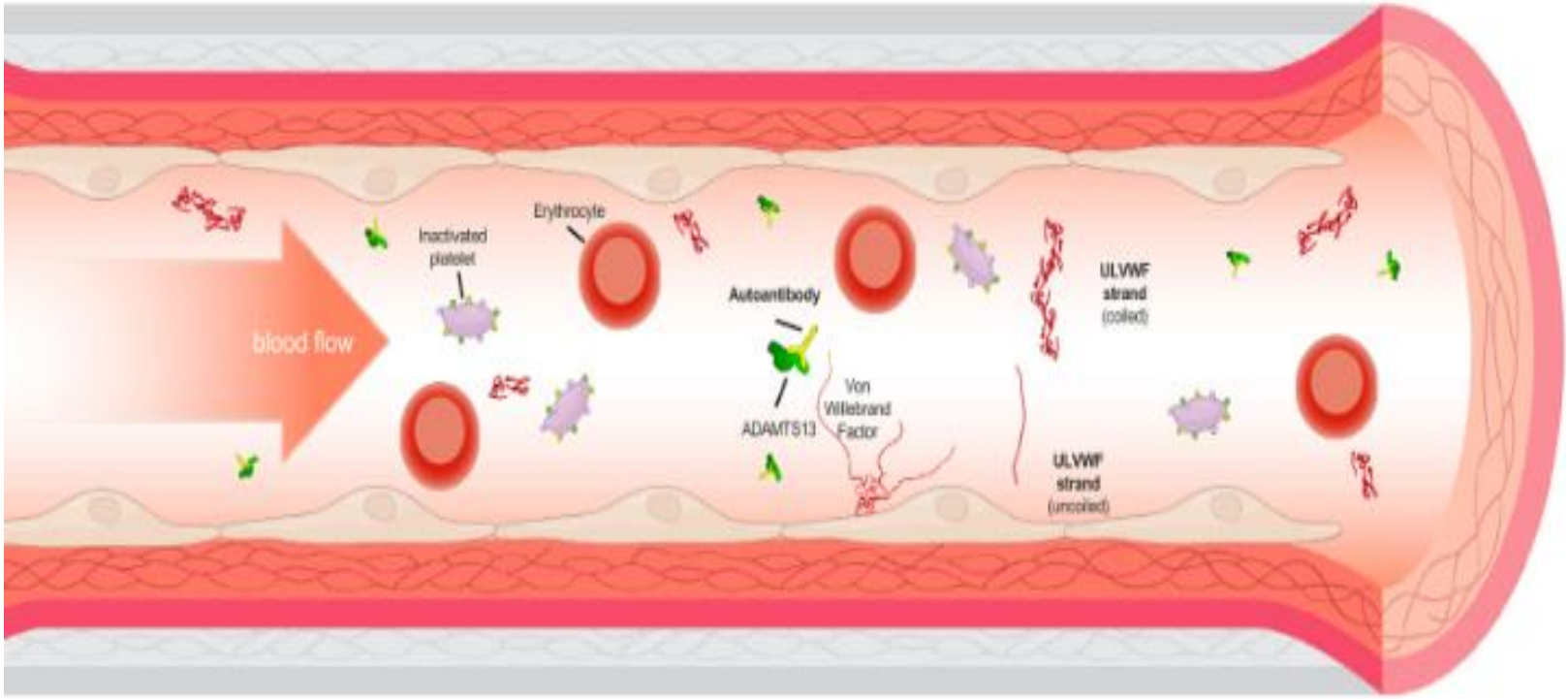
Kremer et al. *Nature Reviews* 2017;3:1-17

Binding and Activation of Platelets (In all Blood Vessels)



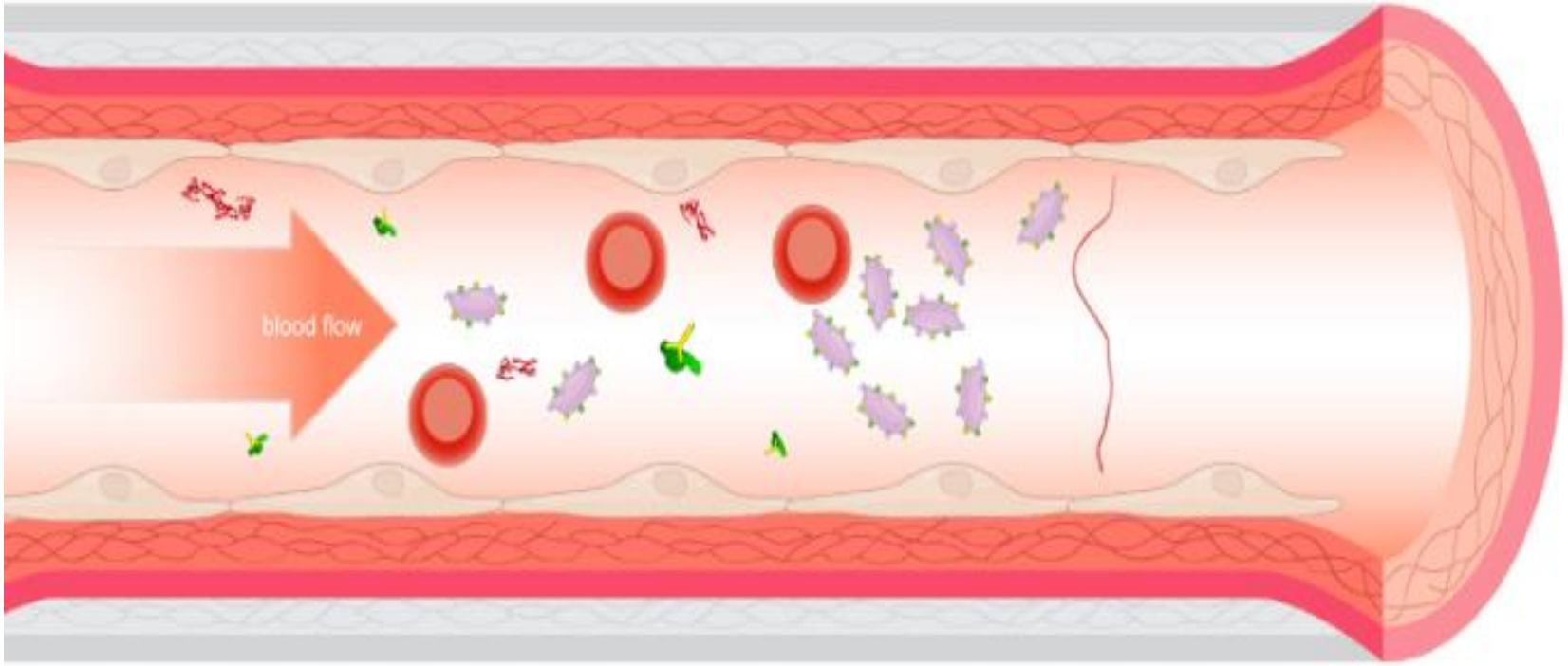
Adapted from Kremer et al. *Nature Reviews* 2017

iTTP – Autoantibodies Targeting ADAMTS13 (Arterioles/Capillaries)



