GIORNATE EMATOLOGICHE VICENTINE

XI edizione

9-10 ottobre 2025

Palazzo Bonin Longare - Vicenza

La riduzione dei danni a lungo termine nel paziente con TTP

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Disclosures

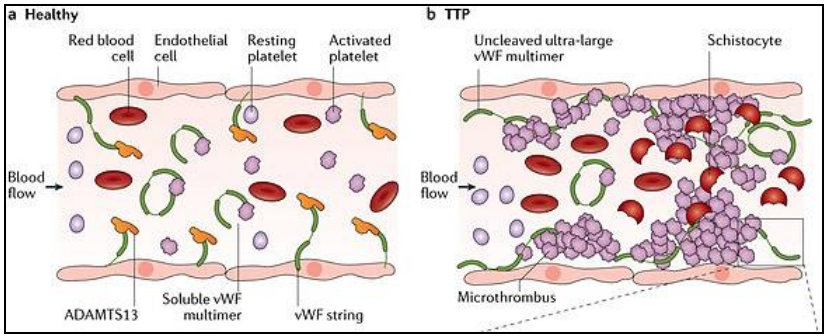
Sanofi: speaker at educational meetings

TTP: a life-threatening disease

Rare thrombotic microangiopathy:

- Platelet consumption → **severe thrombocytopenia**
- Red blood cell fragmentation → **Coombs-negative hemolytic anemia**
- Formation of platelet-rich thrombi in the microcirculation → **tissue ischemia** (**brain,** kidney, heart)
- **90% lethal** if not promptly treated

A microvessel in a healthy individual vs a patient with TTP

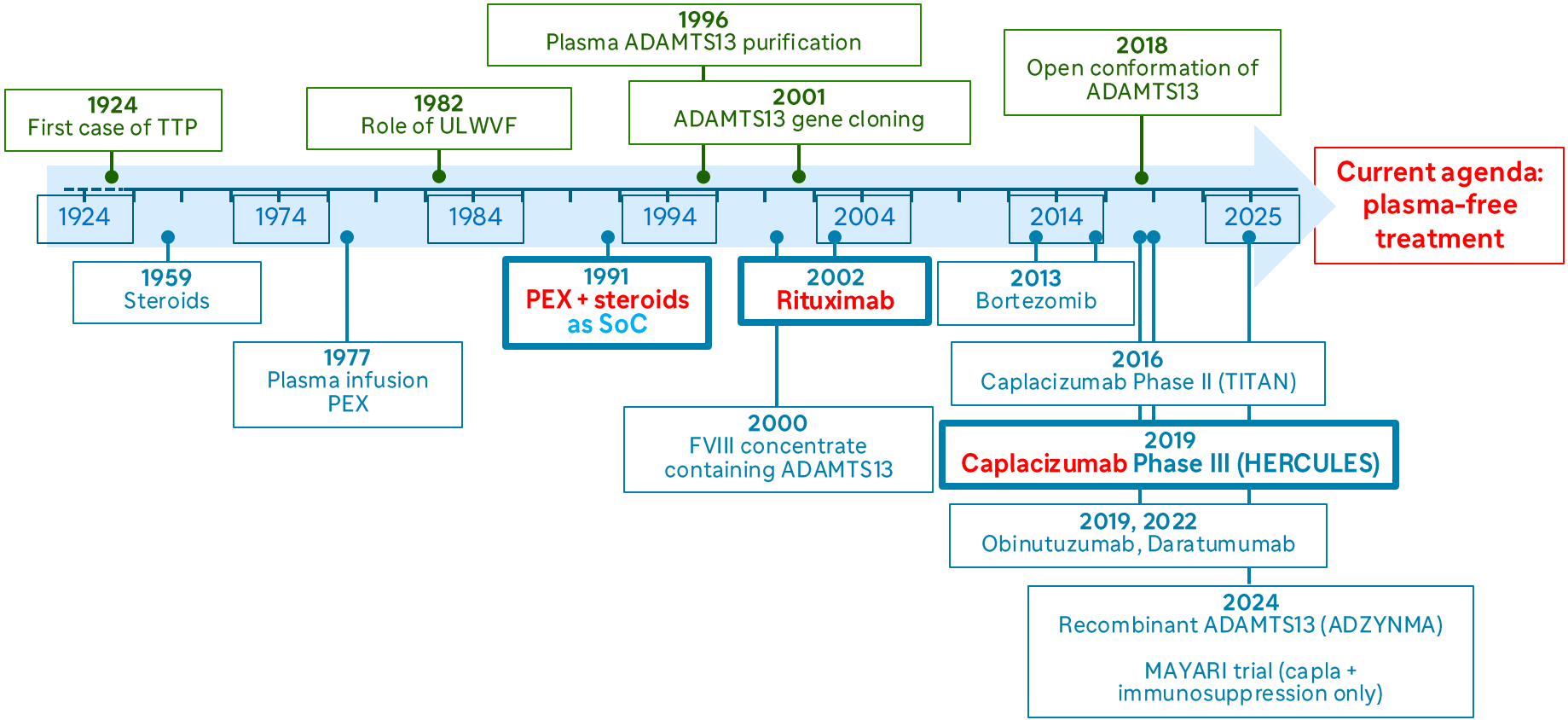


Caused by ADAMTS13 severe deficiency (activity <10% of normal)

- ADAMTS13 gene mutation [**congenital** TTP (**cTTP**)] **5%**
- Autoantibodies [acquired **immune-mediated** TTP (**iTTP**)] **95%**

