Received: 3 June 2025 | Revised: 14 October 2025 | Accepted: 3 November 2025

https://doi.org/10.1016/j.jtha.2025.11.001

REVIEW ARTICLE

Immune-mediated thrombotic thrombocytopenic purpura as a model of systemic microvascular dysfunction: moving from an acute to a chronic disorder

Pasquale Agosti[1,2] | Elio Ingenito[2] | Addolorata Truma[1] | Andrea Artoni[1] | Flora Peyvandi[1,2]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

[2]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Correspondence
Flora Peyvandi, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Pace 9, 20122, Milan, Italy.
Email: flora.peyvandi@unimi.it

Funding information
This study was partially supported by the Italian Ministry of Health—Bando Ricerca Corrente (RC2024) and was supported by the Italian Ministry of Education and Research (MUR; "Dipartimenti di Eccellenza" Programme 2023-2027 [Department of Pathophysiology and Transplantation], Università degli Studi di Milano). The Hemostasis & Thrombosis Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is a member of the European Reference Network (ERN) on Rare Haematological Diseases (ERN-EuroBloodNet) Project ID number 101157011. ERN-EuroBloodNet is partly cofunded by the European Union within the framework of the Fourth EU Health Programme.

Abstract

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare and life-threatening thrombotic microangiopathy. More and more studies clearly show a high prevalence of several adverse long-term health issues following recovery in these patients. Therefore, nowadays, the paradigm of iTTP as an acute episodical disease is quickly changing and should be considered a chronic disorder. The present review focuses on the 2 main long-term complications occurring during clinical remission in these patients (ie, cardiovascular and neurological complications). Our goal is to provide an updated overview of this topic, explaining the main related pathogenic mechanisms and highlighting how iTTP is emerging as a model not only of acute systemic microvascular dysfunction but also of chronic systemic microvascular dysfunction. The most accredited hypothesis supporting the chronicity of the disease is that, after recovery from an acute iTTP episode, a state of cumulative microvascular damage could persist and progress over time. However, the trajectory remains rather unpredictable, and there is still poor evidence on preclinical biomarkers able to identify those patients at higher risk of long-term cardiovascular and neurological complications, as well as drugs able to prevent chronic cardiac or brain organ damage. To date, there are no clear guidelines in this field, and clinical practice is quite heterogeneous across reference centers. A task force within the scientific community would be important for standardizing the most appropriate monitoring tools and preventive approaches to long-term complications in iTTP patients.

KEYWORDS
ADAMTS13, microangiopathies, microcirculation, small vessel diseases, thrombotic thrombocytopenic purpura

Manuscript handled by: Hanny Al-Samkari

Final decision: Hanny Al-Samkari, 3 November 2025

1 | INTRODUCTION

1.1 | Thrombotic thrombocytopenic purpura as a model of microcirculation dysfunction

The term "microcirculation" refers to the "terminal end" of the systemic circulation, including the smallest blood vessels (diameters < 20 μm), such as arterioles, capillaries, and venules, where the exchange of nutrients, gases, and waste products between blood and tissues occurs [1].

In the presence of microcirculatory dysfunction (MCD), tissue perfusion becomes inadequate, contributing to tissue damage and affecting vascular tone regulation and the coagulation state [2].

MCD plays a key role in many disorders, such as hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, and neurodegenerative diseases [3–7]. Moreover, growing evidence supports the concept that MCD is a systemic, multiorgan pathologic process characterized by shared pathways that affect organs, such as hemostasis, inflammation, and the immune and complement systems, through complex crosstalk among the heart, brain, and kidneys [8–11].

