iTTP Clinical Research Highlights: ISTH 2025

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Learning Objective: Describe the latest research about iTTP presented at ISTH 2025 and its clinical relevance in real-world settings.

Planner/Faculty Educator Dr. Chaturvedi discloses the following relevant financial relationships with ineligible companies:

- Scientific Advisory Board/Consultant: Sanofi, Takeda, Sobi, argenx, Star Pharma, RallyBio, Novartis, Alexion
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This accredited continuing education program is supported by an educational grant from Sanofi.

TTP – acute, life-threatening episodes of systemic microvascular thrombosis

Incidence, 1.7-3 per million per year

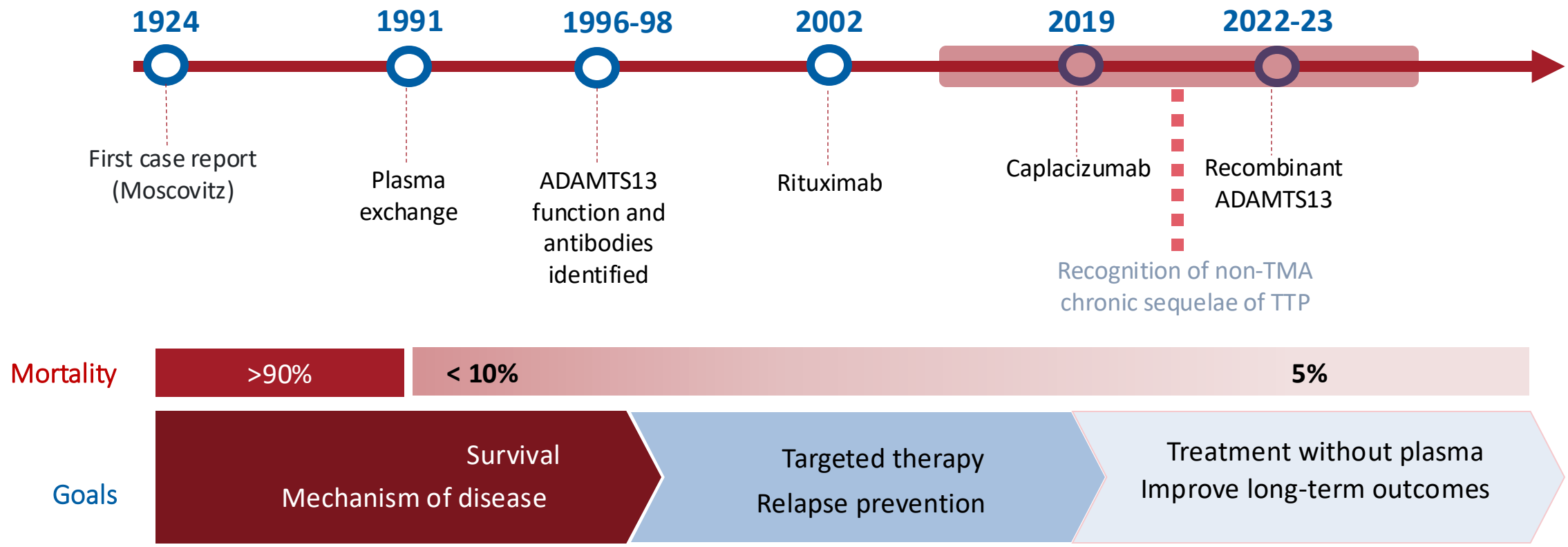
ADAMTS13 deficiency: 95% autoimmune (iTTP), 5% congenital (cTTP)

Pregnancy may precipitate episodes

Untreated, acute episodes are > 90% fatal

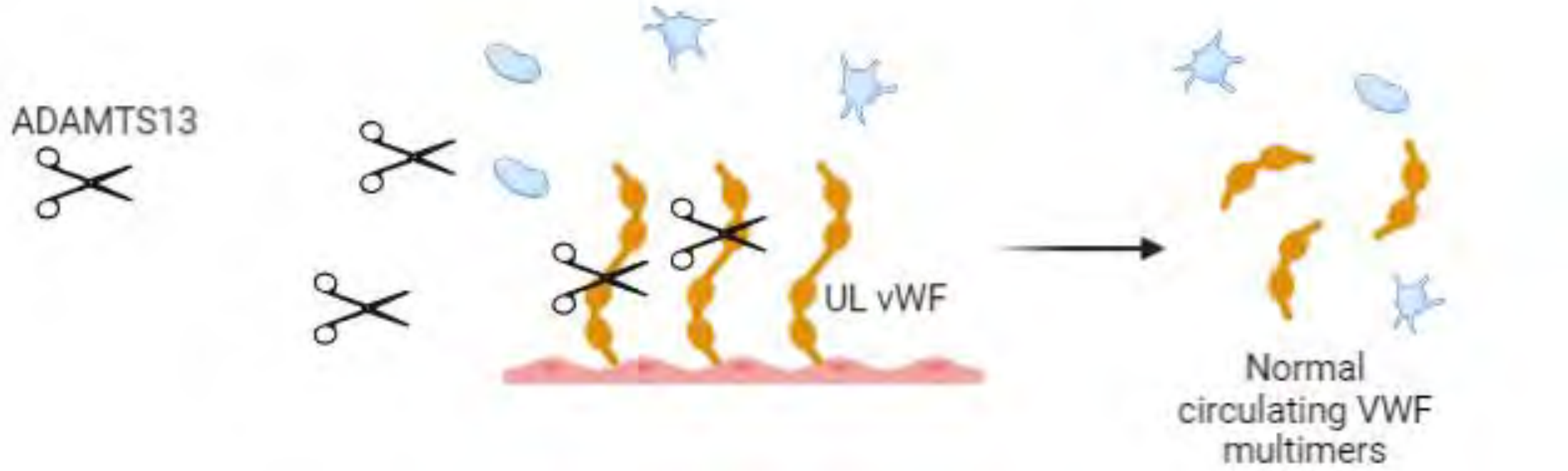
George JN. Blood 2010

1925 – 2023:
TTP evolves from an acute fatal disorder to a chronic disease



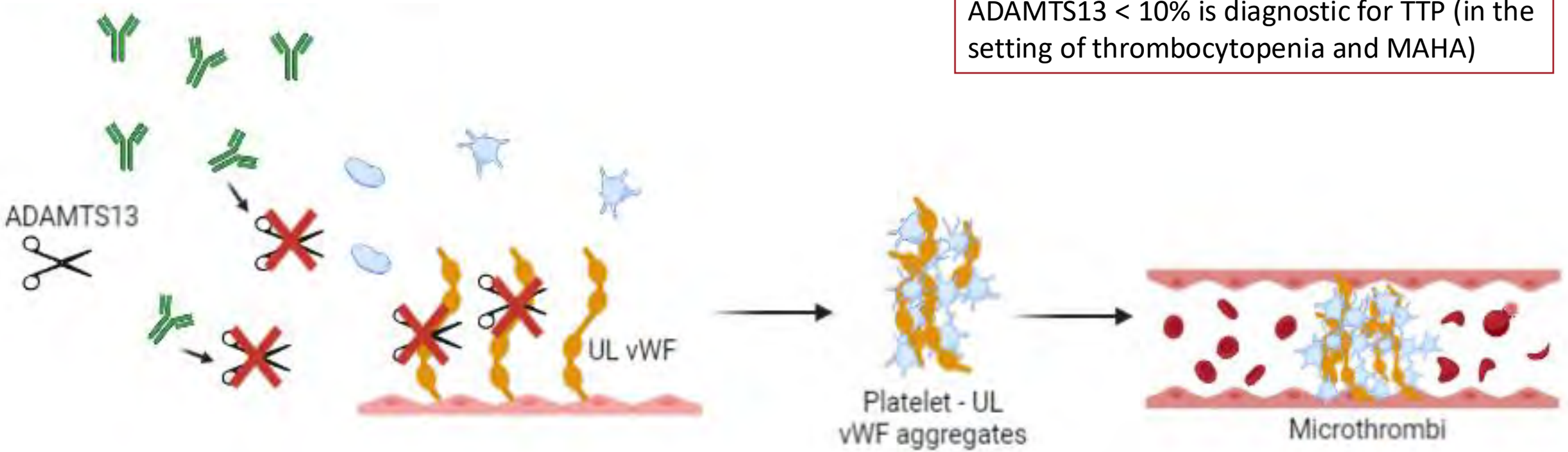
Adapted from Selvakumar, Liu, Chaturvedi. Frontiers Med 2022