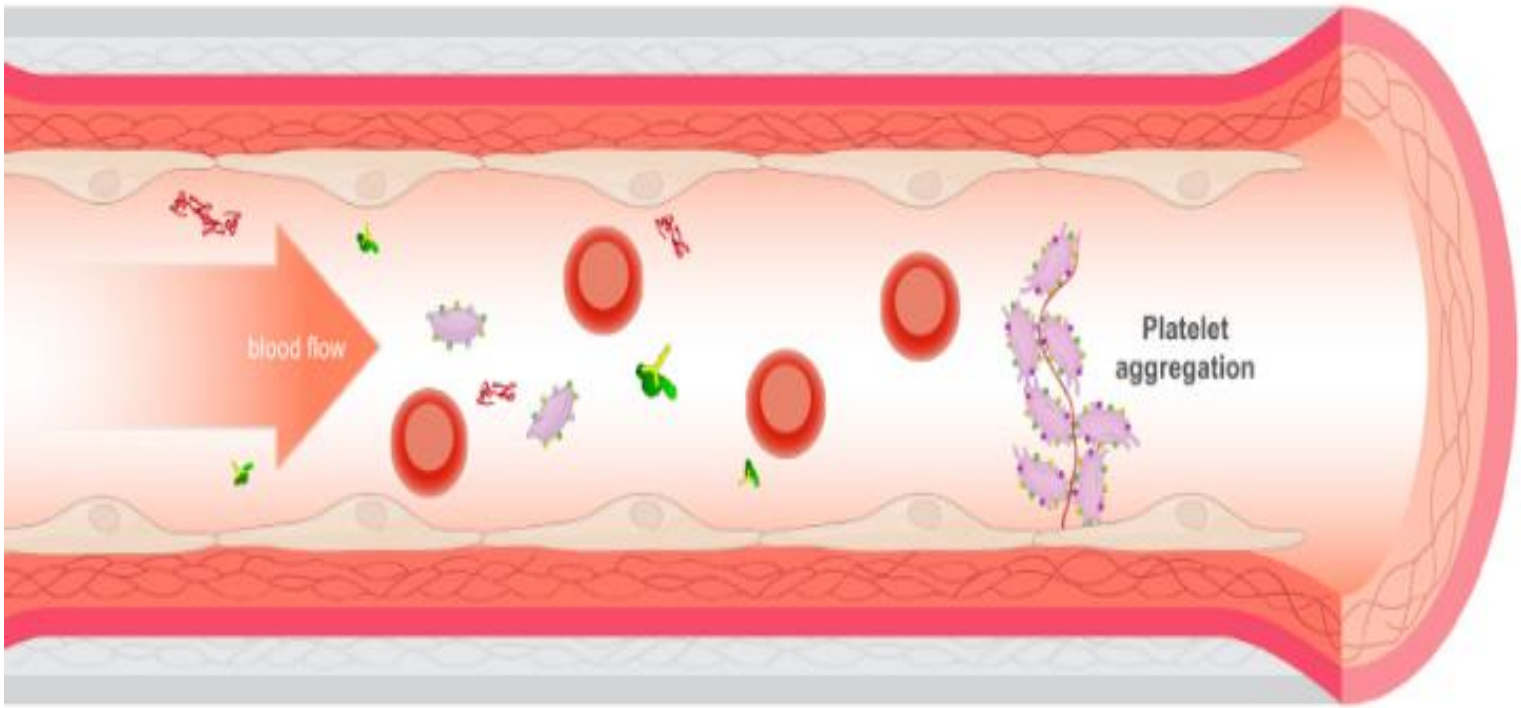
Kremer et al. *Nature Reviews* 2017;3:1-17

iTTP – Thrombotic Microangiopathy (TMA) (Arterioles/capillaries)