Bhandari S, et al. N Engl J Med. 2019;
Zheng XL, et al. J Thromb Haemost. 2020

101 years of TTP



Cataland SR, et al. Blood. 2024

The impact of **CAPLACIZUMAB** on short-term outcomes

Results of the Capla1000+ project
An international, multicenter, retrospective study

	Capla + PEX (N=1015)	PEX (N=510)	p-value
Outcome			
3-month survival	98.5%	94%	<0.001 *
Clinical response	99%	94%	<0.001
Exacerbation rate	4%	32%	<0.001
Refractoriness	1%	10.1%	<0.001
Number of TPE to achieve clinical response	5 (4–8)	7 (4–16)	<0.001
Time to ADAMTS13 activity ≥20% (days)	29 (17–50)	31 (17–65)	0.07

* irrespective of rituximab use

Caplacizumab-related bleeding → **21%** patients

- 11% minor bleedings (>nose, gingival, bruises)
- 4% clinically relevant non major bleedings
- **2% major** bleedings (>digestive, menorrhagia)

Coppo P, et al. EClininalMedicine. 2025

Long-term management of iTTP: the need for follow-up

- 30-50% of iTTP patients eventually **relapse**
  (even >5 years after the first event)

- iTTP survivors can develop **long-term complications**
  (cerebrovascular and cardiovascular disease, neurocognitive impairment)

Two kinds of complications during iTTP follow-up

1

Complications with low ADAMTS13 (activity < 20%)

- iTTP relapse

2

Complications with slightly reduced/normal ADAMTS13 (activity > 20%)

- Major adverse cardiovascular events (MACE)
- Depression and PTSD
- Cognitive impairment

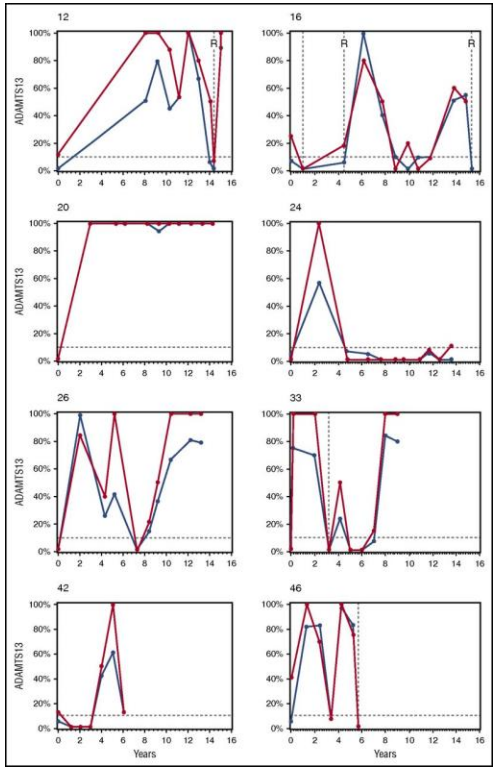
Increased mortality in iTTP survivors
1.8 times higher than matched general population

Data from the Oklahoma registry: 64% of deaths due to MACE, 18% due to iTTP relapse

Deford CC, et al. Blood. 2013;
Sukumar S, et al. Blood Adv 2022

How to prevent iTTP relapses: ADAMTS13 monitoring during remission

Low ADAMTS13 activity levels (< 20%) are associated with increased risk of clinical relapse



Data from the Oklahoma TTP Registry

- 10/17 (59%) patients with ADAMTS13 <10% during remission relapsed
- None of 24 patients with normal ADAMTS13 relapsed

Monitor ADAMTS13 during remission:

- Monthly for the first 3 months

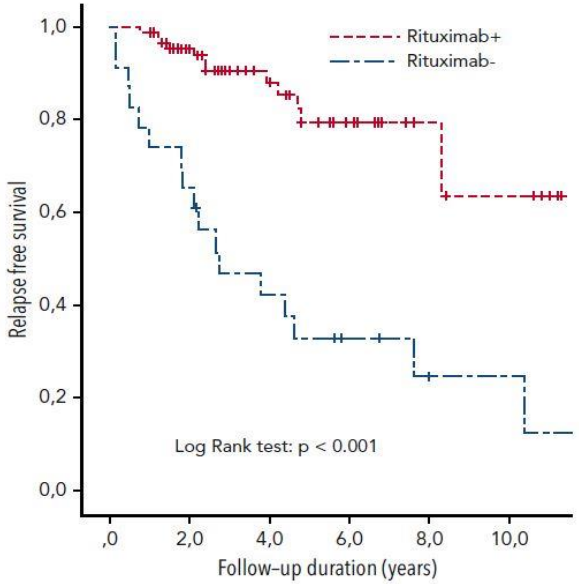
- Every 3-4 months for the first 2 year

- Then every 6-12 months (if stable) LIFELONG

Page EE, et al. Blood. 2016

How to prevent iTTP relapses: pre-emptive rituximab

- In case of ADAMTS13 relapse (activity <20%) during remission, **rituximab treatment** prevents clinical relapses
- Median duration of response: 17.5 months
- Retreatment with rituximab is successful



Pre-emptive rituximab (375 mg/mq/week x 4 weeks)
suggested for TTP patients in remission
who have low ADAMTS13 levels