Normal physiology of VWF and ADAMTS13



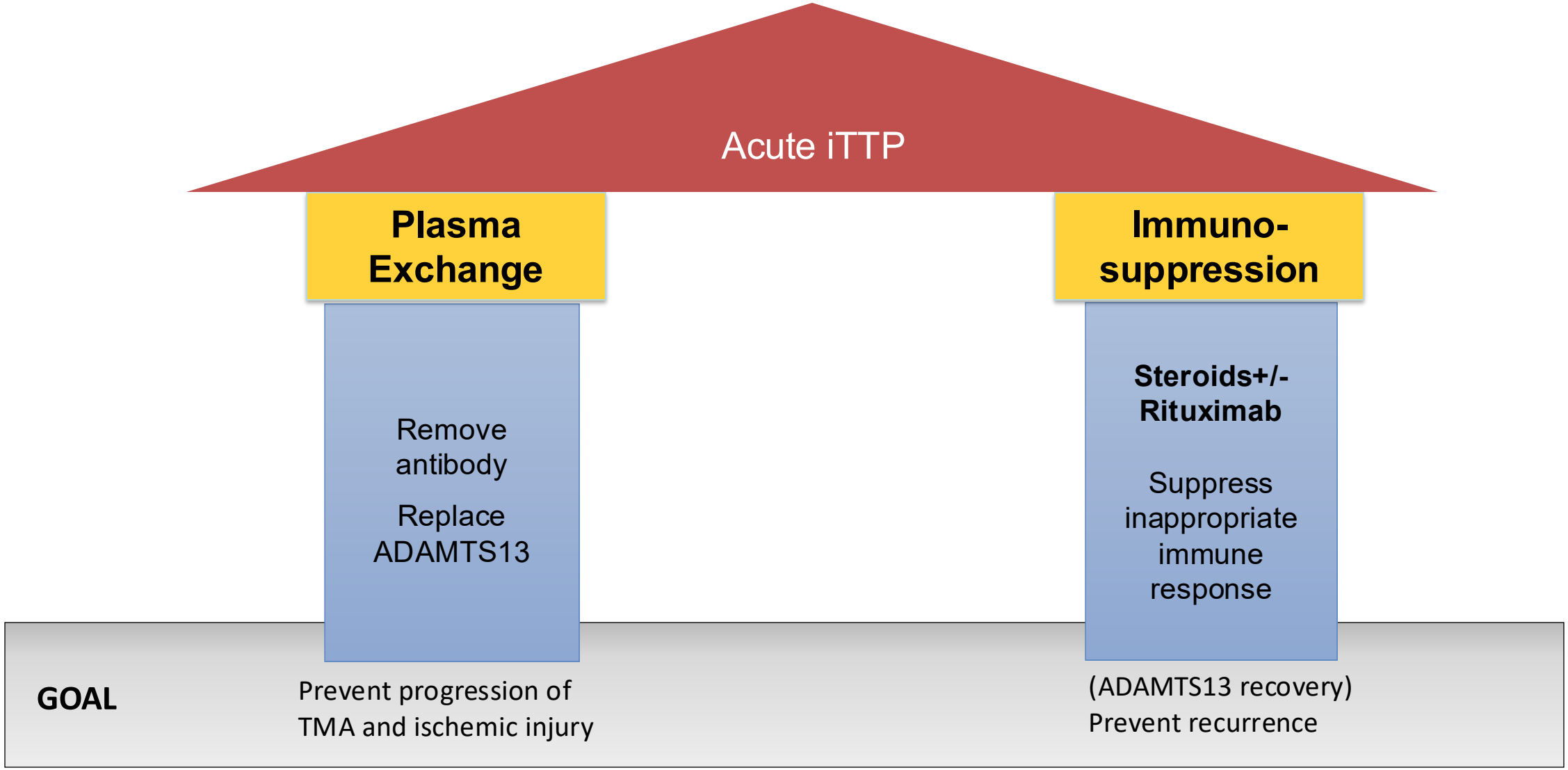
Pathogenesis of TTP

ADAMTS13 < 10% is diagnostic for TTP (in the setting of thrombocytopenia and MAHA)

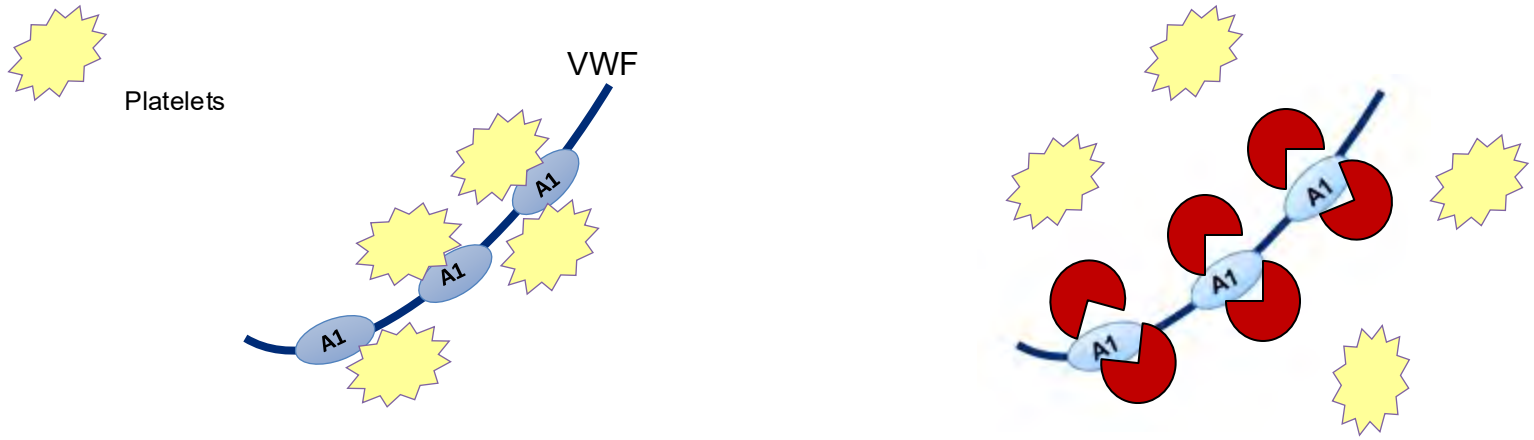


Clinical Management

Acute iTTP treatment 1991-2019



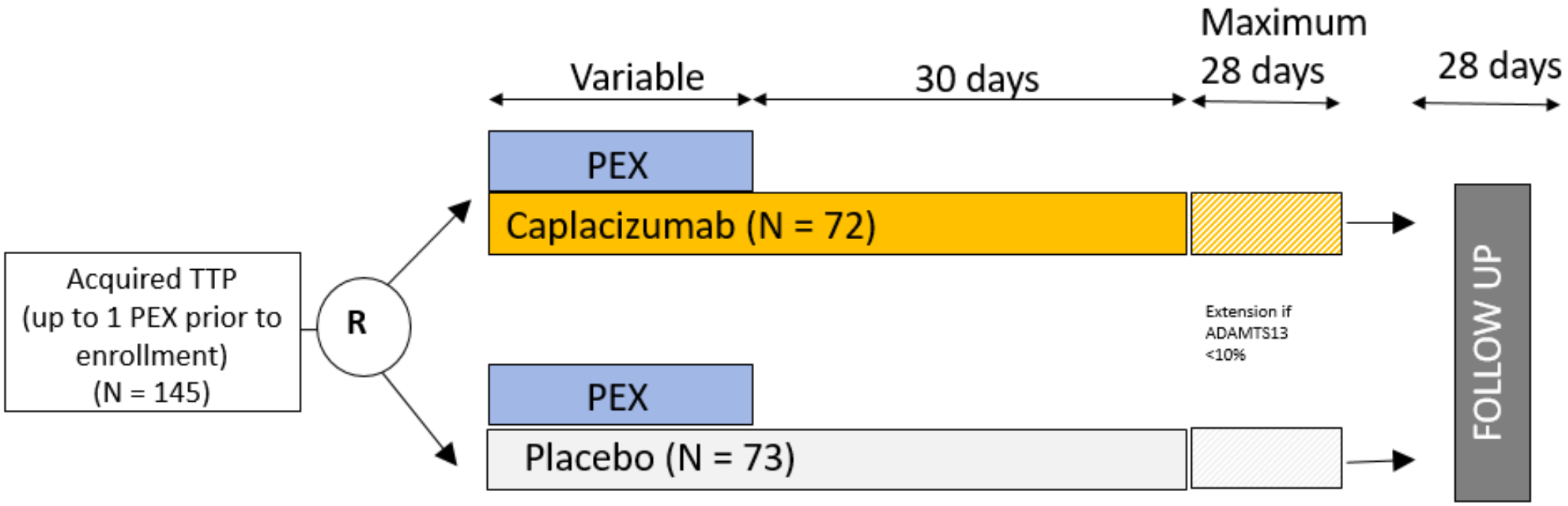
Caplacizumab: mechanism



- Caplacizumab - nanobody that binds to A1 domain of VWF and blocks VWF-platelet interaction