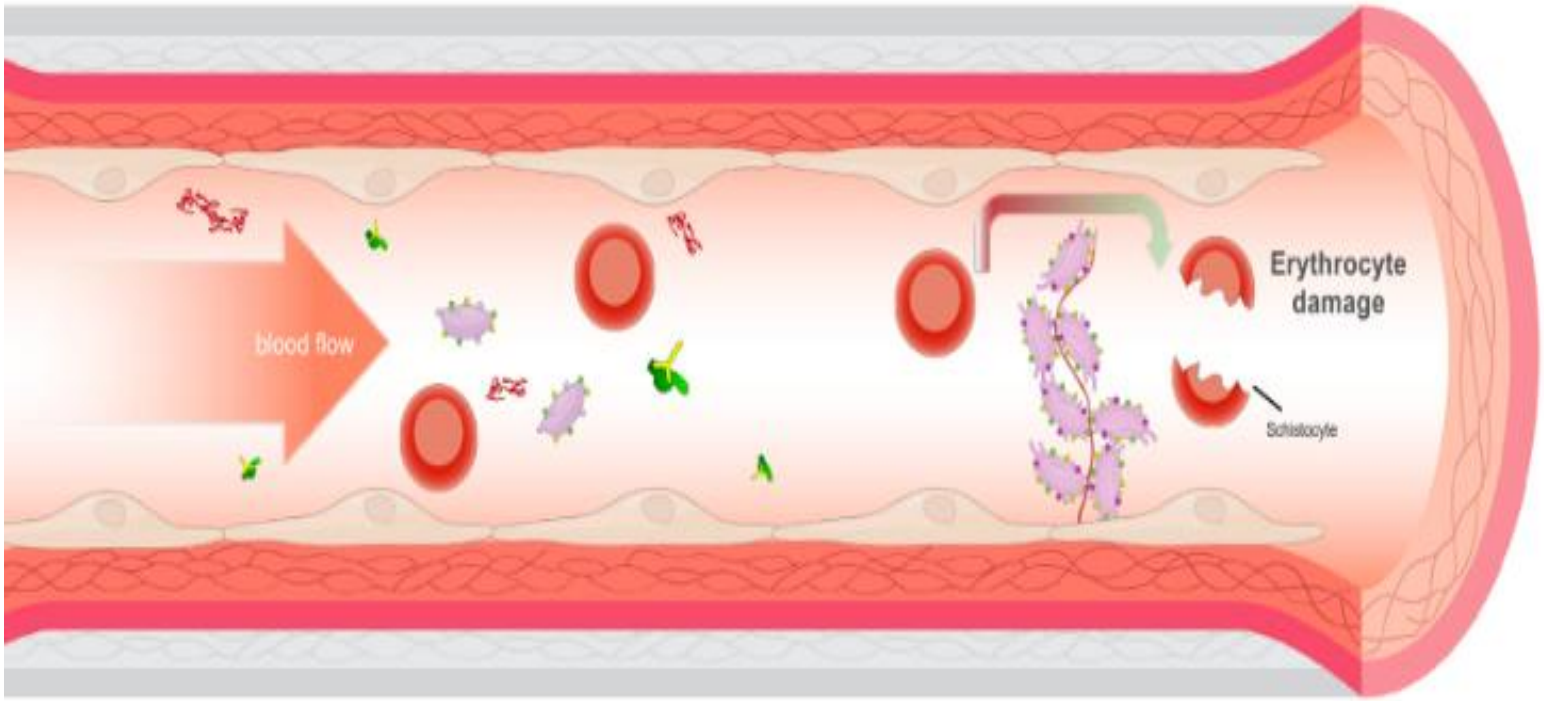
Kremer et al. *Nature Reviews* 2017;3:1-17

iTTP – Thrombotic Microangiopathy (TMA) (Arterioles/capillaries)



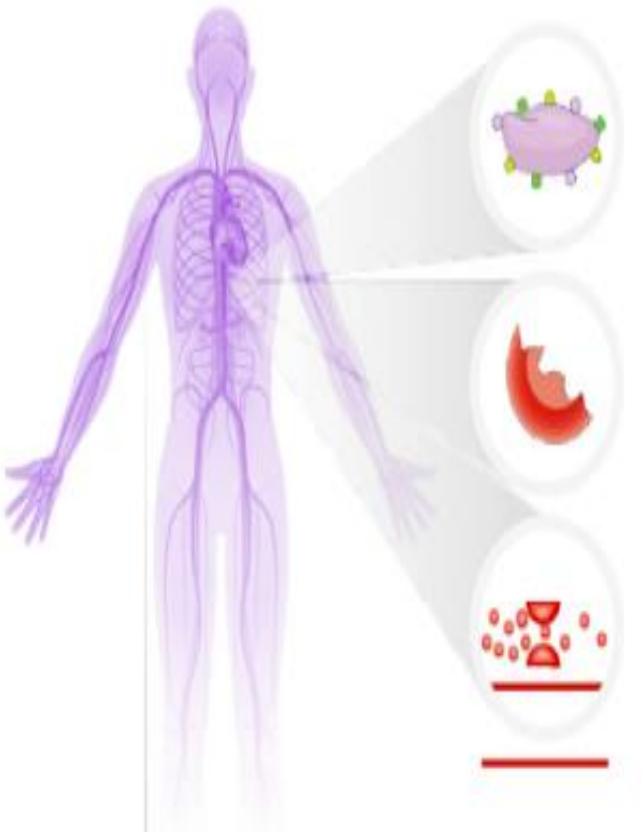
Kremer et al. *Nature Reviews* 2017;3:1-17

iTTP – Thrombotic Microangiopathy (TMA) (Arterioles/capillaries)



Kremer et al. *Nature Reviews* 2017;3:1-17

Consequences of Microvascular Thrombi



Thrombocytopenia with platelet count <30 x 10^{9}/L

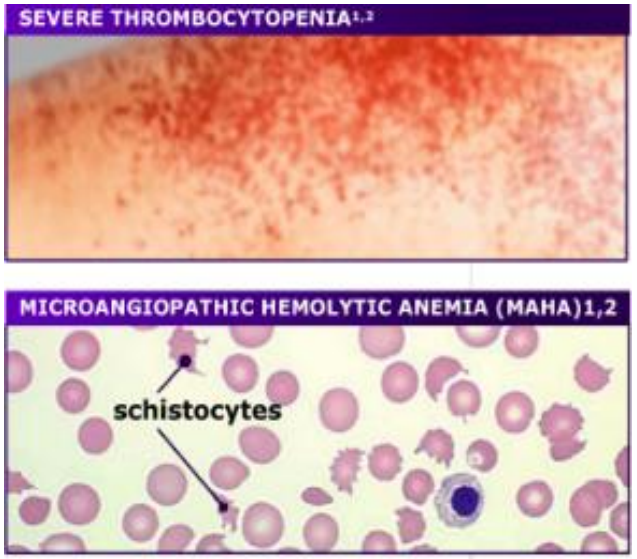
Microangiopathic hemolytic anemia or MAHA with presence of schistocytes

Organ ischemia (heart, kidneys, brain, digestive system…)

1.Scully *et al Br J Haematol 2012*
2. Sadler *Blood* 2017

Clinical presentation of iTTP

- Brain:~60% patients (headache, confusion, stroke, coma, seizures)
- Heart:~25% patients (EKG abnormalities, myocardial infarction)
- Gastrointestinal :~35% patients (abdominal pain and diarrhea)
- Kidney:~10-27% patients (proteinuria/hematuria, renal failure uncommon)



With low ADAMTS13 Levels

1.Scully *et al Br J Haematol 2012*
2.Joly BS et al. *Blood.*2017
3.Page *et al Blood ADV* 2017

Under diagnosis with high mortality rate

- Mortality rate is up to 90% without treatment
- Prompt symptom recognition is essential
- Insufficient disease awareness and delays in care can lead to poor patient outcomes
- Despite appropriate first line treatment (PLEX and immunosuppression), mortality rate is 20%
- 42% are refractory to PLEX and immunosuppression
- 95% achieve normalization of plt count, 87% achieve remission
- Exacerbation (within 30 days) 53% (median time of 10 days)
- Relapses (30-50%) within 1-2 years with same mortality rate compared to de novo