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening thrombotic microangiopathy, with a reported annual incidence of 2 to 6 cases per million people, and a mortality rate <5% if adequately treated [12–14]. TTP may serve as a paradigmatic model of MCD. Indeed, the underlying pathogenic mechanism of the disease is a severe deficiency of the von Willebrand factor (VWF) cleaving protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). ADAMTS13 deficiency leads to the accumulation of ultralarge VWF multimers that, under shear stress, bind to platelets, resulting in microvascular occlusion by platelet-rich thrombi and, ultimately, microangiopathic hemolytic anemia, consumptive thrombocytopenia, and multiorgan ischemia [12,15]. The disease is characterized by an episodic course, with a wide spectrum of clinical manifestations and various degrees of organ damage during the acute phase, secondary to the involvement of microvessels, primarily in the brain, kidneys, and heart [12,15–17]. In >95% of cases, a severe deficiency of ADAMTS13 activity results from the development of autoantibodies inhibiting the proteolytic activity of ADAMTS13 and/or accelerating its clearance (immune-mediated TTP [iTTP]) [15,18]. This form is more common in adult women (female-to-male ratio 3:1) aged 30 to 40 years. In about 5% of cases, severe ADAMTS13 deficiency results from genetic alterations in the *ADAMTS13* gene (hereditary or congenital TTP [cTTP]) [12,15]. Interestingly, recent large-scale analyses of large genome and exome sequencing data from apparently healthy individuals have revealed a higher-than-expected number of carriers of *ADAMTS13* pathogenic variants, leading to an estimated global cTTP prevalence of approximately 20 cases per million, 10 times higher than previously assumed [19]. These findings suggest that cTTP may be substantially underdiagnosed, although diagnosis is made in the context of a thrombotic microangiopathy presentation with evidence of persistent severe ADAMTS13 deficiency (<10% of normal) and absence of anti–ADAMTS13 antibodies. Furthermore, these findings raise the possibility that genetic variation in *ADAMTS13* could influence enzyme activity more broadly, potentially modulating disease susceptibility and phenotype not only in hereditary TTP but also in acquired forms of TTP.

2 | NEW PARADIGM ABOUT iTTP: FROM AN ACUTE TO A CHRONIC DISEASE

Traditionally, iTTP was considered an acute condition, and survivors were expected to return to their previous condition after recovery from an acute episode. The risk of disease relapse was considered the only complication during clinical remission. However, more and more studies clearly show a high prevalence of several adverse long-term health issues following recovery in these patients [20–24]. Data stemming from the Oklahoma TTP registry showed a significantly higher mortality rate (19%) compared with an age- and sex-matched United States or Oklahoma reference population, with cardiovascular disease as the leading cause of death [25]. Male sex, advanced age, and the number of iTTP episodes have been associated with increased mortality. Moreover, specific comorbidities (obesity, hypertension, major depression, and systemic lupus erythematosus) have been found to be more prevalent in these patients than expected and may contribute to reducing survival rate [23,25].

Interestingly, as suggested by Upreti et al. [26], after recovery from an acute episode of iTTP, a state of subclinical vasculopathy may lead to a state of cumulative vascular injury resulting from the complex interplay among large VWF multimers, inflammation, platelets, complement, and endothelial activation. This cumulative vascular injury may play a relevant role in increasing the risk of major adverse cardiovascular events (MACEs; ischemic stroke and acute coronary syndrome) and neurocognitive deficits, which are among the main long-term complications observed in these patients during remission.

Moreover, elevated VWF levels due to persistently low ADAMTS13 activity during clinical remission, together with ischemic injury from systemic microvascular thromboses during acute TTP episodes, may play a key role in causing persistent organ damage.

Therefore, nowadays, the traditional paradigm of iTTP as an acute or episodic disease is quickly changing. As explained above, iTTP may be considered a chronic disorder, and recovery from an acute episode may not represent the end of care but rather the beginning of long-term clinical management [22,27].

The main goal of the present review is to provide an updated overview of the 2 main long-term complications occurring during clinical remission in iTTP patients, cardiovascular and neurological complications, explaining the main pathogenic mechanisms and highlighting how iTTP is emerging as a model not only of acute systemic microvascular dysfunction but also of chronic systemic microvascular dysfunction.

TABLE 1 Long-term cardiovascular complications in immune-mediated thrombotic thrombocytopenic purpura patients during clinical remission.