  - Faster resolution of thrombocytopenia
  - Prevents end organ ischemia

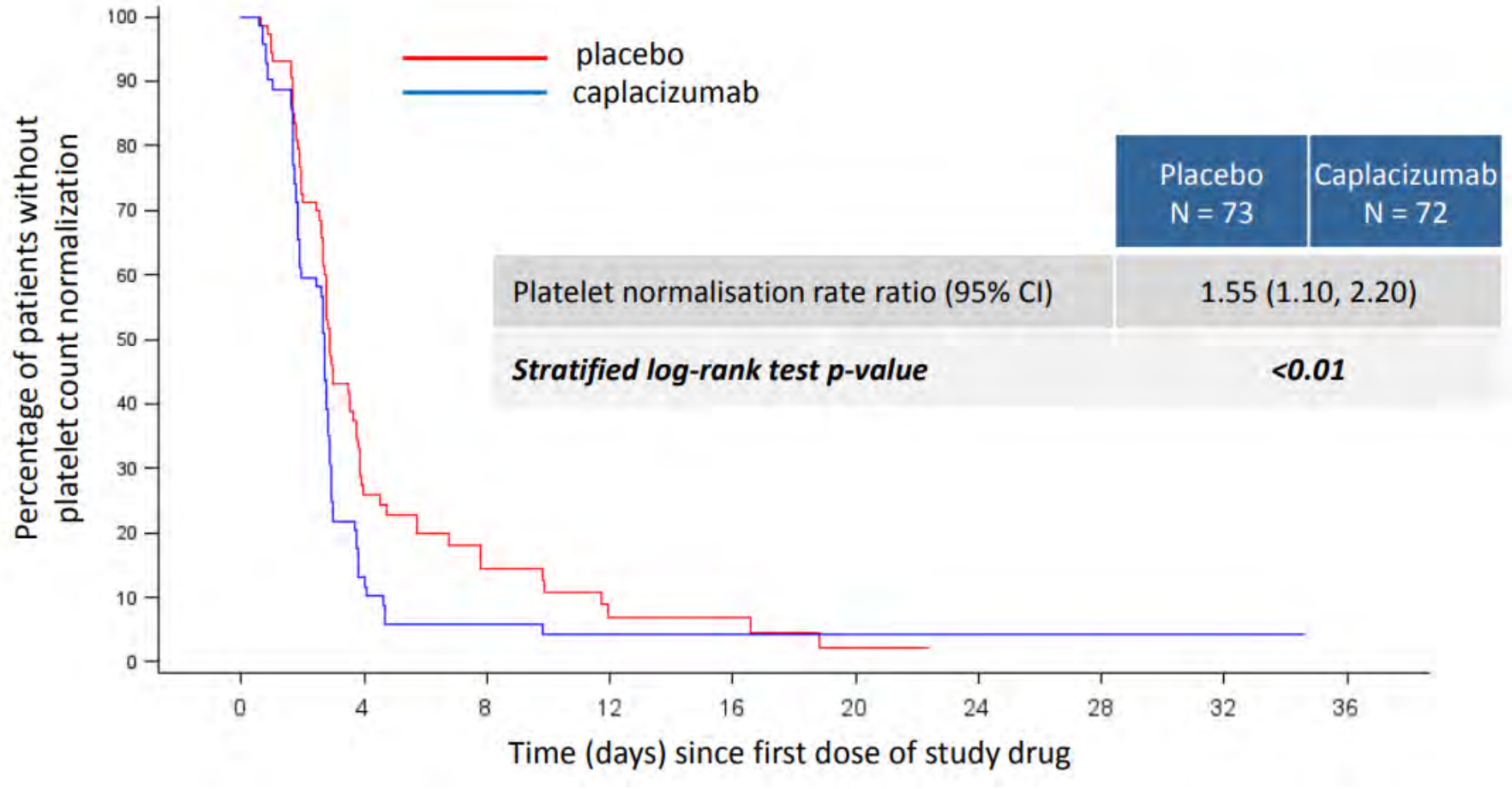
HERCULES - phase III trial of caplacizumab in TTP



- **Primary endpoint**: time to platelet count response (≥ $150x10^9$/L)
- **Secondary endpoints**: (i) TTP-related death, recurrence, thromboembolic events, (ii) refractoriness to tx, (iii) time to normalization of 3 organ damage markers

Scully et al. NEJM 2019

HERCULES: Time to Platelet Count Response (Primary Endpoint)



	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 : platelet count ≥ 150×10^9 /L with subsequent stop of daily PE within 5 days

Scully et al. NEJM 2019

HERCULES: Secondary endpoints, safety

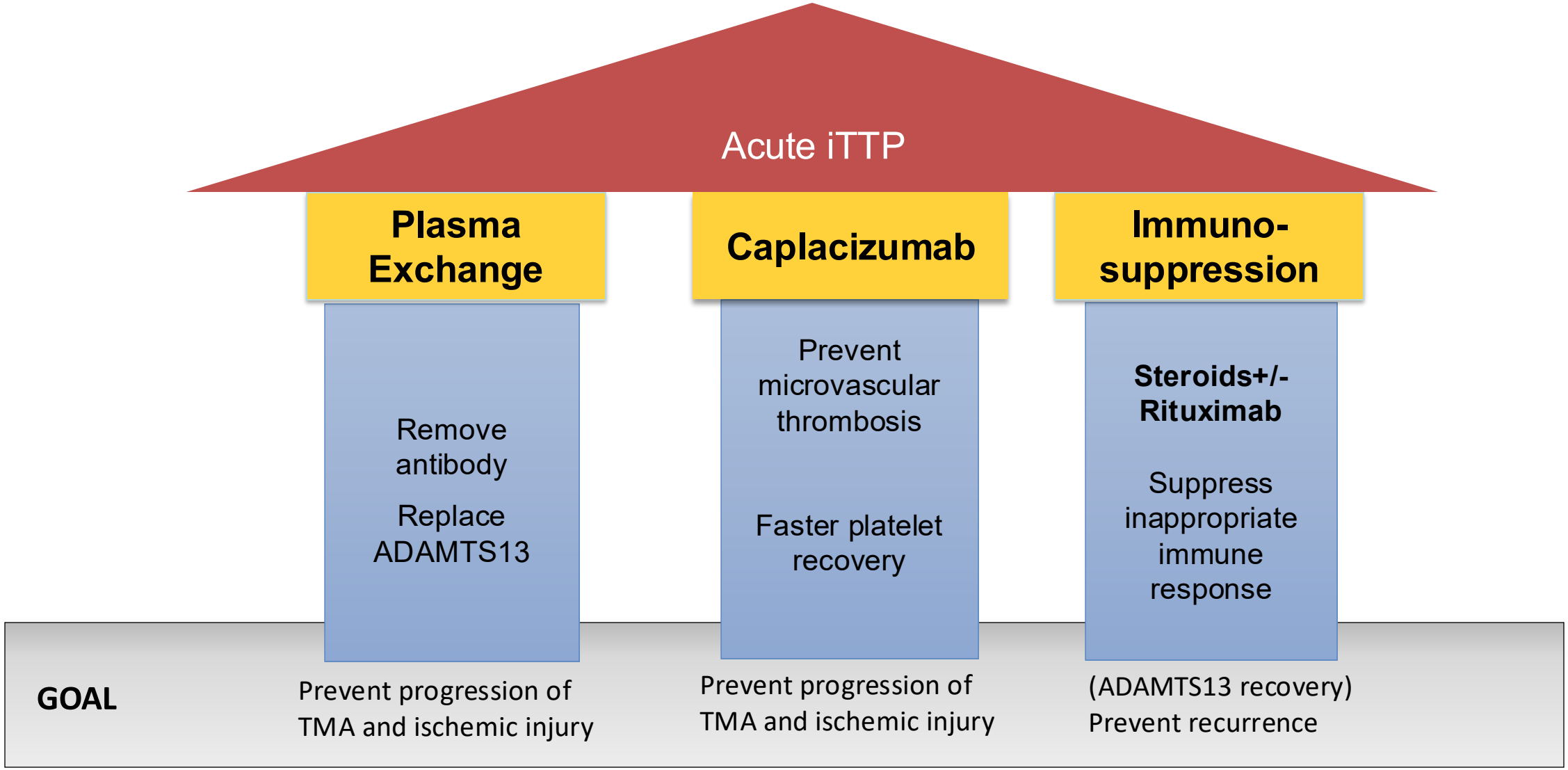
- Composite of TTP related death, recurrence and thromboembolic event with Caplacizumab
  - 12.7% versus 49.3%, 74% reduction

Recurrence	Caplacizumab	Placebo
TTP recurrence	12.7%	38.4%
During study (within 30 days of PEX)	4.2%	38.4%
During follow-up	9.1%	0

- Mild mucocutaneous bleeding was the predominant side effect (46% vs. 23%) -> major concern with caplacizumab use

Scully et al. NEJM 2019

Acute iTTP treatment in 2024



Clinical Response and Refractoriness in Immune Thrombotic Thrombocytopenic Purpura