PLEX plasma exchange

1. Joly *Blood* 2017; 2. Coppo *Res Pract Throm Haemost* 2019*;* 3. Goel *Transfusion* 2016; 4.Hovinga *Nat Rev Dis Primers* 2017*;* 5.Sayani *Blood* 2015*; 6.*Blombery *J Blood Med* 2014; 7.Chiasakul *Hematology* 2018; 8.Hovinga *Blood* 2018

Conditions with similar clinical presentations

Systemic lupus erythematosus (SLE)	Vascular abnormalities (arterial/arteriolar thrombosis)
Atypical hemolytic uremic syndrome (aHUS)	Low haptoglobin, elevated LDH and creatinine, and presence of schistocytes
HELLP (hemolysis, elevated liver enzymes and low platelets)	Hemolysis, elevated liver enzymes, thrombocytopenia and renal damage
Disseminated intravascular coagulation	Microvasculature damage leading to possible organ dysfunction

ADAMTS13 levels can confirm TTP, but turn around times can be lengthy
A clinical prediction score may aid in differential diagnosis of TTP while awaiting ADAMTS13 results

PLASMIC Score

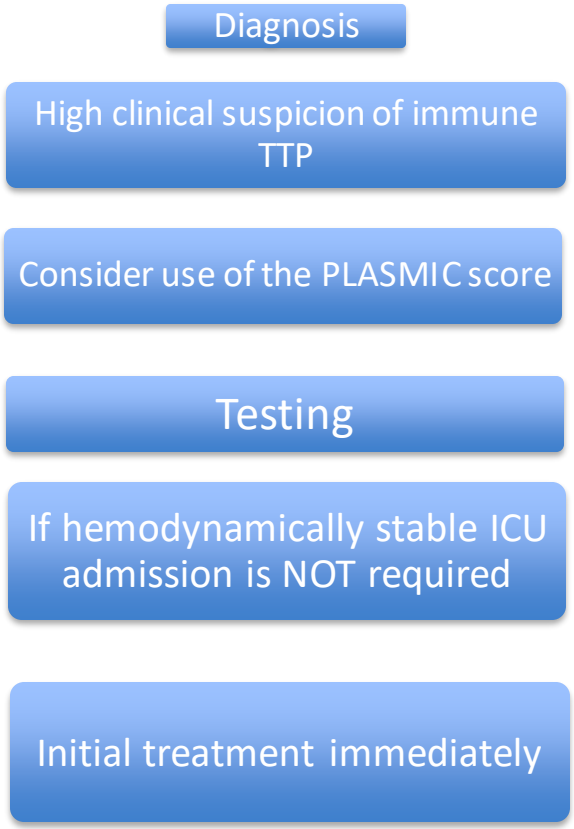
- Generated in 2017 as tool of clinical prediction using dataset from the Harvard TMA Research Collaborative, a multi-institutional registry-based effort to study TTP and allied disorders (n=214)

- Endorsed by ISTH Guidelines and USTMA for pretest determination of severe ADAMTS13 deficiency

Parameters	Plasmic Score
Platelet count	$<30x10^9/L$ (+1)
Serum creatinine level	<2.0 mg/dL (+1)
Hemolysis	+1
No active cancer in previous year	+1
No history of solid organ or SCT	+1
INR<1.5	+1
MCV<90fL	+1

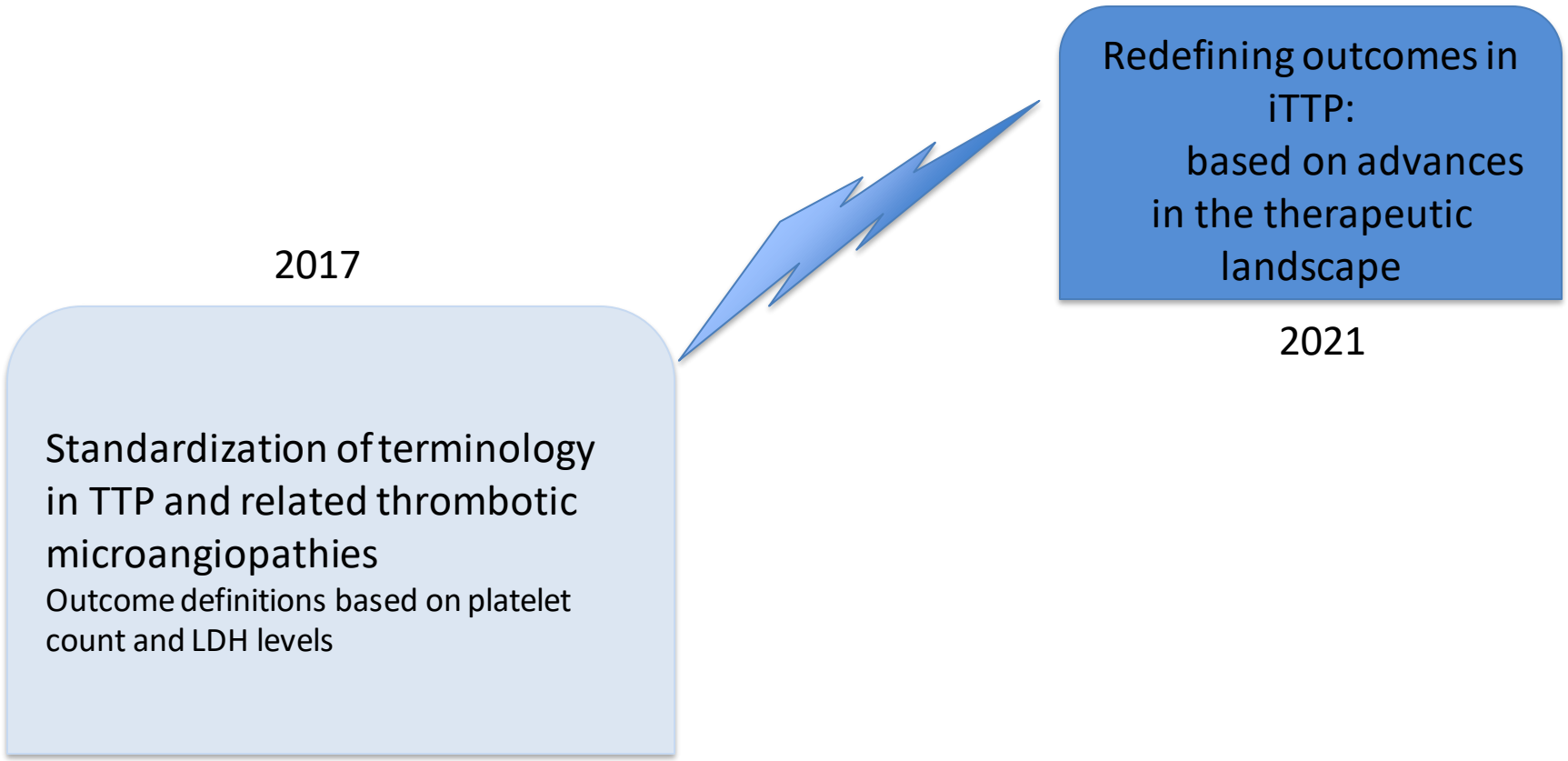
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	**0-4: 0%-4%**
	5: 5%-24%
	6-7: 62%-82%