Author (y)	Study design	Sample size (*n*)	Research question	Main findings	Limitations
Deford et al. [23] (2013)	Cohort study (Oklahoma TTP-HUS Registry)	57	Mortality rate during long-term follow-up; prevalence of main comorbidities.	TTP survivors have a greater risk of poor health and premature death	- Small sample size - The cross-sectional analysis design did not identify occurrences over a longer period of time
Upreti et al. [26] (2019)	Cohort study	137	Incidence of stroke; predicting the value of remission ADAMTS13 levels.	A higher risk of ischemic stroke during remission than in controls. ADAMTS13 activity levels <70% are associated with an increased risk of ischemic stroke.	- Small sample size - Limited follow-up - Included only strokes for which patients were hospitalized at JHH - No ADAMT-13 levels at the time of stroke - Heterogeneous frequency of ADAMTS13 measurements
Brodsky et al. [28] (2021)	Multicenter cohort study (Johns Hopkins University and Ohio State University)	181	Incidence of MACE; risk factors of MACE.	A higher incidence of MACEs during remission; earlier onset of MACEs than expected; ADAMTS13 is not associated.	- Small sample size - Limited follow-up - Retrospective data collection - Missed MACE managed in other centers
Sukumar et al. [25] (2022)	Cohort study	222	Main cause of mortality in iTTP patients.	Cardiovascular disease is the leading cause of death in iTTP survivors, who have a 2-fold higher mortality rate than the reference population.	- Small sample size - Limited number of deaths (29)
Chaturvedi et al. [29] (2023)	Cohort study	42	To determine the prevalence of SCI during TTP remission. To investigate the association between SCI and cognitive impairment.	MRI evidence of brain infarction is common in iTTP survivors. SCI was associated with cognitive impairment.	- Selection bias (single-center study) - Limiting generalizability - Small sample size - Missing data on ADAMTS13 - The study started in the precaplacizumab era
Yu et al. [30] (2025)	Cohort study	42	To evaluate the natural history of SCI during clinical remission and its association with the risk of stroke and cognitive decline.	SCI was progressive during clinical remission and correlated with a higher risk of stroke and cognitive impairment.	- Small sample size - Single-year MRI follow-up - Limited generalizability to other cohorts - Treatment heterogeneity

The table summarizes the main studies reporting data on long-term cardiovascular complications in iTTP patients during clinical remission.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HUS, hemolytic-uremic syndrome; iTTP, immune-mediated thrombotic thrombocytopenic purpura; JHH, Johns Hopkins Hospital; MACE, major adverse cardiovascular event; MRI, magnetic resonance imaging; SCI, silent cerebral infarction; TTP, thrombotic thrombocytopenic purpura.

3 | SEARCH STRATEGY AND SELECTION CRITERIA

We conducted a comprehensive search of Medline (PubMed) for full-text articles published in the English language from January 1, 2000, to August 31, 2025, using the following free-text terms in titles/abstracts: "thrombotic thrombocytopenic purpura" matched with "neurocognitive complication,*" "depression," "cognitive impairment," "cognitive decline," "major adverse cardiovascular event,*" "cardiovascular complication,*" "ischemic stroke," or "acute coronary syndrome." Preclinical studies, as well as case reports and case series, were excluded. Human articles resulting from this search (original articles and reviews) and relevant references cited in those articles were reviewed by 2 independent clinicians. The final reference list of original articles was selected based on the relevance of the topic covered in this narrative review. Therefore, only original articles exploring the cardiovascular and neurocognitive complications occurring during clinical remission in iTTP patients were selected and included in Tables 1 [23,25,26,28–30] and 2 [23,29,30–47].

4 | LONG-TERM CARDIOVASCULAR COMPLICATIONS: EVIDENCE FROM OBSERVATIONAL DATA

In a study by Deford et al. [23], the prevalence of hypertension (19%) and diabetes (9%) at the time of iTTP diagnosis was comparable with the general population. After a median follow-up of 7 years, it was found that iTTP survivors showed a higher prevalence of obesity, particularly morbid obesity (body mass index $\geq$40), as well as hypertension, compared with the US reference population [23]. In another study, patients in remission also exhibited significantly increased urinary albumin excretion, a known marker of increased cardiovascular risk [48].

Consistent with the observed increased prevalence of cardiovascular morbidities and risk factors, iTTP survivors show a significantly higher risk of ischemic stroke than expected during clinical remission. This has been clearly shown in a study enrolling 137 consecutive iTTP patients at the Johns Hopkins Hospital, of whom 18 (13.1%) experienced a stroke during remission over a median observation period of 3.08 years. This was 5-fold higher than the expected prevalence of an age- and sex-matched reference population (2.6%). Interestingly, among the 52 patients for whom ADAMTS13 activity was measured during remission, an ADAMTS13 activity level <70% was associated with an increased risk of ischemic stroke [26].