Kühne L et al. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

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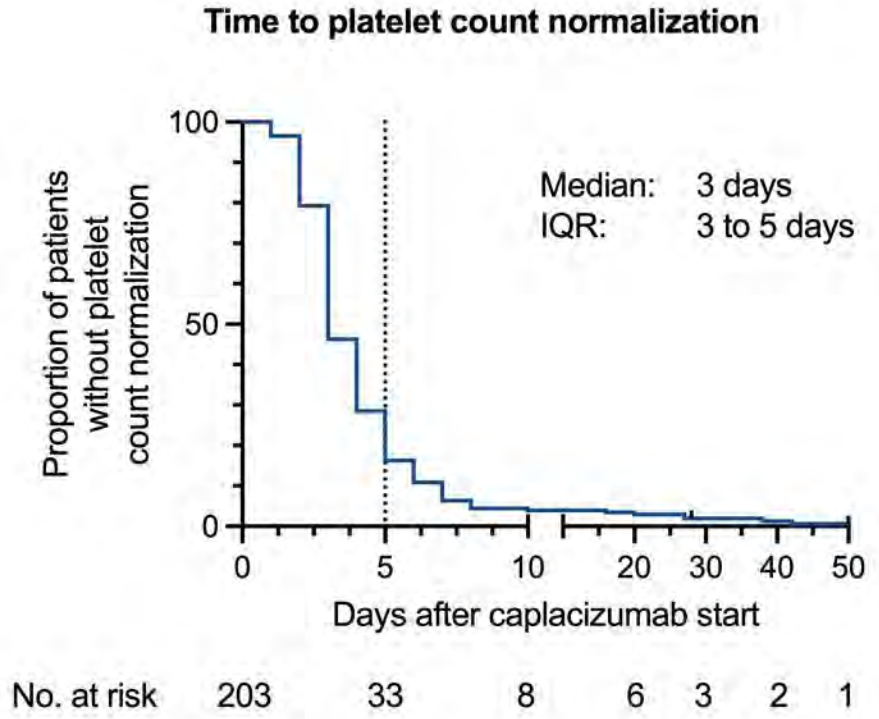
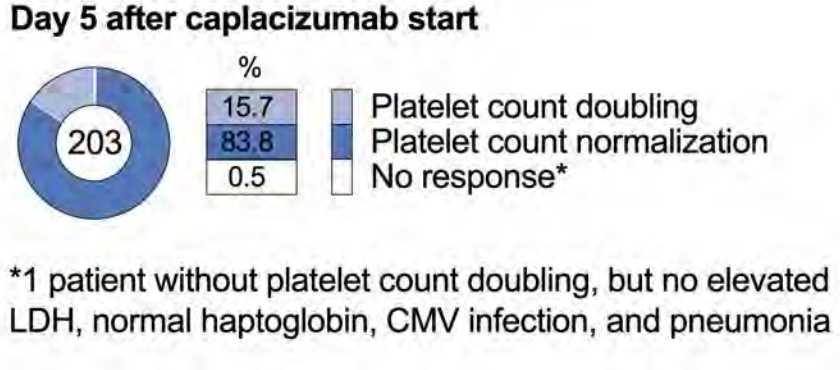
REACT 2020 Study

- Analysis to identify whether delayed platelet count recovery (with caplacizumab) indicates true refractoriness.
- Retrospective analysis of 203 caplacizumab-treated patients with iTTP from REACT-2020 registry

Formal refractoriness	2 pts (0.9%), both with missed doses or infections
Common causes of delayed response (> 5 days)	CMV, EBV, pneumonia, autoimmune or malignant disease

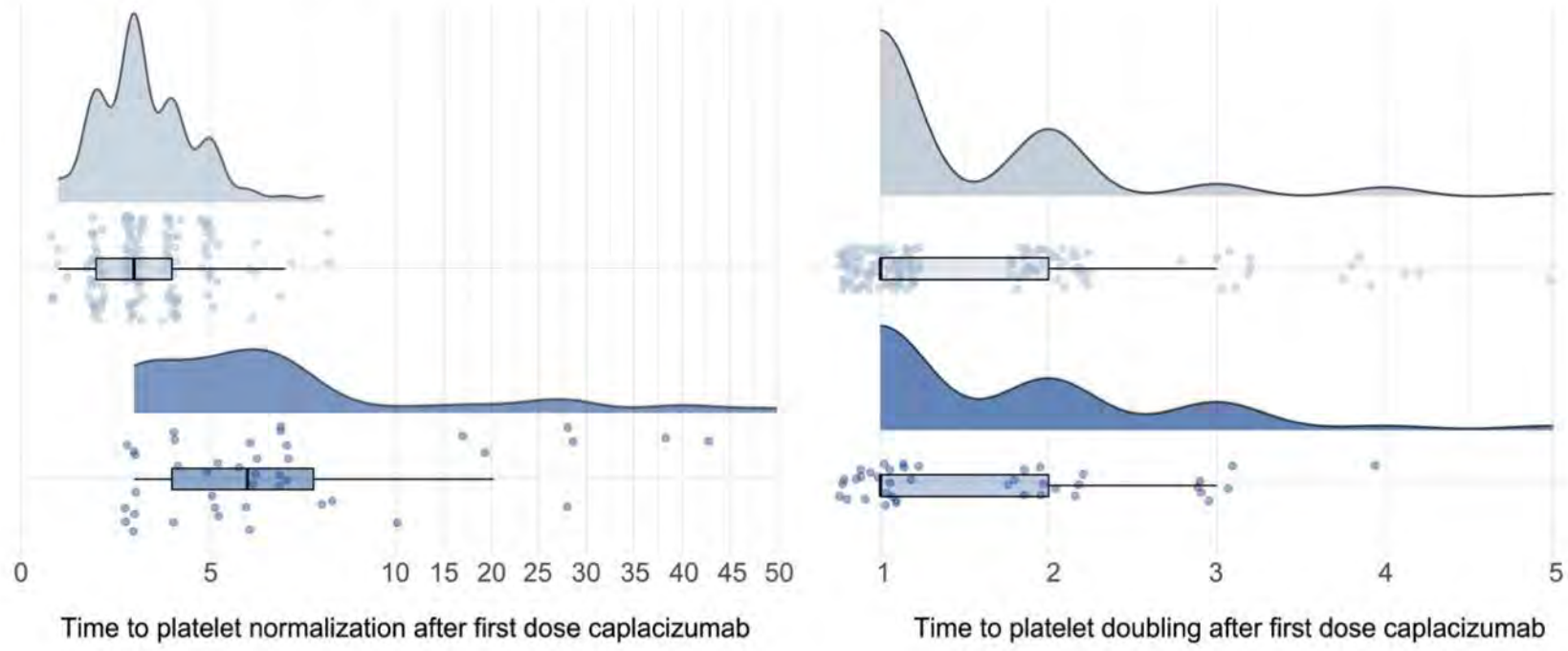




Kühne L et al. Clinical response and refractoriness in immune thrombotic thrombocytopenic purpura. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Comorbidities contribute to delayed response/ refractoriness

Differential analysis of time to platelet count doubling and time to platelet count normalization.
Upper (grey) panel: iTTP patients without concomitant diseases. Lower (blue) panel: iTTP patients with concomitant diseases.