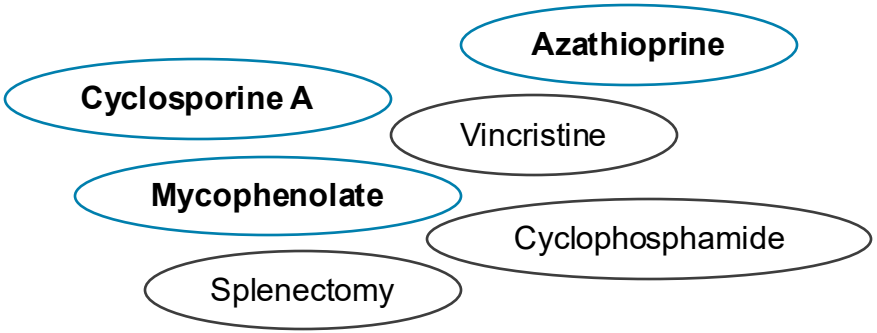
(conditional recommendation in the ISTH guidelines)

BUT…

- **10-15%** of patients do not respond to rituximab (> Black people)
- **ADAMTS13 relapse-free survival** may progressively **shorten**

Jestin M, et al. Blood. 2018; Long Zheng X, et al. J Thromb Haemost. 2020; Fatola A, et al. Blood Adv. 2025

What if rituximab doesn't work: the "traditional" immunosuppressants



Organ toxicity

Indefinite treatment duration

Pre-emptive azathioprine

48 subjects

- ADAMTS13 remission in 68% of patients
- Toxicity: gastrointestinal 44%, hepatopancreatic 28%, leukopenia 11%, acute myeloid leukemia n=1

Pre-emptive cyclosporine A

14 subjects

- ADAMTS13 remission in 93% of patients
- 40% relapse when discontinued
- Toxicity: kidney failure, gastrointestinal, gum hypertrophy

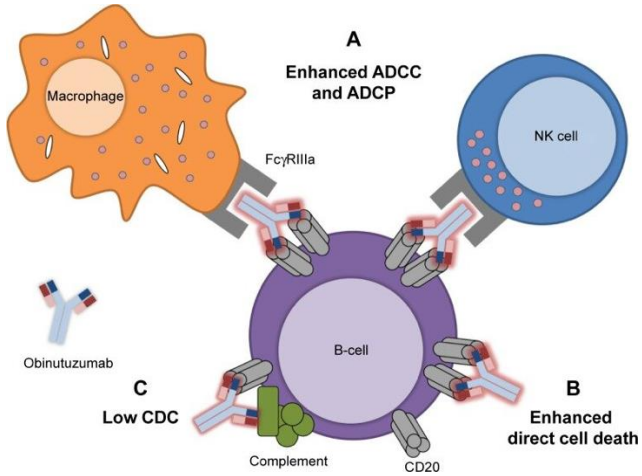
Bichard C, et al. Blood Adv. 2022;
Comparon C, et al. Eur J Haematol. 2023

What if rituximab doesn't work: **alternative anti-CD20 treatments**

OBINUTUZUMAB

French registry on **60 iTTP patients**:

- **77% ADAMTS13 remission** in **rituximab-refractory** patients (96% in rituximab-intolerant patients)
- 2-years relapse-free survival: 68% for RTX-refractory (84% for RTX-intolerant)
- Toxicity: n=6 mild/moderate infusion reactions



Doyle AJ, et al. Br J Haematol. 2022;
Weisinger J, et al. Am J Hematol. 2025

What if rituximab doesn't work: **bortezomib**

17 Italian patients
in the caplacizumab era

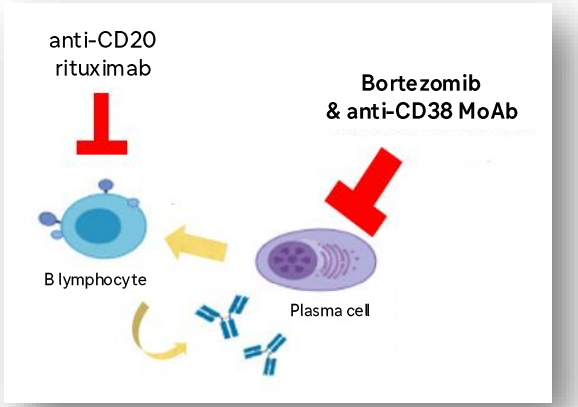
17/17 rituximab-refractory

11/17 refractory also to other treatments

- **Response: 59%** of patients
  (5 ADAMTS13 CR, 5 ADAMTS13 PR)
- Median **duration** of response: **22 months**

Toxicity:

- **47% of patients** (mainly G1-2 neurotoxicity)
- More frequent if ≥2 cycles



Use bortezomib to discontinue capla/PEX in refractory patients

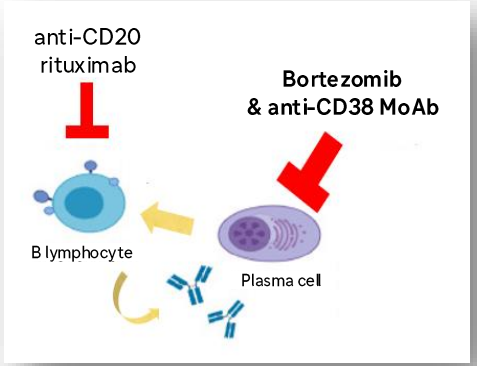
Watchful waiting after 1 cycle

Giannotta JA, et al. J Thromb Haemost. 2025

What if rituximab doesn't work: **daratumumab**

French registry on **7 patients** and 9 episodes (8 ADAMTS13 relapses + 1 acute TTP):

- All rituximab-refractory (1 bortezomib-refractory)
- **8 responses** (5 ADAMTS13 partial remission, 3 ADAMTS13 complete remission)
- Median duration of response: 9 months
- Toxicity: 5 mild infusion reactions