Two years later, in another study, the prevalence of MACEs during clinical remission (a composite of myocardial infarction, stroke, and cardiac revascularization) and the related risk factors were estimated in 2 large iTTP cohorts (Johns Hopkins University and Ohio State University). Of 181 patients followed for at least 3 months after recovery from an acute episode, 28.6% experienced a MACE over a median follow-up of 7.6 years. Stroke was the most common type of MACE (18.2%). Compared with the general US population, iTTP survivors experienced their first stroke at a younger age during remission. Age, ethnicity, and diabetes mellitus were associated with MACEs, whereas ADAMTS13 activity during remission was not significantly associated [28].

Emerging evidence also highlights the relevance of silent cerebral infarctions (SCIs) in iTTP patients during remission [29,30]. Among iTTP survivors, magnetic resonance imaging (MRI) evidence of SCIs is common. In a study enrolling 36 iTTP patients during clinical remission, SCIs were present in half of the patients (n = 18), and >40% of patients with a SCI (n = 8) had a history of stroke [29].

Interestingly, SCI may progress over time, even in the absence of acute episodes or ADAMTS13 relapse, as clearly shown in a study evaluating the natural history of SCI in 42 iTTP patients during clinical remission [30]. New or progressive SCIs were observed in 28.6%. Interestingly, a higher baseline SCI burden, assessed by the modified Age-Related White Matter Changes score, correlated with SCI progression, whereas age, hypertension, diabetes, or average remission ADAMTS13 activity did not. Over a median follow-up of 32 months, the authors reported a 14.3% stroke rate, with a significantly higher risk of stroke in those patients with a higher baseline Age-Related White Matter Changes score. These findings underscore the importance of early detection of baseline SCI burden and close monitoring of its progression.

The main studies reporting data on long-term cardiovascular complications in iTTP patients during remission are summarized in Table 1.

5 | LONG-TERM NEUROLOGICAL COMPLICATIONS: EVIDENCE FROM OBSERVATIONAL DATA

A wide heterogeneity of chronic neurological symptoms and complications has been reported in iTTP patients after recovery, ranging from posttraumatic stress disorder (PTSD), depression, impaired quality of life, loss of memory, and cognitive impairment [31–47,49].

Anxiety and depression are among the most frequently reported issues during remission. This is not unexpected, as survival from any critical illness is known to increase the risk of depression (eg, as observed in survivors after acute stroke). In addition to the severity of an acute iTTP episode, autoimmunity (eg, systemic lupus erythematosus) and obesity are recognized risk factors for major depression in TTP patients as well as in the general population. In a study enrolling 103 patients with thrombotic microangiopathy (52 with iTTP), the authors assessed the prevalence of anxiety symptoms, PTSD, and depression at a median of 72 months after hospital discharge by telephone interviews and using the 36-item Short Form questionnaire. Half of patients suffered from anxiety symptoms, 27% showed PTSD, and 14% depression [44].

Regarding neurocognitive deficits, a study of 24 iTTP patients in remission found significantly poorer performance than expected in 4

TABLE 2 Long-term neurological complications in immune-mediated thrombotic thrombocytopenic purpura patients during clinical remission.