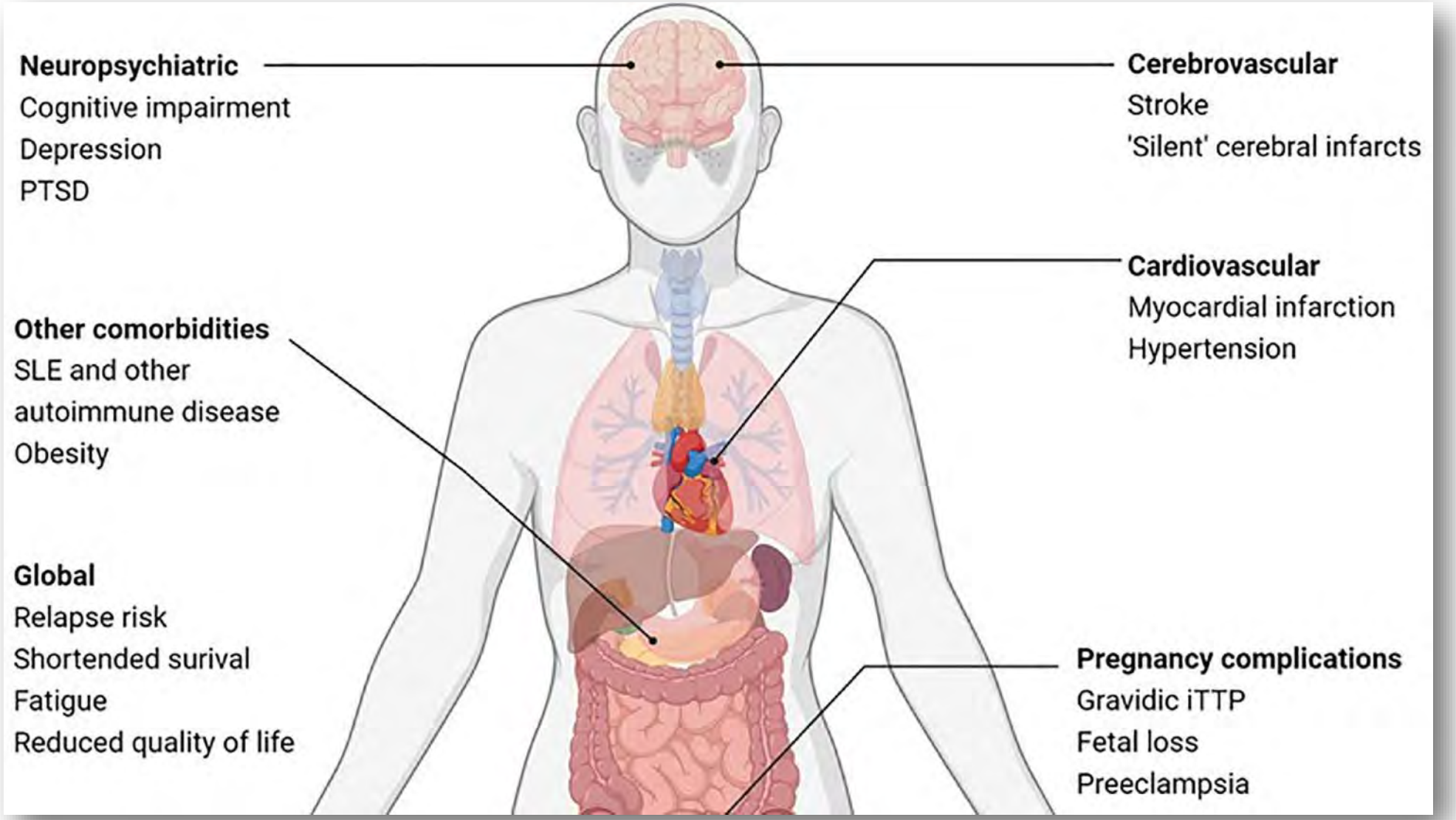


Kühne L et al. Clinical response and refractoriness in immune thrombotic thrombocytopenic purpura. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Conclusions

- iTTP refractoriness is extremely rare in caplacizumab-treated patients.
- Observation of prolonged times to platelet recovery should prompt further diagnostic workup to identify concomitant diseases and factors potentially counterfeiting uncontrolled iTTP, instead of primarily intensifying iTTP treatment.

TTP survivors are at risk for multiple adverse outcomes



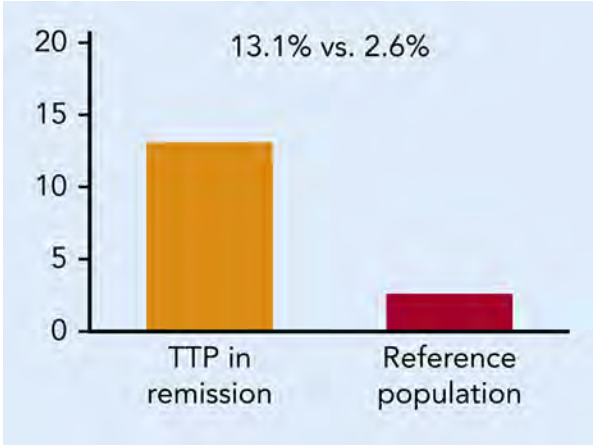
Selvakumar S, et al. Front Med. 2023;10.1137019.15 / 64134%

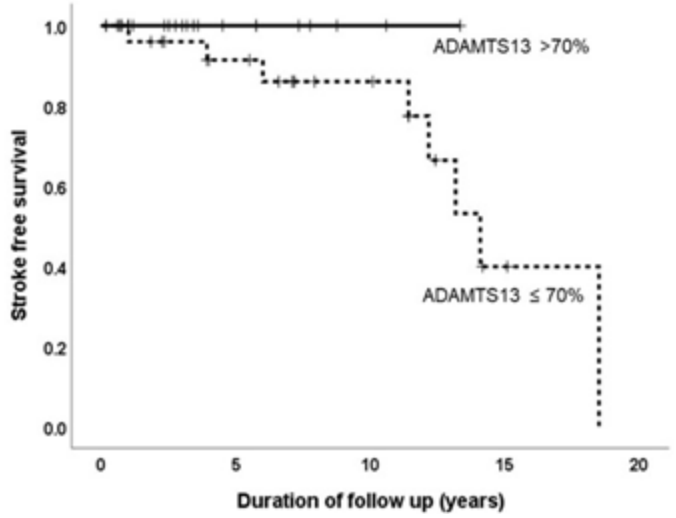
Persistent inflammatory and prothrombotic profile is associated with stroke risk in iTTP remission

Ahuja et al. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Stroke and vascular disease in iTTP survivors

- iTTP survivors are at increased risk of stroke and cardiovascular events.
- Reduced ADAMTS13 levels during clinical remission are associated with stroke risk.
- Cardiovascular disease is the leading cause of death in iTTP survivors.

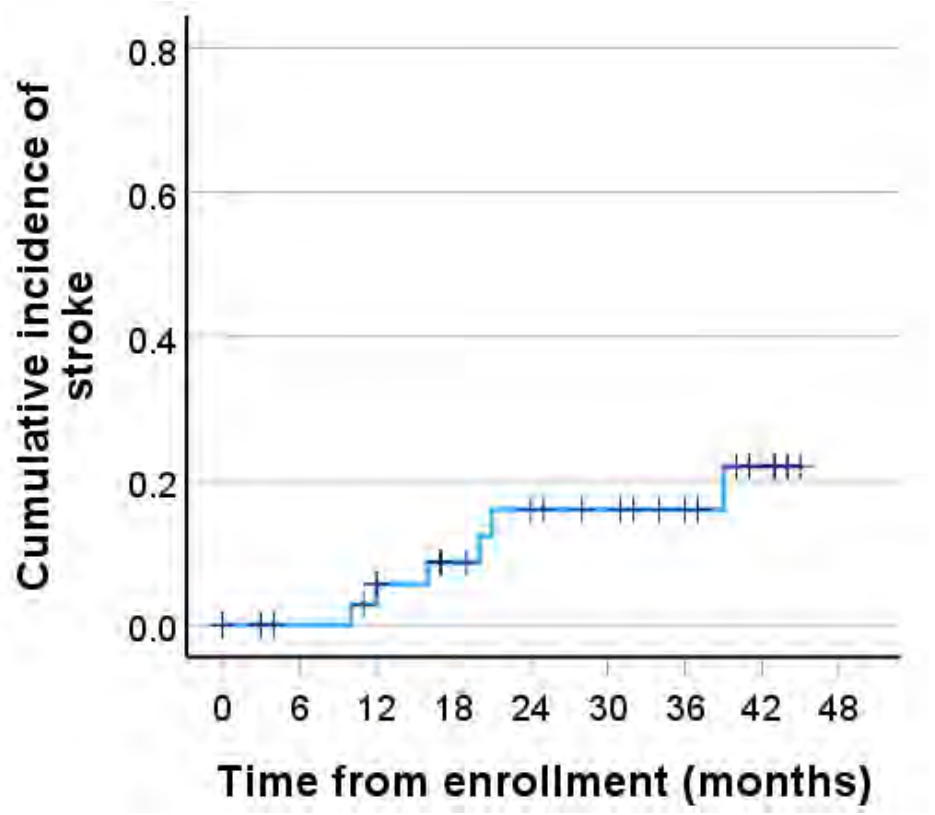




Upreti, et al. *Blood*. 2019, Sukumar et al. Blood Adv 2020, George JN. Hematology (ASH Education Program) 2018

ADAMTS13 deficiency does not entirely account for the increased vascular risk in iTTP survivors

- High rate of stroke in iTTP cohorts even when close to normal ADAMTS13 activity is maintained.
  - Median age: 47.5 (34.2, 54.2) years
  - Median avg. ADAMTS13: 73% (52%, 96%)
- Traditional cardiovascular risk factors are prevalent in iTTP cohorts but do not explain all of the increased risk.



Chaturvedi et al. ASH Meeting 2024 (Manuscript under revision)

Biomarkers and Stroke Risk During iTTP Remission

- Assessed whether a persistent proinflammatory/prothrombotic state during iTTP remission contributes to stroke risk
- Cross-sectional biomarker analysis comparing 48 iTTP remission samples to 22 healthy controls and 38 acute iTTP samples
- Cohort: 108 samples (38 acute iTTP, 48 remission iTTP, 22 controls) from the Johns Hopkins iTTP registry.
- 41 biomarkers measured using multiplexed chemiluminescence immunoassay (Meso Scale Discovery, USA).