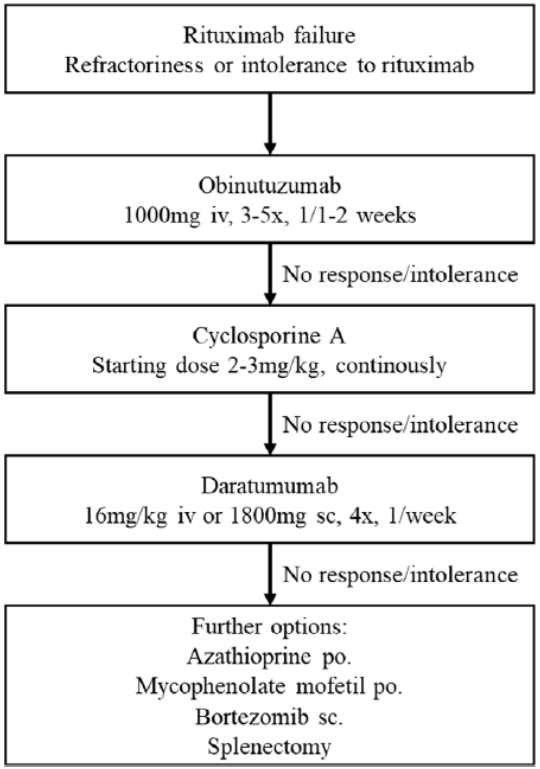
DartTP Study

Observational, international, multicentric study on daratumumab in iTTP

First 20 patients → poster ad ASH 2025

Weisinger J, et al. Br J Haematol. 2024

How to choose among second-line immunesuppressants in iTTP?



Our preferences:

- **Daratumumab sc/iv 4-8 weeks**

… but lacks long-term follow-up data

- **Azathioprine 0.5-1 mg/kg/day**
- **Mycophenolate mofetil 1-2 g/day**

Consider patient's values:

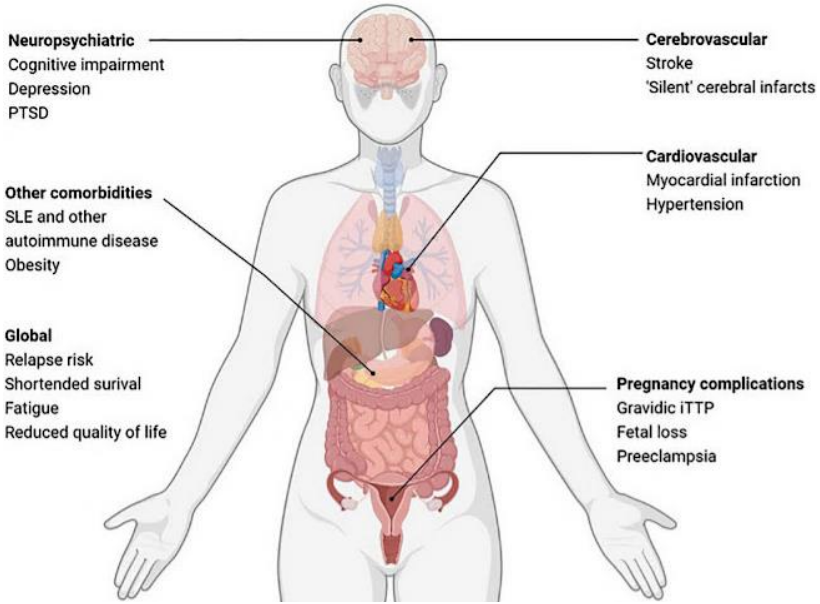
stability of response → Oral drugs

vs

fixed-term treatments → Monoclonal Abs

Weisinger J et al, Br J Haematol 2025

Long-term complications and comorbidities



Paradigm shift

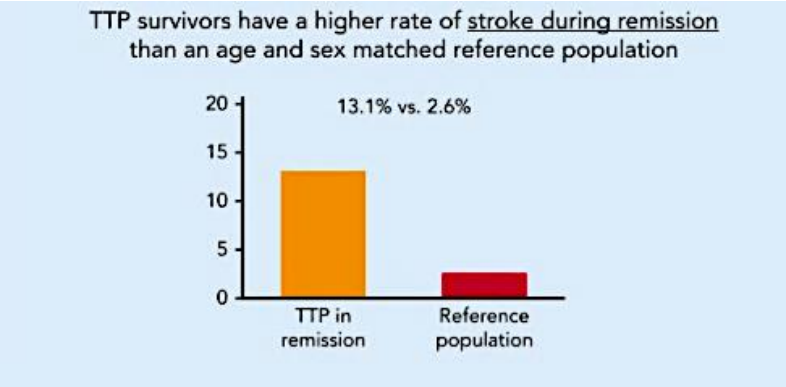
from a merely acute episodic disease

to a chronic disease

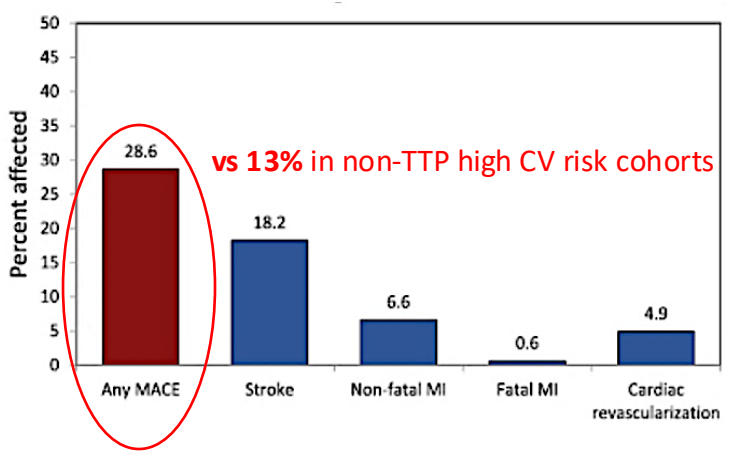
Selvakumar S, et al. Front Med. 2023

Major Adverse Cardiovascular Events (MACE) during TTP remission

Johns Hopkins cohort



Johns Hopkins + Ohio State cohorts

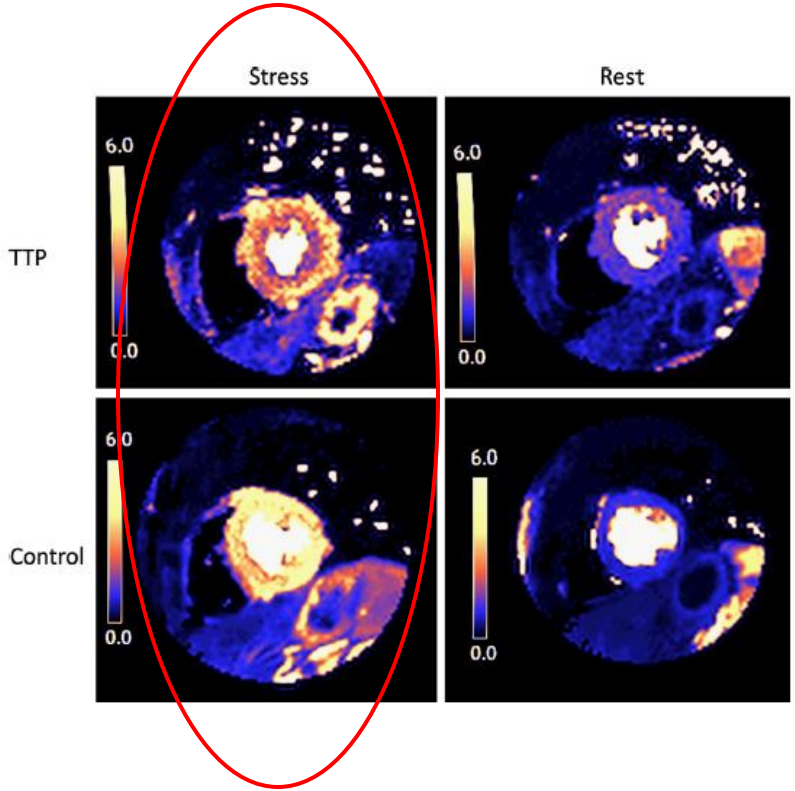


MACEs occur at younger ages

10/20 years earlier in TTP men/women vs general population

Upreti H, et al. Blood. 2019;
Brodsky MA, et al. Am J Hematol. 2021;
Sukumar S, et al. Blood Adv. 2022

TTP survivors exhibit impaired stress perfusion on cardiac MRI vs controls



- **Reductions** in quantitative **stress perfusion** in the TTP cohort in the **endocardium**
- **NO** correlation with ADAMTS13 activity and traditional CV risk factors

Endothelial dysfunction
may contribute to the higher cardiovascular mortality and increased frequency of MACE

Sukumar S, et al. Am J Hematol. 2025

Why so many MACEs in iTTP survivors: traditional cardiovascular risk factors?

- Hypertension, obesity, and autoimmune diseases (SLE) are more prevalent in iTTP survivors
- TTP patients during remission have increased urinary albumin secretion, a risk factor for CVD

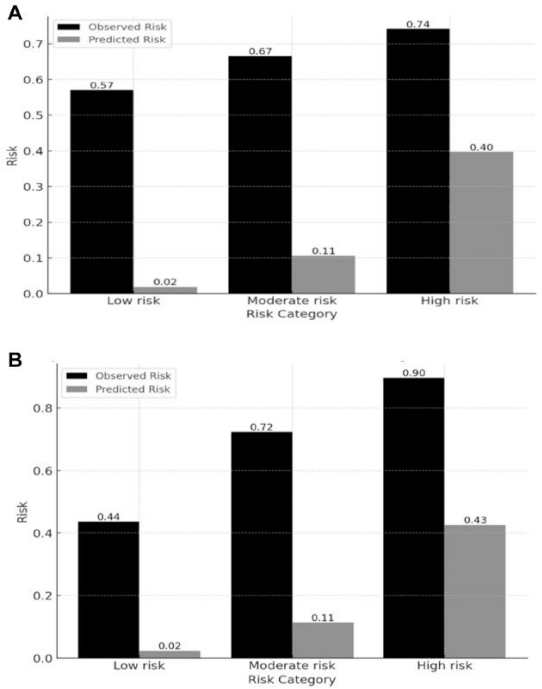
Received: 15 April 2025 | Revised: 9 July 2025 | Accepted: 7 August 2025
https://doi.org/10.1016/j.rpth.2025.103005

ORIGINAL ARTICLE

Standard cardiovascular risk prediction scores underestimate risk in immune-mediated thrombotic thrombocytopenic purpura survivors

Binish Javed[1,2] | Jenna Brown[1] | Jay Meade[1] | Vijay Nambi[3] | Ang Li[4] | Shruti Chaturvedi[1] | Senthil Sukumar[4]