Author (y)	Study design	Sample size (*n*)	Research question	Main findings	Limitations
Kennedy et al. [31] (2009)	Cohort study	24	To evaluate cognitive function in iTTP.	iTTP patients showed significantly lower performance on 4 of the 11 cognitive domains.	- Small sample size - Baseline cognitive function not available
Lewis et al. [32] (2009)	Cohort study	128	Long-term mental issues after acute TTP recovery.	Persistent cognitive impairment after TTP recovery is independent of ADAMTS13 levels.	- Unknown basal HRQoL before TTP episode - Interviewer bias, patient recall bias, and survey nonresponse bias
Cataland et al. [33] (2011)	Cohort study	27	To investigate the risk of developing persistent neurological injury after recovery from an acute TTP episode.	High rate of cognitive impairment and MRI abnormalities.	Small sample size
Deford et al. [23] (2013)	Cross-sectional study	57	To compare the prevalence of specific clinical conditions with the expected (US reference population).	Higher prevalence of hypertension and major depression than expected. Higher mortality than expected.	- Small sample size - Cross-sectional design
Han et al. [34] (2015)	Cohort study	61	To describe the frequency, severity, and clinical course of depression and cognitive impairment during remission of iTTP patients.	High rate of severe depression; depression and cognitive impairment were not associated with relapses or ADAMTS13 activity < 10% during remission.	- Small sample size - Low compliance with evaluations
Falter et al. [35] (2017)	Cohort study	104	To investigate the prevalence of depression and cognitive deficits during remission of iTTP patients.	Significantly higher rates of depression and cognitive impairment in TTP survivors.	- Self-reported measures of cognitive status - No sex-matched controls
Chaturvedi et al. [36] (2017)	Cross-sectional study	236	To estimate the prevalence of PTSD and depression symptoms in survivors of TTP.	High prevalence of PTSD and depression in TTP survivors.	- Referral/selection bias self-reported diagnoses of TTP - No information on neurocognitive deficits - No information on other comorbidities and exposure to military, sexual, or other trauma - No information regarding the stability or trajectory of symptoms
Terrell et al. [37] (2019)	Cohort qualitative study	16	To identify TTP patients' attitudes toward pharmacotherapy and counseling.	Patients believed TTP was life-altering and traumatic and that counseling improved depressive symptoms. Some patients were not sure pharmacotherapy was effective and expressed fears related to potential addiction and side effects.	- Selection bias - Not generalizable - Social desirability bias/stigma - Heterogeneous experiences - Not complete information on management history
Riva et al. [38] (2020)	Cross-sectional study	35	To assess neuropsychological sequelae, emotional well-being, and quality of life in	Compromised memory and attention functions, persisting anxiety/depression symptoms,	- Small sample size - Absence of a control group - Cross-sectional design

(Continues)

TABLE 2 (Continued)

Author (y)	Study design	Sample size (*n*)	Research question	Main findings	Limitations
			iTTP patients in remission.	and a reduced quality of life in patients recovering from acute iTTP.	- The neurocognitive and emotional status and quality of life before the first episode of TTP were not assessed
Alwan et al. [39] (2020)	Cohort study	131	To evaluate the usefulness of cerebral MRI in predicting cognitive impairment in TTP survivors.	The primary MRI finding in these patients was hyperintense white matter lesions. An abnormal MRI was associated with lower cognitive performance.	- Small sample size - No cerebral MRI for patients without neurological symptoms - Neuropsychology assessment was limited to patients who reported symptoms
Holmes et al. [40] (2021)	Cross-sectional (online survey)	50	To describe HRQoL, cognitive functioning, and work productivity of survivors following acute episodes of iTTP in the United Kingdom.	Significant impairments in all domains.	- Limited generalizability - Selection bias
Falter et al. [41] (2021)	Cross-sectional	104	To determine whether life circumstances and personality have an influence on the development and severity of depression and anxiety in iTTP patients, and how they impact quality of life.	High prevalence of depression and anxiety in iTTP patients with a more negative attitude to life, low resilience, reduced quality of life, and cognitive performance. The number of comorbidities had an influence on depression.	- Self-reported questionnaires, no examination by a clinician - Low response rate - Selection bias - Missing clinical data - No data on mental illness or resilience before the iTTP diagnosis
Graciaa et al. (2022) [42]	Cohort study	18	To evaluate clinical features, comorbidities, treatment response, and long-term outcomes in pediatric patients with iTTP.	73% of patients had long-term cognitive delay, learning difficulties, and severe depression.	- Small sample size - Retrospective nature of data collection - Short follow-up - A small proportion had formalized neuropsychological assessments
Kelley et al. (2023) [43]	Cohort qualitative study	44	To understand subjective recovery from the patients' perspective.	Anxiety, depression, fatigue, and cognitive issues affected patients' relationships and work productivity, and reduced the possibility of returning to their previous level of functioning.	- Selection bias (enrollment from 2 sites that focused on researching long-term outcomes and low educational level) - Self-reported data collection - No data collection on neurological manifestations of previous episodes - No data on drug and alcohol abuse - No association of symptoms with demographic characteristics
Azoulay et al. (2023) [44]	Cross-sectional (phone interviews)	103 (52 iTTP, 51 aHUS)	To investigate the prevalence of mental issues during remission of iTTP patients.	Higher rate than expected of PTSD and depression; factors independently associated with PTSD symptoms were male sex, lower platelet count at	- Limited response rate - Cross-sectional design - No data on cognition or neurological function