Ahuja D et al. Persistent inflammatory and prothrombotic profile is associated with stroke risk in iTTP remission. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Biomarker profiles in acute iTTP and iTTP remission

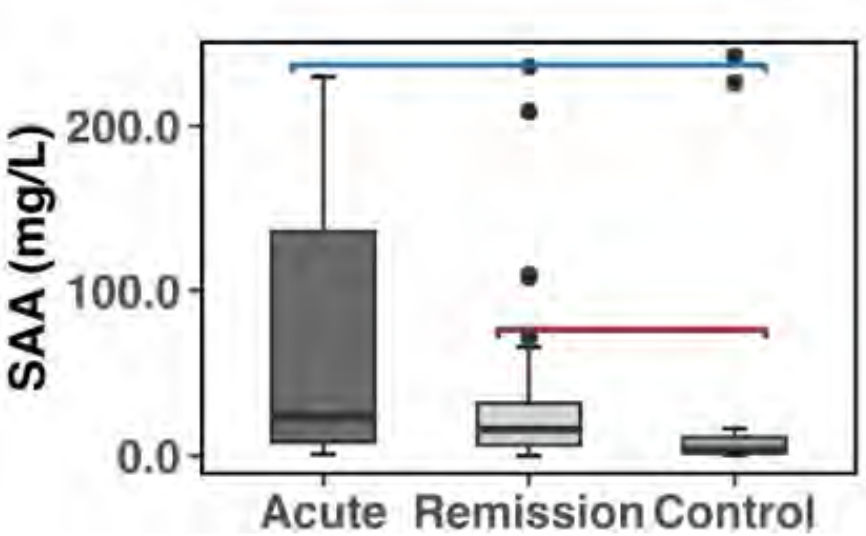
Analytes in pg/ml, all median (IQR)	Acute iTTP (n = 38)	Remission iTTP (n = 48)	Control (n = 22)	P (Remission vs. ctrl)*	P (Acute vs. ctrl)*
IL-1α	0.80 [0.49- 1.55]	0.76 [0.38- 1.53]	3.94 [2.34- 8.94]	**<0.0001**	**<0.0001**
TM (ng/mL)	5.40 [4.51- 6.38]	4.96 [3.86- 6.24]	3.32 [2.78- 3.65]	**<0.0001**	**<0.0001**
PIGF	6.21 [4.41- 8.84]	4.80 [3.45- 6.27]	2.99 [2.59- 3.40]	**<0.0001**	**<0.0001**
P-Selectin (ng/mL)	63.49 [50.24- 79.88]	43.84 [34.11- 52.48]	27.76 [25.06- 30.97]	**<0.0001**	**<0.0001**
VEGFD	847.95 [626.92- 1120.78]	955.15 [672.10- 1175.90]	621.44 [487.48- 699.51]	**<0.0001**	**0.0012**
bFGF	3.10 [1.75- 5.04]	2.21 [1.58- 3.56]	1.05 [0.91- 1.44]	**0.0001**	**<0.0001**
VEGFC	338.29 [235.68- 436.98]	697.65 [473.84- 840.32]	441.66 [388.06- 533.10]	**0.0003**	0.0038
TNF-β	0.22 [0.14- 0.49]	0.21 [0.15- 0.48]	0.70 [0.30- 1.59]	**0.0004**	0.0029
Eotaxin-3	11.25 [5.25- 21.17]	7.79 [3.85- 14.03]	16.79 [11.52- 19.84]	**0.0006**	0.0789
SAA (mg/dL)	23.29 [8.25- 135.98]	16.00 [6.60- 31.79]	3.34 [1.55- 11.29]	**0.0009**	**0.0003**
TIE2 (ng/mL)	2.28 [1.91- 4.90]	2.27 [1.89- 5.05]	1.76 [1.51- 2.20]	0.0028	0.0047
IL-6	1.68 [0.55- 3.78]	1.33 [0.67- 2.81]	0.57 [0.39- 0.95]	0.0051	0.0076
IL-16	1312.60 [591.43- 1888.58]	198.82 [135.84- 285.56]	156.42 [122.90- 175.86]	0.0209	**<0.0001**