USTMA Consortium Expert Consensus



According to the USTMA: the PLASMIC score does NOT confirm or exclude the diagnosis of iTTP and does not take in consideration patients with comorbidities

IWG iTTP Outcome Definitions Development



2017 vs 2021 IWG Outcomes Definitions: Emphasis on ADAMTS13 Testing

Outcome	2017 definition	2021 definition
Clinical response	Sustained plt count>150x10^9/L and LDH <1.5xULN	Sustained plt count>150x10^9/L and LDH <1.5xULN and n clinical evidence of new or progressive ischemic organ injury
Exacerbation	After a clinical response, decreased in plt count<150x10^9/L and increase in LDH within 30 days from stopping PLEX	After a clinical response and before a clinical remission, plt<150x10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-VWF therapy
Remission	Plt count>150x10^9/L and LDH <1.5xULN For >30 days after stopping PLEX	Clinical remission: Sustained clinical response with either (a) no TPE and no anti-VWF therapy for >30 days or (b) with attainment of partial or complete ADAMTS13 remission • **Partial ADAMTS13 remission: ADAMTS13 activity >20%** • **Complete ADAMTS13 remission: ADAMTS13 activity >LLN**
Relapse	After a clinical remission: plt count<150x10^9/L	Clinical relapse: After a clinical remission, plt<150x10^9/L **w/wo clinical evidence of new ischemic organ injury; with documentation of severe ADAMTS13 def.** **ADAMTS13 relapse: ADAMTS13 decrease to <20% after achieving partial or complete ADAMTS13 remission**

1.Scully *et al Br J Haematol 2012*
2.Cuker *Blood* 2021

Patients in clinical remission who do not achieve an ADAMTS13 remission or who experience an ADAMTS13 relapse are at increased risk of clinical response

The new 2020 ISTH guidelines provide a useful tool for the diagnosis and management of adult patients with suspected TTP

ISTH Guidelines Overview of Recommendation Levels

Strong recommendation

- The panel is confident that the desirable effects of the recommendation outweigh the undesirable effects
- Most patients would accept the recommended course of action, while only a small proportion would not
- Most clinicians should follow the recommended course of action, and the recommendation can be adopted as a policy in most situations
- Usually based on high-quality evidence

Conditional recommendation

- The panel believes that the desirable effects of the recommendation probably outweigh the undesirable effects
- Most patients would accept the suggested course of action, but many would not
- Clinicians should note that different choices will be appropriate for different patients
- Policy making and standard setting around conditional recommendations should be undertaken with caution; it requires substantial debate and engagement of a wide range of stakeholders (e.g., patients, treating physicians, insurance company/payer)

ISTH Guidelines for Diagnosis and Management Adult Patients With Suspected TTP

Timely access to ADAMTS13 Testing

Patients with *high* pretest probability of TTP:

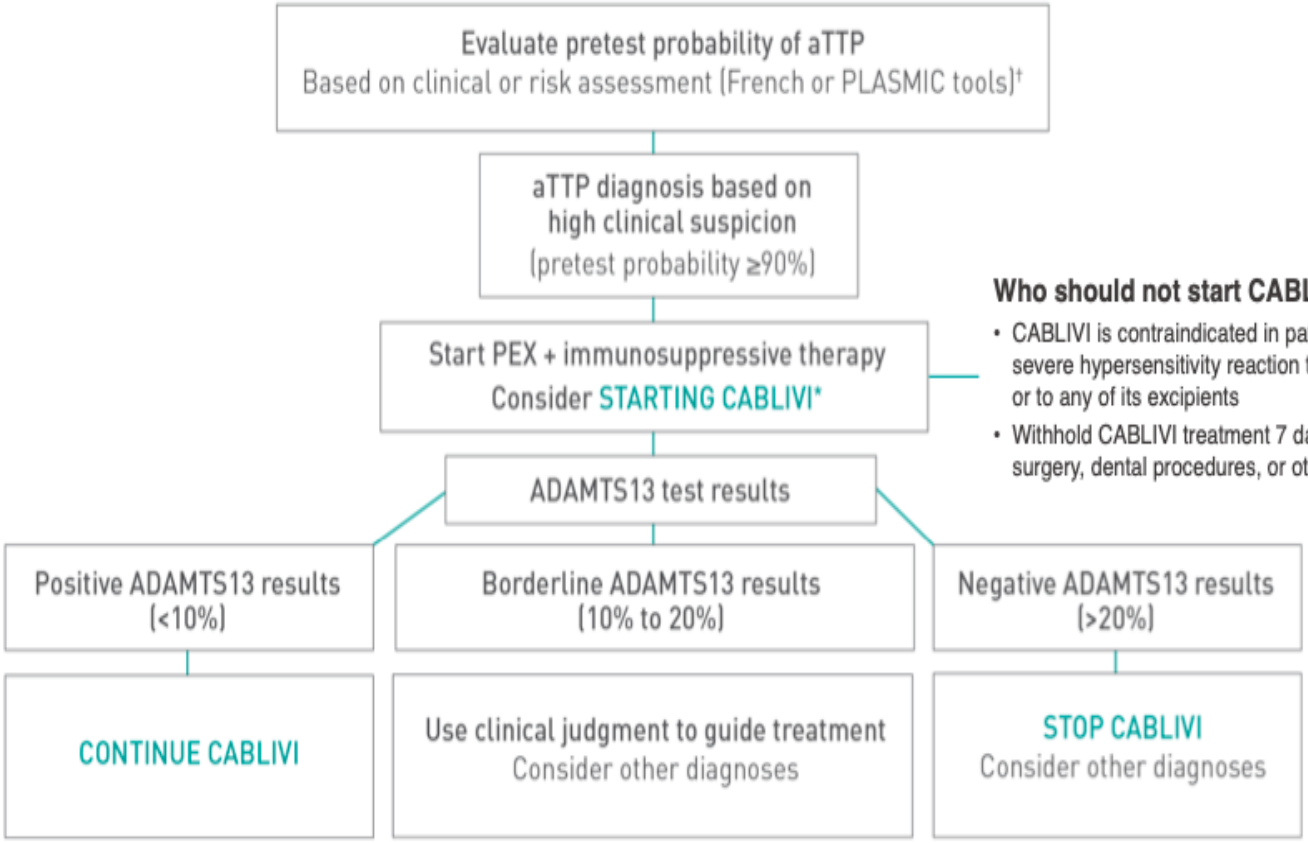
Consider early administration of caplacizumab before receiving ADAMTS13 activity results