(Continues)

TABLE 2 (Continued)

Author (y)	Study design	Sample size (*n*)	Research question	Main findings	Limitations
				onset, and current treatment.	- Exclusion of caplacizumab-treated patients - 10-y recruitment period (time bias) - Use of instruments for screening (not diagnosis)
Chaturvedi et al. [29] (2023)	Cohort study	42	To determine the prevalence of SCI during TTP remission; to investigate the association between SCI and cognitive impairment.	MRI evidence of brain infarction is common in iTTP survivors. SCI was associated with cognitive impairment.	- Selection bias (single-center study), limiting generalizability - Small sample size - Missing data on ADAMTS13 - The study started in the precaplacizumab era
Hannan et al. [45] (2024)	Cross-sectional	20	To investigate brain changes (white matter) in iTTP patients during remission using advanced MRI and correlate these changes with mood and neurocognitive tests.	The frontal lobe and cingulate cortex are the main affected regions. MRI alterations in these areas correlated with reduced scores in concentration, short-term memory, and verbal memory.	- Small sample size for the control group (n = 5) - Selection bias (age range of participants) - No standardized scale to classify white matter changes - No data on the MRI at the time of previous TTP episodes
Mulas et al. [46] (2024)	Cohort study	39	To investigate long-term consequences (reduced quality of life, cognitive impairment, anxiety, and depression) in iTTP patients, and the role of caplacizumab and rituximab.	The majority of patients reported anxiety (72%) or depression (82%). No differences between patients treated with or without caplacizumab in the physical or mental domains. Patients receiving rituximab had lower scores in mental health.	- Small sample size - Different stages of the disease (bias)
Boothby et al. [47] (2025)	Cohort study	38	To assess the feasibility of a prospective study aimed at evaluating neuropsychological and cognitive function in iTTP patients in remission, and to evaluate novel biomarkers.	At 2-y follow-up, the authors did not observe a significant change in neurocognition. No association between cognitive function and ADAMTS13 activity was found. Cognitive impairment correlated with soluble thrombomodulin levels.	- Intersite heterogeneity in treatment modalities and laboratory testing - Lack of access to imaging data - More severely affected patients may have been less likely to complete the study (selection bias for the COVID-19 pandemic)
Yu et al. [30] (2025)	Cohort study	42	To evaluate the natural history of SCI during clinical remission and its association with the risk of stroke and cognitive decline.	SCI was progressive during clinical remission and correlated with a higher risk of stroke and cognitive impairment.	- Small sample size - Single-year MRI follow-up - Limited generalizability to other cohorts - Treatment heterogeneity

The table summarizes the main studies reporting data on long-term neurological complications in iTTP patients during clinical remission.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS, atypical hemolytic-uremic syndrome; HRQoL, health-related quality of life; iTTP, immune-mediated thrombotic thrombocytopenic purpura; MACE, major adverse cardiovascular event; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder; SCI, silent cerebral infarction; TTP, thrombotic thrombocytopenic purpura.

of 11 cognitive domains after adjusting for age, sex, and education level. The affected domains included complex attention and concentration, data processing speed, verbal fluency, and rote memorization [31]. In another study of 27 patients, 63% presented with neurocognitive impairment, affecting particularly visual learning and memory domains [33]. Interestingly, increasing evidence supports a higher risk of neurocognitive impairment in the presence of neuroimaging abnormalities.

In particular, in a study investigating brain white matter changes in 20 iTTP patients in remission compared with 6 healthy controls, the main affected regions in iTTP were the frontal lobe and cingulate cortex. Interestingly, MRI-identified pathological changes in these areas correlated with a reduction in concentration, short-term memory, and verbal memory scores [45]. In addition to hyperintense white matter lesions, evidence of SCI has been associated with an increased risk of cognitive impairment in these patients during clinical remission [29].