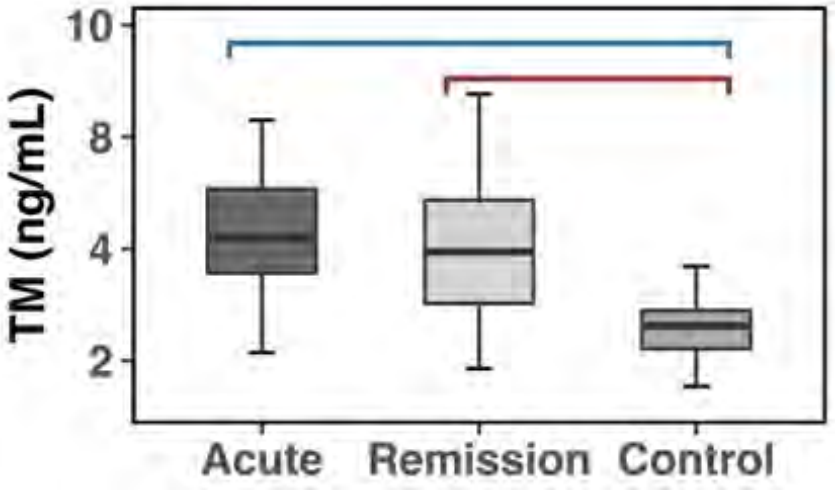
*P<0.00122 is significant

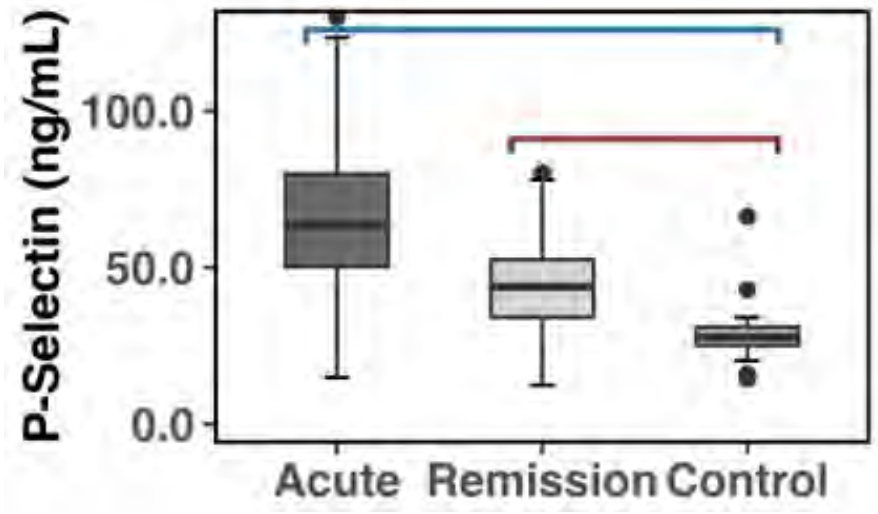
Elevated in remission vs controls

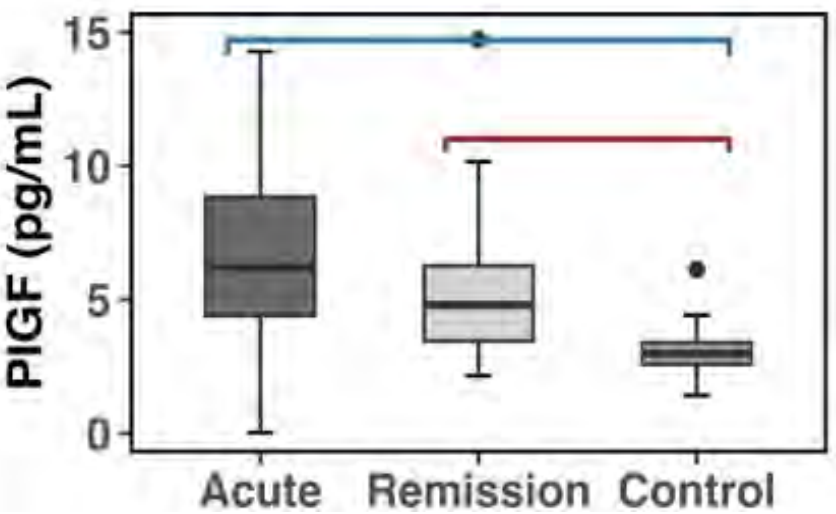
Lower in remission vs controls

Endothelial activation and inflammation markers in iTTP remission



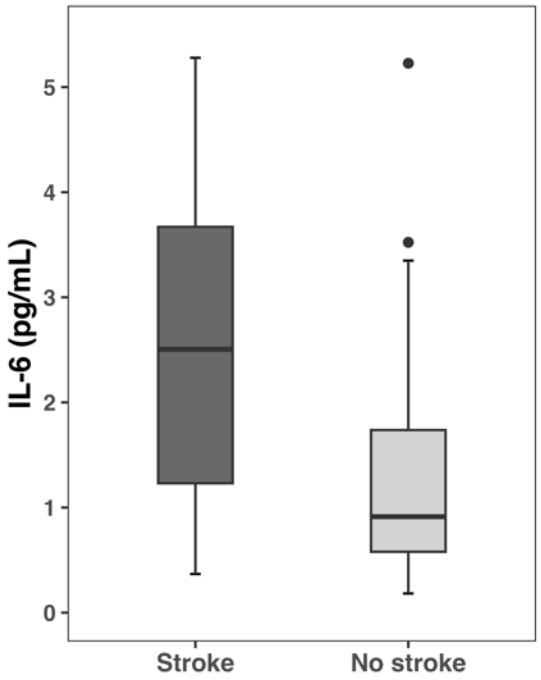


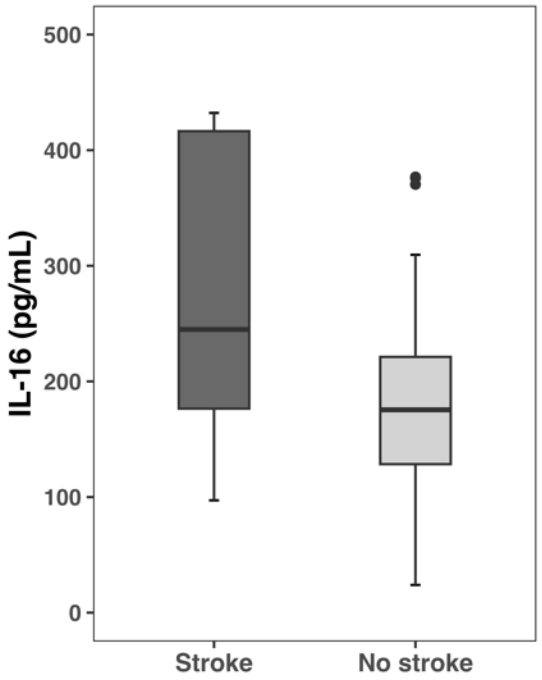


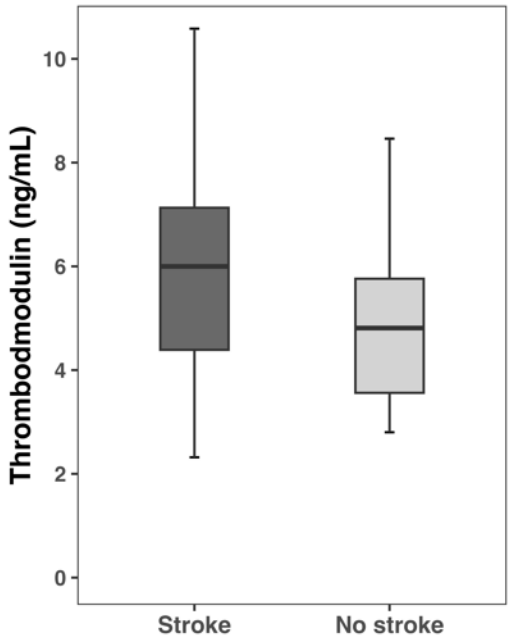


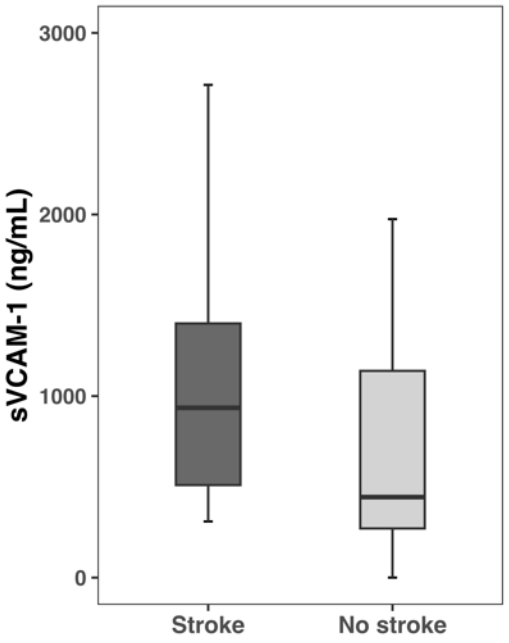
*P<0.00122 is significant

Biomarkers associated with stroke









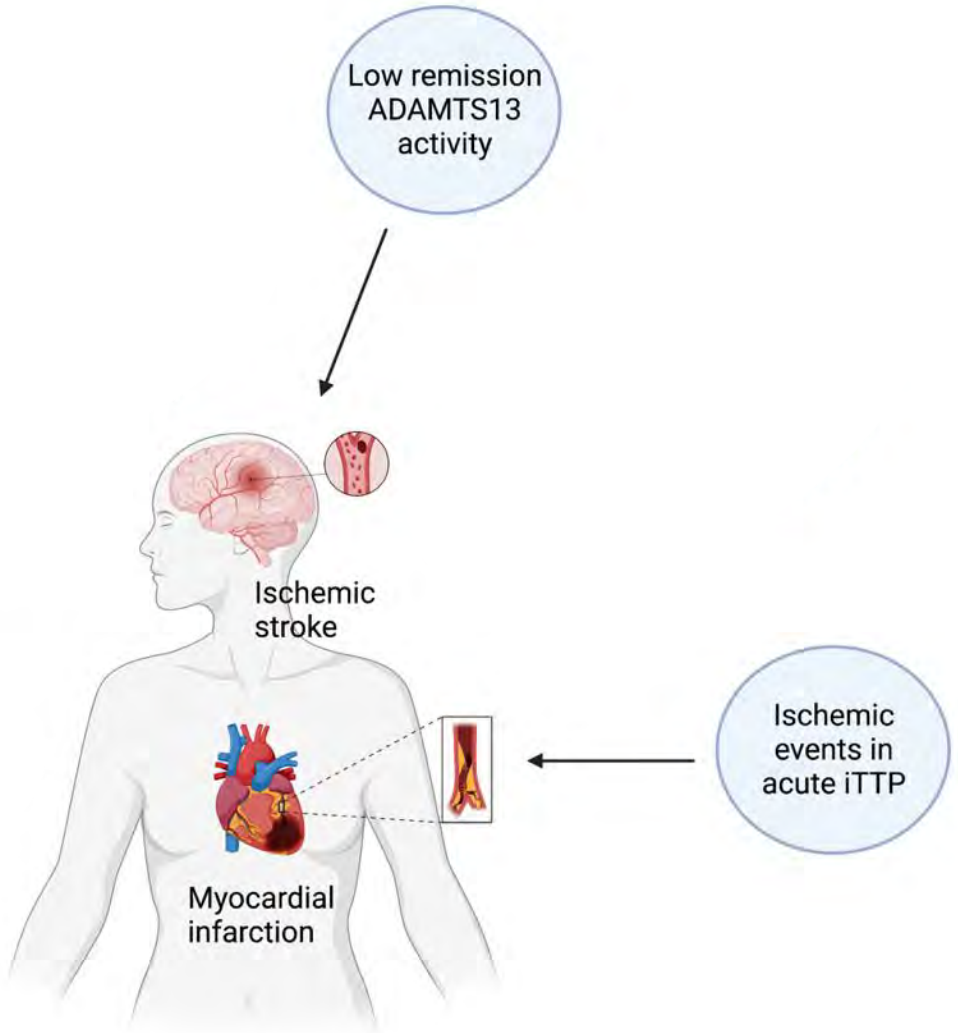
Marker level, median (IQR)	IL-6	IL-16	Thrombomodulin	VCAM-1
Stroke (18)	2.51 (1.23, 3.67)	244.95 (176.46, 416.45)	6.00 (4.39, 7.13)	935.25 (509.52, 1400)
No stroke (30)	0.91 (0.58, 1.74)	175.47 (128.44, 222.18)	4.81 (3.56, 5.76)	443.37 (270.78, 1138.67)
P value	0.012	0.017	0.048	0.039

Model performance – candidate biomarkers alone

Predictor	AUC	Sensitivity	Specificity	PPV	NPV	F1-score
IL-6 ≥ 1.83 pg/mL	0.72 (0.55 – 0.87)	66.67 % (35.7 – 85%)	76.67 % (58.6 –92.9%)	63.16 % (37.5 – 85.7%)	79.31 % (61.3 – 91.2%)	0.65 (0.36 – 0.79)
IL-16 ≥ 237.9 pg/mL	0.71 (0.55 – 0.87)	50 % (20 – 81.2%)	76.67 % (53.6 – 100%)	56.25 % (35.3 – 100%)	71.88 % (57.9 – 89.3%)	0.53 (0.29 –0.76)
Thrombomodulin ≥ 5.87 ng/mL	0.67 (0.49 – 0.84)	55.56 % (25 – 78.9%)	80 % (56.2 – 96.8%)	62.5 % (33.3 - 90%)	75 % (58.3 – 88.5%)	0.59 (0.31 – 0.75)
sVCAM-1 ≥ 540.04 ng/mL	0.68 (0.52 – 0.82)	72.22 % (50 – 92.3%)	56.67 % (34.5 – 77.8%)	50 % (31.8 – 70.6%)	77.27 % (61.3 – 93.4%)	0.59 (0.41 – 0.76)
IL-6 & IL-16	0.79 (0.64 – 0.92)	66.67 % (36.8 – 85%)	80 % (65.4 – 96.8%)	66.67 % (41.7 – 92.9%)	80 % (63 – 92.5%)	0.67 (0.41 – 0.82)