- If ADAMTS13 activity<10%, continue caplacizumab and monoclonal antibody therapy
- If ADAMTS13 activity is borderline (10-20 IU/dL or 10-20% of normal), clinical judgment is required
- If ADAMTS13 activity >20%, stop caplacizumab

Patients with *low or intermediate* pretest probability of TTP: Withhold caplacizumab until ADAMTS14 activity results are available

- If ADAMTS13 activity<10%, consider adding caplacizumab and monoclonal antibody therapy
- If ADAMTS13 activity is borderline (10-20 IU/dL or 10-20% of normal), clinical judgment is required
- If ADAMTS13 activity >20%, do not use caplacizumab

Conditional recommendations 1 and 2 in the context of low certainty of evidence



Adapted from ISTH guidelines

ISTH Guidelines for Diagnosis and Management Adult Patients With Suspected TTP

No reasonable access to ADAMTS13 Testing

- Regardless of the pretest probability of TTP: Caplacizumab not to be used
- For previously diagnosed relapse patients, treatment can be undertaken without the need for ADAMTS13 confirmation
- Conditional recommendation 3 in the context of low certainty evidence

Zheng *et al J Thromb Haemost* 2020

ISTH Guidelines for Treatment of iTTP: Recommendations

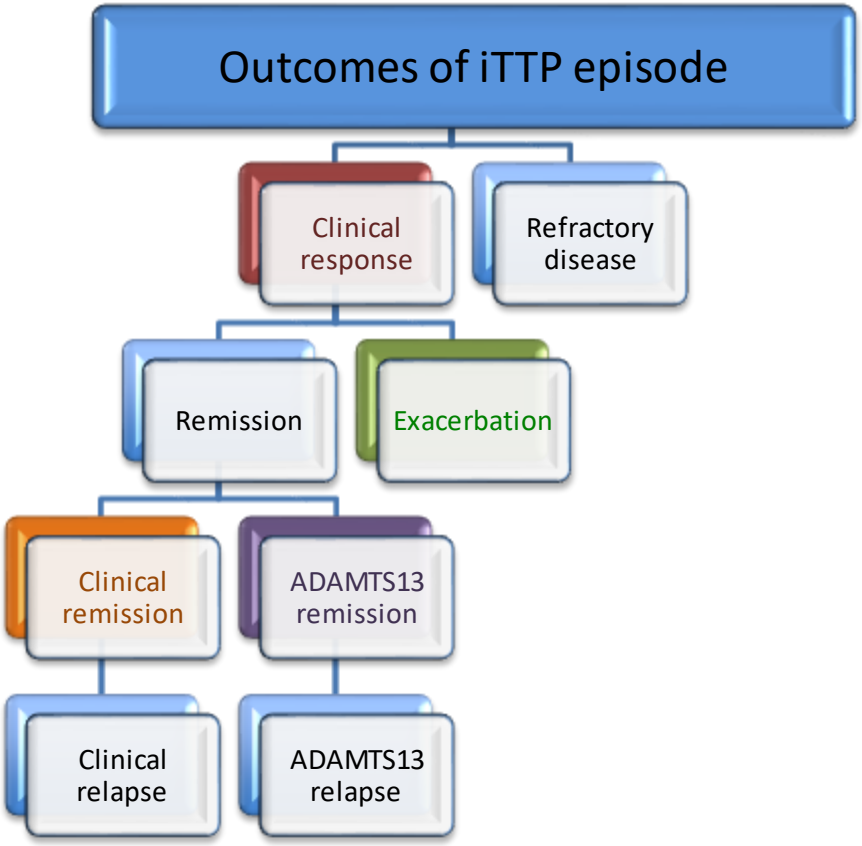
#1 *Strong*	For patients with *iTTP* experiencing a ***first acute event,*** the panel ***recommends*** the addition of corticosteroids to therapeutic plasma exchange (TPE) over TPE alone
#2 *Strong*	For patients with *iTTP* experiencing a ***first acute event,*** the panel ***suggests*** the addition of rituximab to corticosteroids and TPE over TPE alone
#3 *Strong*	For patients with *iTTP* experiencing ***a relapse,*** the panel ***recommends*** the addition of corticosteroids to TPE over TPE alone
#4 *Strong*	For patients with *iTTP* experiencing a ***relapse,*** the panel ***suggests*** the addition of rituximab to corticosteroids and TPE over TPE alone
#5 *Strong*	For patients with *iTTP* experiencing a ***acute event (first event or relapse),*** the panel ***suggests*** the use of caplacizumab* over not using it