Whether cognitive impairment progresses beyond 1 year after the acute iTTP episode remains a matter of debate. In this regard, in a study of 42 iTTP survivors, although cognitive function improved in those without SCI progression, SCI progression increased the risk of persistent cognitive decline [30]. In order to provide an answer to this important question, a prospective, multicenter pilot study enrolling 38 iTTP patients during remission was designed [47]. The authors did not see any significant change in neurocognitive findings, such as immediate memory and visuospatial abilities, over a 2-year follow-up. Based on these findings, they suggested that a longer period of at least 5 to 10 years should be necessary to detect any trends in neurocognitive function in this population. Interestingly, they also found a correlation between soluble thrombomodulin levels and cognitive impairment, suggesting this as a novel preclinical biomarker able to predict cognitive impairment. The ADAMTS13 activity did not correlate [47]. The main studies reporting data on long-term neurological complications in iTTP patients during remission are summarized in Table 2.

6 | LIMITATIONS OF THE INCLUDED STUDIES

No interventional studies were included in the present review. Moreover, as reported in Tables 1 and 2, most studies have several limitations. The most common limitations were the limited sample size, the study design (retrospective or cross-sectional in most cases), the heterogeneity of the study sample, the selected endpoint measures, and selection bias, which limited the generalizability of the main findings.

7 | THE PATHOBIOLOGICAL MECHANISMS BEHIND LONG-TERM COMPLICATIONS AND POTENTIAL PREVENTIVE THERAPEUTIC APPROACHES

A persistent imbalance between elevated levels of large multimeric VWF and low ADAMTS13 activity during remission may induce a prothrombotic state, which could play a key role in developing long-term cardiovascular and neurological complications in iTTP survivors. Indeed, the accumulation of larger procoagulant VWF multimers increases platelet activation and aggregation, as well as endothelial and complement activation. Consistent with this hypothesis, data from large population-based cohort studies reported an increased risk of coronary artery disease and cerebrovascular disease in individuals with lower ADAMTS13 activity and/or higher VWF levels, independent of traditional atherogenic cardiovascular risk factors [50–55]. Notably, experimental murine models have demonstrated a direct role of ADAMTS13 in the progression of atherosclerosis and the development of ischemic stroke [56–62]. However, in iTTP patients, the role of ADAMT-S13 activity during remission as an independent predictor of MACEs remains controversial. Upreti et al. [26] and Brodsky et al. [28] suggested that ADAMTS13 could be a more significant risk factor for cerebral thrombosis than coronary thrombosis, because of the differences in the features of brain endothelial cells compared with coronary endothelial cells. The more accepted hypothesis is that ADAMTS13 and traditional cardiovascular risk factors are not mutually exclusive and may act additively to increase the risk of ischemic events.

The aforementioned prothrombotic mechanisms may also contribute to the increased risk of neurocognitive deficits. Indeed, the role of microcirculation dysfunction in cerebral small vessel disease and the related cognitive impairment is well known. Moreover, more and more studies suggest a potential pathogenic role for the imbalance between high VWF levels and low ADAMTS13 activity, as well as for the VWF-glycoprotein Ib axis, in dementia (including Alzheimer's type) in the general population [63–65]. The persistence of subcortical microvascular lesions after recovery from an acute iTTP episode may result in chronic subclinical neurological injury with similar mechanisms already reported in hypertension, sickle cell disease, and other microvascular disorders. Moreover, the severity of ischemic brain cell injury occurred during an acute episode, leading to a high white matter lesion burden, could influence the risk of neurologic sequelae. Consistent with this hypothesis, the brain MRI findings of a cohort of 42 iTTP survivors showed a significant correlation between baseline SCI burden and SCI progression, the latter associated with a higher risk of stroke and cognitive impairment [30]. Other proposed mechanisms contributing to neurocognitive deficits in these patients include alterations in specific neurotransmitters (increased dopamine and noradrenaline and reduced serotonin and gamma-aminobutyric acid, GABA levels) and neuroinflammation [31–34,44].

Based on the aforementioned main pathogenic mechanisms, several preventive therapeutic strategies for these long-term complications have been proposed and are currently under investigation. The rationale for antiplatelet agents (eg, aspirin) during clinical remission in iTTP patients for primary cardiovascular prevention (with no history of MACEs) remains controversial. Some authors suggest that aspirin prophylaxis during disease remission may be beneficial only in selected patients (eg, at high cardiovascular risk) [66,67]. Another proposed drug in this field is rituximab, currently used in clinical practice during

remission to prevent relapse in patients with ADAMTS13 activity <20% [68,69]. However, to date, there is insufficient evidence to confirm a preventive effect of this drug on long-term cardiovascular complications. Further studies are needed to demonstrate the association between ADAMTS13 activity levels during remission and MACE rates and to identify the optimal ADAMTS13 target level to prevent ischemic stroke and/or any MACE.