- MACEs in 37.8% of patients over 3.8 years
- The ASCVD and FHS models demonstrated
  - poor discrimination (c-statistics = 0.5)
  - poor calibration



Deford CC, et al. Blood. 2013; Little DJ, et al. Am J Kidney Dis. 2014; Javed B, et al. Res Pract Thromb Haemost. 2025

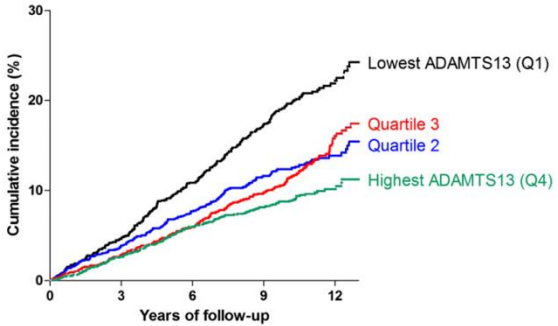
Why so many MACEs in iTTP survivors: a role for ADAMTS13 levels?

Lessons from the congenital TTP

- 20-30% of cTTP patients have stroke/TIA
- regular plasma/rADAMTS13 prophylaxis reduces stroke/TIA incidence (19.0% → 1.5%)

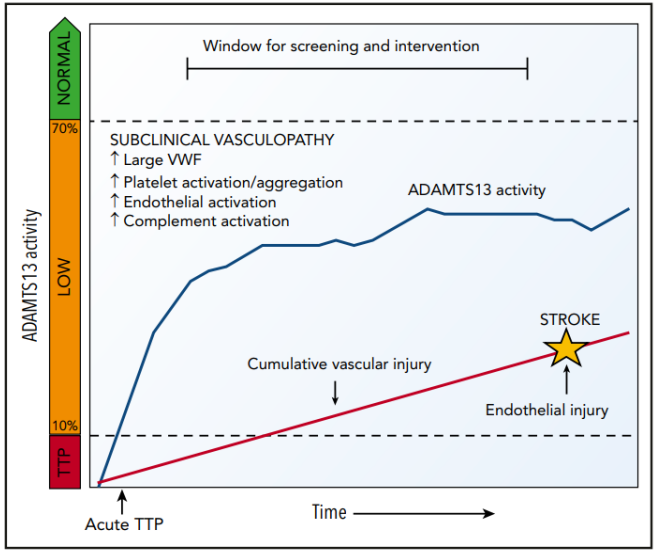
Lessons from general non-TTP cohort studies

- 5941 individuals >55 years without a history of stroke/TIA (Rotterdam Study)
- Low ADAMTS13 activity associated with the risk of ischemic stroke and improved the accuracy of risk predictions beyond traditional risk factors



No. at risk					
Quartile 1	1486	1304	1079	846	253
Quartile 2	1485	1366	1232	1053	292
Quartile 3	1485	1394	1270	1104	309
Quartile 4	1485	1399	1295	1153	279

The importance of the VWF:ADAMTS13 ratio

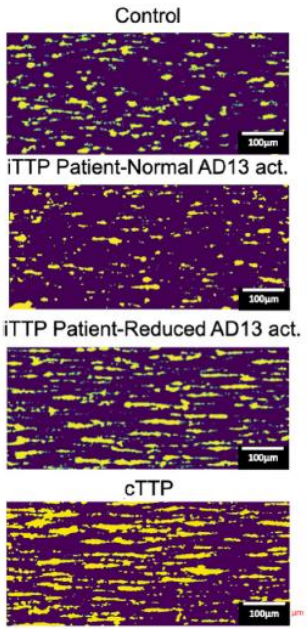


Sonneveld MAH, et al. Blood. 2015; Stubbs MJ, et al. Blood. 2025

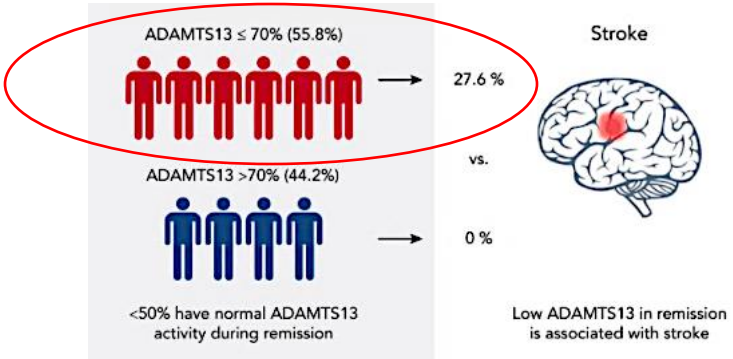
Why so many MACEs in iTTP survivors: a role for ADAMTS13 levels?