Footnotes: Metrics include absolute value with 95% CI obtained through 1000 bootstraps iterations
Abbreviations: AUC (Area under the curve); PPV: Positive predictive value, NPV: Negative predictive value

A more comprehensive model of vascular disease in TTP



Adapted from Sukumar et al. J Clin Med 2023

Conclusions

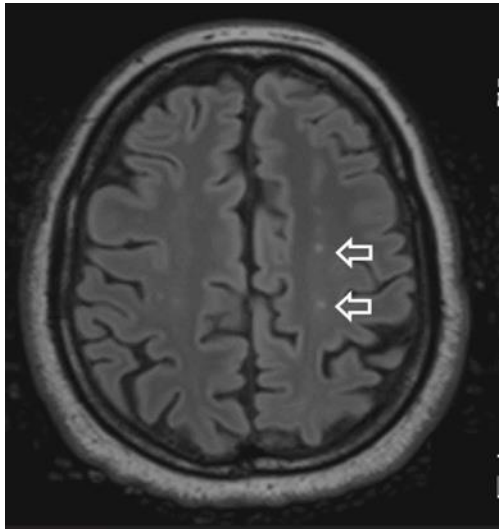
- Markers of inflammation and endothelial activation remain elevated in iTTP remission.
- Inflammatory (IL-6, IL-16) and endothelial (thrombomodulin,VCAM-1) markers in iTTP remission are associated with incident stroke.
- Clinical implications and future directions
  - These biomarkers may improve cardiovascular risk stratification in iTTP
  - Targeting inflammation (colchicine, canakinumab etc) may reduce morbidity from stroke in iTTP survivors.

Jenny et al. Neurology 2019, McCabe et al. Stroke 2023

The burden of cerebral small vessel disease in immune-mediated thrombotic thrombocytopenic purpura

Truma et al. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Silent infarcts (evidence of cerebral small vessel disease) are prevalent in TTP remission (> 50%)



Cognitive impairment

Unclear whether these lesions are progressive during clinical remission

Chaturvedi et al. Blood 2023

Prevalence and Progression of cSVD in iTTP

- Evaluated how common and progressive cerebral small vessel disease (cSVD) is in patients with iTTP
- Prospective MRI study during acute iTTP (median 7 days from admission) and after 1 year of remission

Variables	Acute (n=20)	After 1 year follow-up (n=10)
Female, n (%)	13 (65)	7 (78)
Age at episode (years), median	52	54
First episode, n (%)	16 (80)	8 (80)
Neurological signs/symptoms at presentation, n (%)	17 (85)	10 (100)
Hypertension, n (%)	6 (30)	2 (20)
Diabetes, n (%)	0 (0)	0 (0)
Obesity, n (%)	2 (10)	0 (0)
Smoking, n (%)	7 (35)	5 (56)
Hyperlipidemia, n (%)	7 (35)	4 (40)
Previous MACE, n (%)	0 (0)	0 (0)
Positive DWI, n (%)	7 (35)	0 (0)

Truma A et al. The burden of cerebral small vessel disease in immune-mediated thrombotic thrombocytopenic purpura. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Prevalence and Progression of cSVD in iTTP

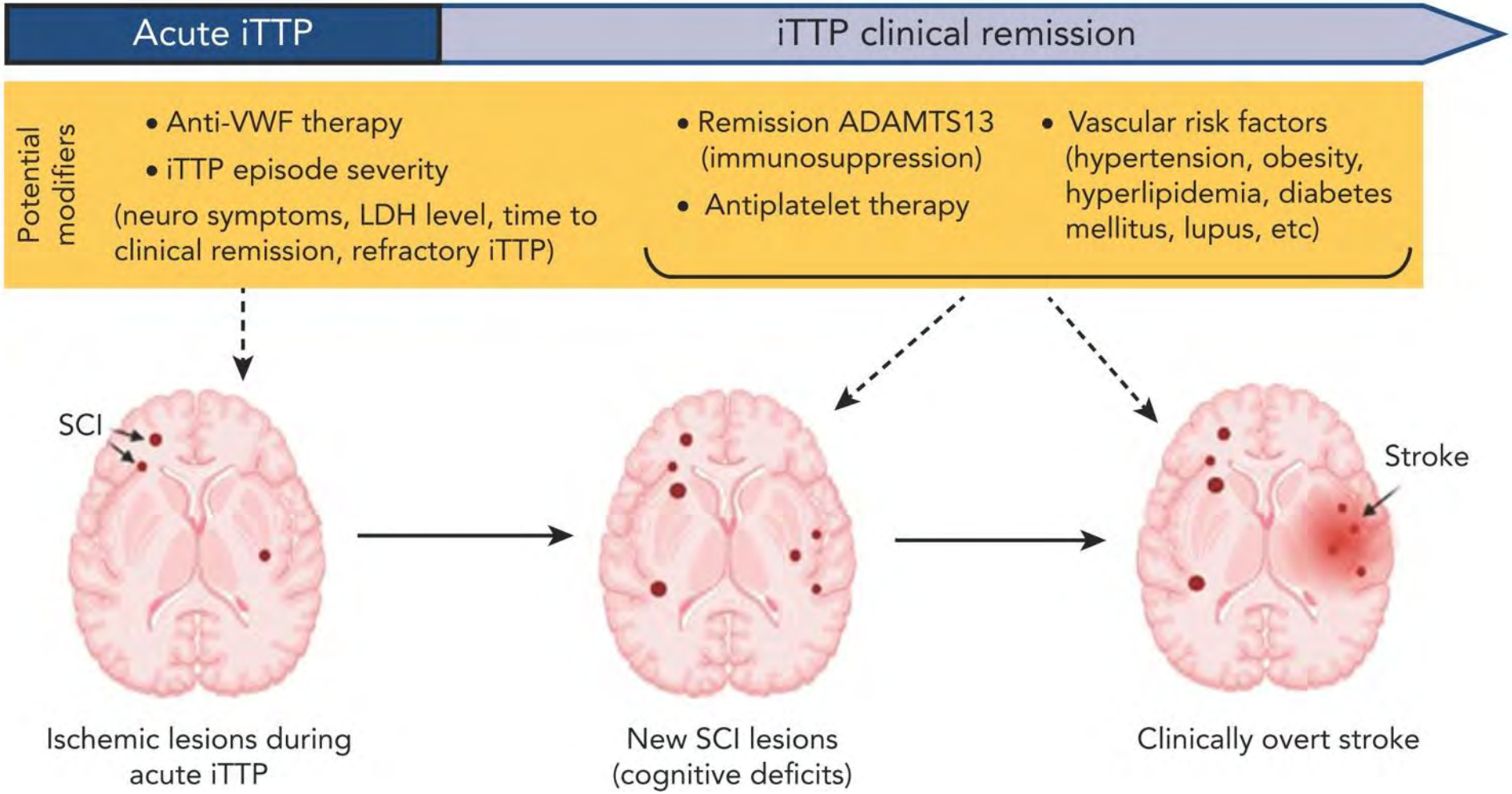
- During the acute phase, cSVD had a prevalence of 85% with a median score of 2 (IQR 1-2)

- 2 of 10 patients (all with cSVD at baseline) had progressive cSVD at 1 year MRI follow up
  - one with hypertension
  - one at the fourth iTTP event

Variables	Acute (n=20)	After 1 year follow-up (n=10)
Total cSVD score, n (%)		
0	3 (15%)	0
1	6 (30%)	3 (30%)
2	6 (30%)	4 (40%)
3	5 (25%)	1 (10%)
4	0	2 (20%)
cSVD burden, n (%)		
Low (score 0-1)	9 (45%)	3 (30%)
Moderate to high (score 2-4)	11 (55%)	7 (70%)

Truma A et al. The burden of cerebral small vessel disease in immune-mediated thrombotic thrombocytopenic purpura. Presented at: 33rd Congress of the International Society on Thrombosis and Haemostasis; June 21–25, 2025; Washington, D.C.

Proposed model for neurovascular morbidity in iTTP



Chaturvedi et al. Blood 2023

Clinical Pearls

- Prolonged platelet recovery is rarely a sign of true iTTP refractoriness in the caplacizumab era. Clinicians should evaluate for infections or comorbidities before intensifying treatment.
- Cerebral small vessel disease is common and prevalent during iTTP remission.
- Increased levels of IL-6, IL-16, and thrombomodulin during remission correlate with stroke risk and may enhance risk prediction beyond conventional clinical factors.