*if ADAMTS13 levels are available

ISTH Guidelines for Treatment of TTP: Recommendations

#6 *Conditional*	For patients with *iTTP* who are in ***remission,*** but ***still have low plasma ADAMTS13 activity with no clinical signs/symptoms,*** the panel ***suggests*** the use of rituximab over non-use of rituximab for prophylaxis
#7 *Conditional*	For patients with *cTTP* who are ***in remission,*** the panel ***suggests*** either plasma infusion or a watch-and-wait strategy
#8 *Conditional*	For patients with *cTTP* who are ***in remission,*** the panel ***suggests*** against the use of factor VIII concentrate infusions vs a watch-and-wait strategy
#9 *Strong*	For patients with *iTTP* who are ***pregnant,*** and ***have decreased ADAMTS13 activity but no clinical signs,*** the panel ***recommends*** prophylactic treatment over no prophylactic treatment
#10a *Strong*	For patients with *cTTP* who are ***pregnant,*** the panel ***recommends*** prophylactic treatment over no prophylactic treatment
#10b *Conditional*	For patients with *cTTP* who are ***pregnant,*** the panel ***suggests*** prophylactic treatment with plasma infusion over FVIII

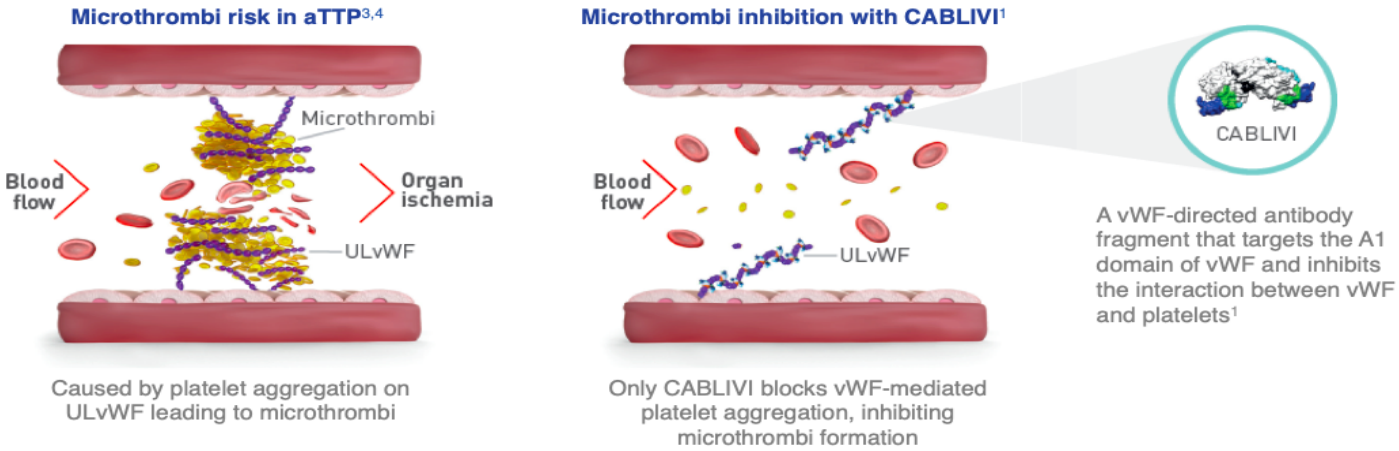
New IWG Consensus Definition: Outcomes and Management Implications



Management

- In general, TPE may be discontinued soon after a clinical response is achieved
- When used in conjunction with immunosuppression, anti-VWF therapy has been shown to reduce the risk of clinical exacerbation
- Immunosuppression may be used to induce ADAMTS13 remission
- Patients with clinical remission who do not achieve an ADAMTS13 remission or who experience an ADAMTS13 relapse are at increased risk of clinical relapse
  - In such patients, preemptive immunosuppression may be used to attain ADAMTS13 remission

What is caplacizumab?



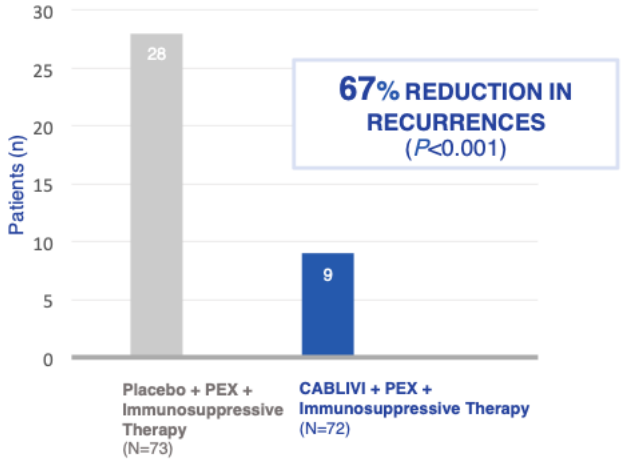
- The first and only targeted therapy to prevent microthrombi in patients with iTTP
- FDA approved in 2019 for the treatment of adult patients with immune thrombotic thrombocytopenic purpura (iTTP), in combination with plasma exchange and immunosuppressive therapy

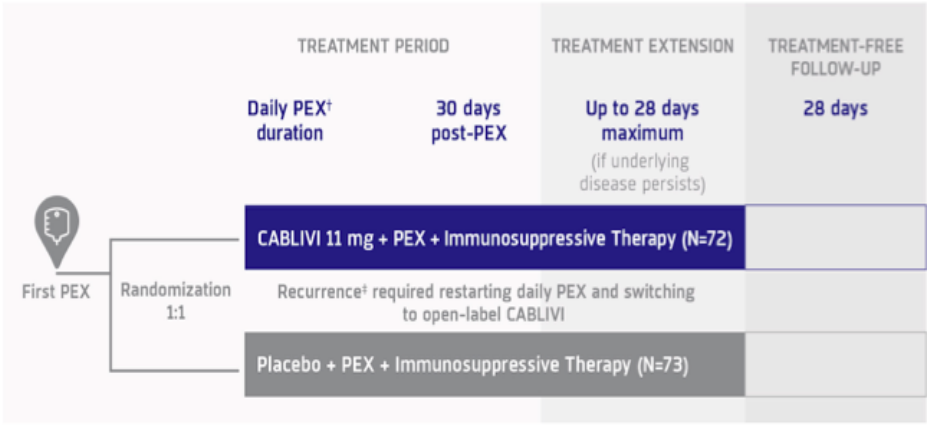
*1.*Scully *NEJM* 2019
2.Kremer *Nat Rev Dis Primers* 2017