Ex vivo evidence in microfluidic chambers

- Platelet coverage increased on surfaces in cTTP and iTTP with normal platelet counts but low ADAMTS13 activity
- Surface coverage positively correlated with VWF:ADAMTS13 ratio



137 patients Johns Hopkins cohort



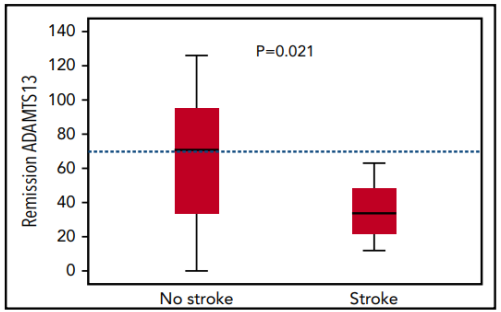


Figure 3. Average remission ADAMTS13 activity in patients without stroke (n = 43) and with stroke (n = 8). Median average remission ADAMTS13 activity

BUT… 181 patients Johns Hopkins + Ohio State University

Cox regression analysis did **NOT** find a significant association of remission ADAMTS13 activity with MACE (HR 0.98 [95% CI 0.97–1.01], p = 0.228)

Upreti H, et al. Blood. 2019; Brodsky MA, et al. Am J Hematol. 2021; Constantinescu-Bercu A, et al. J Thromb Haemost. 2025

Mental health problems in iTTP survivors

Post-Traumatic Stress Disorder

35% of survivors

Depression

80% of survivors

(36% severe)

RISK FACTORS

- younger age
- pre-existing anxiety disorder
- unemployment due to TTP

→ Early detection after discharge

→ Early treatment

WHY?

- Acute TTP is life threatening ?
- Ischemic brain-cell injury during the acute episode ?
- Alterations in neurotransmitters ?

Chaturvedi S, et al. Thromb Res. 2017;
George JN. Hematol Am Soc Hematol Educ Program. 2018

Cognitive impairment in iTTP survivors

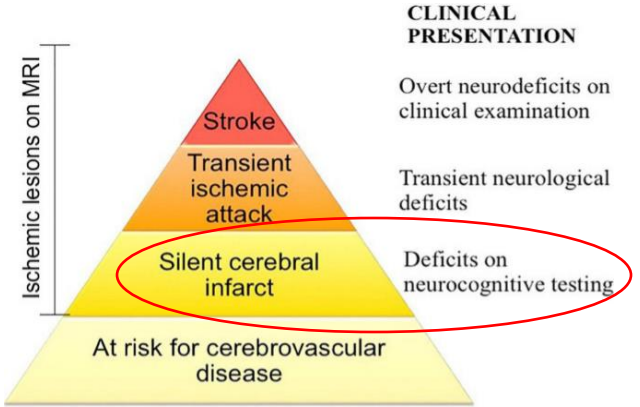
Memory and **concentration deficits** are reported in up to **60%** of iTTP survivors:

- complex attention and concentration skills
- information processing speed
- rapid language generation
- rote memorization

WHY?

- Comorbid **depression**
- Diffuse, subcortical **microvascular lesions** (e.g., patients with hypertension or sickle cell disease)
- **Silent cerebral infarction**

Spectrum of cerebrovascular disease in iTTP



Han B, et al. Am J Hematol. 2015; Cataland SR, et al. Am J Hematol. 2011; Chaturvedi S, et al. Blood. 2023; Selvakumar S, et al. Front Med. 2023

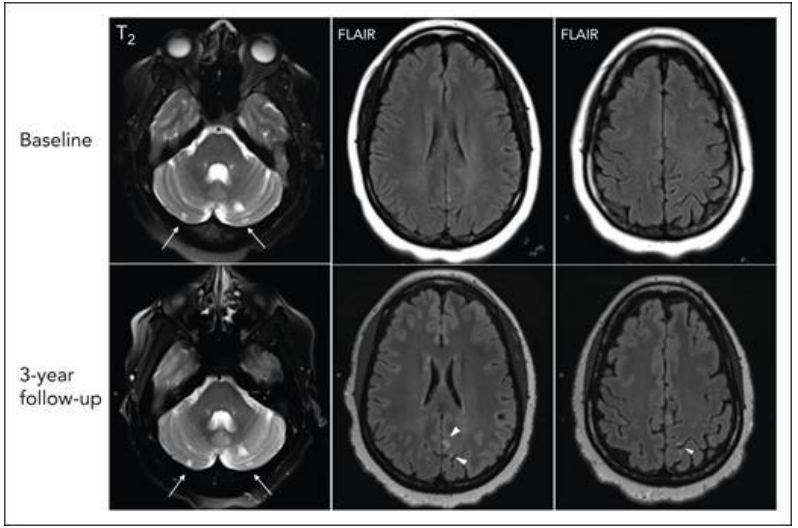
Silent Cerebral Infarctions (SCI) in iTTP

- **SCI in up to 50% of iTTP survivors**
- **MRI is** 2-3 times **more sensitive** than CT

- **Ischemic brain lesions can be progressive**
- New/progressive lesions in 38.5% of patients after 1 year

  in absence of clinical or ADAMTS13 relapse

- **Patients with SCI at baseline developed overt stroke** more frequently than those without (20% vs 0%)

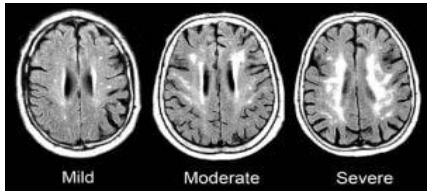


Alwan F, et al. Br J Haematol. 2020; Chaturvedi S, et al. Blood. 2023; Chaturvedi S, et al. ASH annual meeting. 2024

The burden of cerebral Small Vessel Disease (cSVD) in iTTP survivors

Hypertension, DM, SLE…

Microvascular dysfunction



Microvascular damage

White matter hyperintensities, lacune infarct, enlarged perivascular space, microbleeds

Higher cSVD score → higher risk of:

- Stroke
- Dementia
- Mortality

Preliminary results from our iTTP cohort

- Brain MRI at onset → +12 months
- N=25 iTTP vs N=26 controls

→ cSVD prevalence: 48% TTP vs 27% controls

→ Higher cSVD scores in iTTP vs controls

→ cSVD progression in 15% during follow-up, regardless of CV risk factors and time in ADAMTS13 remission

Truma A, et al. Article under revision

So, how to tackle long-term complications in iTTP survivors?

… Collaborating more and more!

The higher the ADAMTS13, the better?

⇩

Optimize immunosuppressive treatment

The microvascular damage starts in the acute phase?

⇩

Caplacizumab to all?

The microvascular damage accumulates during ADAMTS13 remission?

⇩

Strict control of CV risk factors, antiplatelet drugs? Target endothelium?

Matisse H, La Danse. 1909

The need for multidisciplinary care: our annual check-up

Neurologist

Ophtalmologist

Microvessel studies

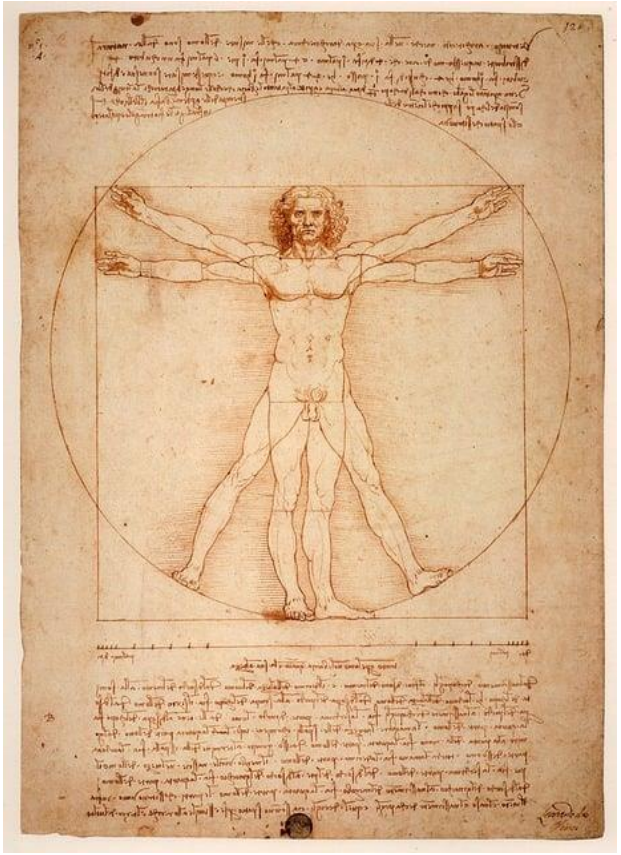
- Brain MRI + neuropsycho tests
- OCT angiography
- Nail capillaroscopy

Neuropsychologist

Cardiovascular studies

- Echocardiography
- Supra-aortic trunks and renal arteries doppler
- Metabolic profile + urinary albumine/creatinine ratio
- Behavioral / pharmacological correction of CV risk factors

Internal Medicine specialist



Psychology service

- Screening for PTSD and depression
- Psychotherapy

Psychologist

Hematologist

Immunosuppressive treatment (IST) re-evaluation

- Obtain higher ADAMTS13 levels
- Prevent relapses
- Avoid IST toxicity

Conclusive remarks

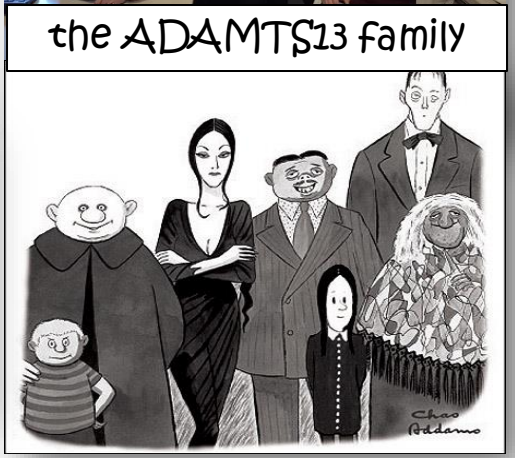
- TTP should no longer be managed as an emergency episodic condition, but as a chronic disease requiring a multidisciplinary approach
- ADAMTS13 monitoring is crucial to guide treatment during remission (pre-emptive rituximab)
- 10-15% of patients may not respond to rituximab, making the research on alternative immunosuppression a priority
- Although the current standard of treatment (PEX, immunosuppression and caplacizumab) reduced mortality to <2%, iTTP survivors still display increased mortality during remission because of increased cardio- and cerebro-vascular disease

European Reference Network | Hematological Diseases (ERN EuroBloodNet)

Andrea Artoni
Ilaria Mancini
Ada Truma
Pasquale Agosti

Thank you!

Flora Peyvandi



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Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

“Pensa agli altri” - Maḥmūd Darwīsh

Mentre prepari la tua colazione, pensa agli altri,
non dimenticare il cibo delle colombe.

Mentre fai le tue guerre, pensa agli altri,
non dimenticare coloro che chiedono la pace.

Mentre paghi la bolletta dell’acqua, pensa agli altri,
coloro che mungono le nuvole.

Mentre stai per tornare a casa, casa tua, pensa agli altri,
non dimenticare i popoli delle tende.

Mentre dormi contando i pianeti , pensa agli altri,
coloro che non trovano un posto dove dormire.

Mentre liberi te stesso con le metafore, pensa agli altri,
coloro che hanno perso il diritto di esprimersi.

Mentre pensi agli altri, quelli lontani, pensa a te stesso,
e di’: magari fossi una candela in mezzo al buio.

>500 sanitari per Gaza al Policlinico
Milano, 2 ottobre 2025