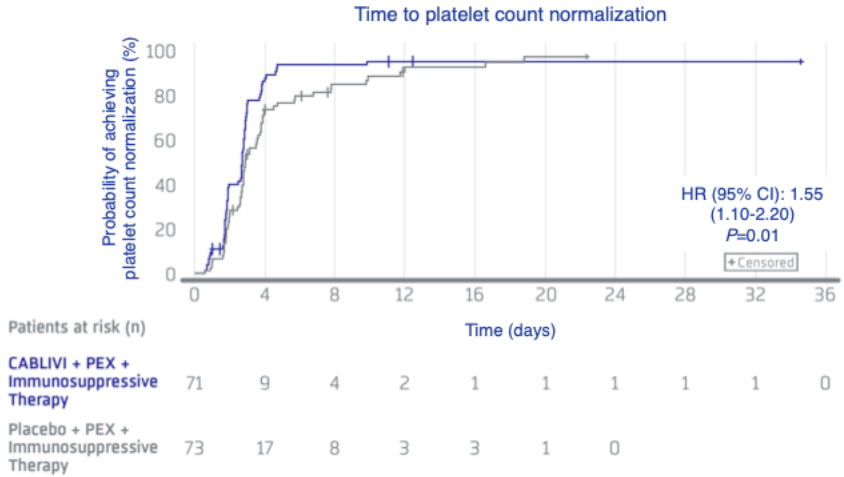
HERCULES Study: Design, Endpoints and Results

- A phase 3 double-blind, randomized controlled trial of 145 adults with iTTP

- Primary endpoint was time to plt count normalization

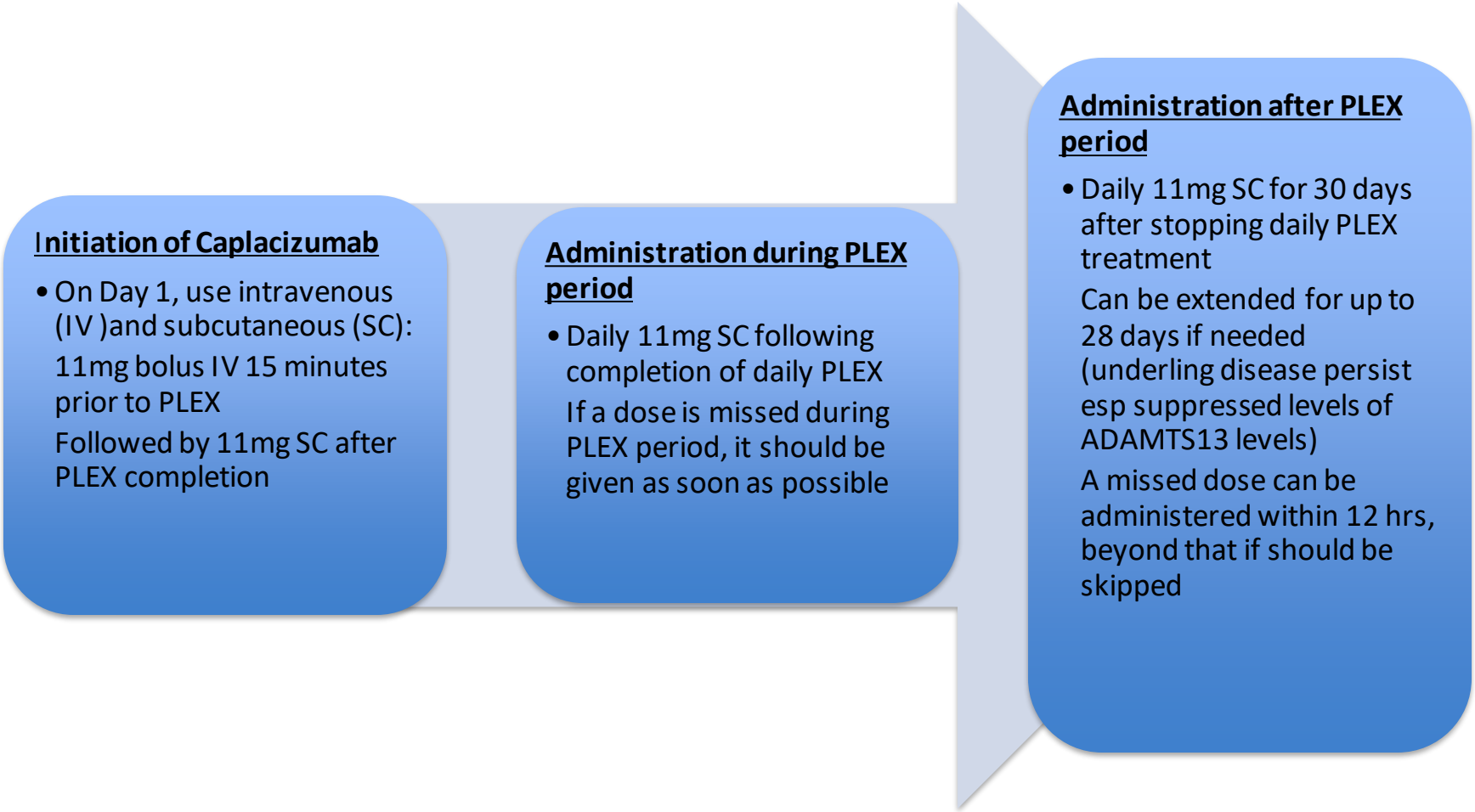






Scully NEJM 2019

Dosing of Caplacizumab



Summary

- iTTP is a rare and life-threatening thrombotic microangiopathy defined by a severe ADAMTS 13 deficiency to accumulation of ultra-large VWF multimers, resulting in dissemination of microvascular platelet-rich microthrombi

- Lack of disease awareness, diagnostic challenges, ultimately intervention and suboptimal treatment can lead to poor outcomes

- Assessment of ADAMTS13 activity is essential to definitively confirm iTTP diagnosis

- The 2021 IWG iTTP outcomes definitions emphasize the importance of both platelet and ADAMTS13 testing in determining patient outcomes

Summary

- Patients in clinical remission who do not achieve an ADAMTS13 remission or who experience as ADAMTS13 relapse are at increased risk of clinical relapse

- The diagnosis and management of adult patients with suspected TTP is guided by the 2020 ISTH guidelines
  - In general, TPE may be discontinued soon after a clinical response is achieved
  - When used in conjunction with immunosuppression, anti-VWF therapy has been shown to reduce the risk of clinical exacerbation
  - Immunosuppression (e.g. corticosteroids, rituximab) may be used to induce ADAMTS13 remission