The preventive role of rituximab and caplacizumab on long-term neurocognitive complications and depression requires further investigation. Indeed, in a study of 39 iTTP survivors [46], no difference was observed between patients treated with or without caplacizumab in physical or mental domains. Moreover, patients treated with rituximab reported lower scores in mental health, likely because these patients had a more severe presentation or recurrent phenotype.

More studies are needed to objectively assess acute brain ischemic damage and its progression during clinical remission, as well as to understand the potential correlation between acute brain damage and the risk of long-term neurocognitive impairment. In this field, the potential role of acute brain ischemic damage and, consequently, the potential beneficial preventive effect of caplacizumab, remains unknown. By reducing microvascular-related ischemic brain damage during an acute TTP episode, it is possible that caplacizumab could be useful to reduce the risk of SCI at baseline and its progression, preventing long-term depression and cognitive impairment. However, this hypothesis needs to be confirmed. In this context, the growing evidence stemming from neuroimaging studies should provide with very useful information. Otherwise, imaging-proven evidence regarding microvascular-related ischemic cardiac damage in acute phase and its progression during clinical remission remains unclear.

8 | IMPLICATIONS IN CURRENT CLINICAL PRACTICE

To date, there is not enough evidence stemming from observational cohort studies on the potential predictive value of biomarkers or trials proving the efficacy of preventive treatments. Moreover, there is no consensus within the scientific community, and there are no clinical practice guidelines regarding the most appropriate approach for iTTP survivors needed to prevent long-term cardiovascular and neurological complications. However, based on growing evidence from observational cohort studies and clinical experience, the following recommendations could be taken into consideration. A multidisciplinary care model, including hematologists, internists, neurologists, cardiologists, and psychologists, should be recommended for management of iTTP patients during clinical remission. A comprehensive long-term clinical care plan, including cardiovascular risk stratification (based on clinical and instrumental examination) and neuropsychological and neuroimaging assessment (cerebral MRI), should be routinely recommended. In particular, regarding cardiovascular prevention, careful screening and monitoring of the traditional cardiovascular risk factors (hypertension, hyperlipidemia, smoking, and diabetes) in iTTP survivors is a widely accepted strategy and should be recommended [22]. The comprehensive clinical anamnesis and evaluation should also take the main cardiovascular risk modifiers (eg, family history of premature cardiovascular disease, psychosocial factors, ethnicity, body mass index and waist circumference, sedentary lifestyle, chronic kidney disease, cancer, chronic inflammatory diseases, chronic obstructive pulmonary disease, heart failure, atrial fibrillation, migraine, sleep disorders, and mental disorders) into account. Moreover, carotid ultrasonography and echocardiography, if not performed in the previous 12 months, should be assessed. Based on the cardiovascular risk category, a personalized treatment goal for each of the main traditional cardiovascular risk factors (blood pressure, hyperlipidemia, and hyperglycemia) should be defined. Although the risk of MACEs in these patients during remission seems to be significantly higher-than-expected based on age, sex, and traditional cardiovascular risk factors and related validated scores (eg, Systematic COronary Risk Evaluation 2, SCORE2 [70]), to date, there are no sufficient data to support the use of antiplatelet agents in primary cardiovascular prevention in these patients. In other words, aspirin should be chronically administered only in iTTP patients with a history of acute coronary syndrome or ischemic stroke occurred in or out the previous TTP episodes. However, this topic remains questionable, considering that the observed MACE rate in this population seems to be consistent with a population with high or very high cardiovascular risk (eg, with clinically established atherosclerotic cardiovascular disease). Moreover, it has to be noted that the proportion of patients with a history of MACE and thus requiring aspirin is likely underestimated because of the high proportion of SCI in these patients. Considering the high prevalence of SCI and the relevance of its early detection in order to prevent SCI progression, stroke, and long-term cognitive impairment, a cerebral MRI screening should be performed in these patients in acute phase and at least once during clinical remission after at least 6 months of recovery, although a long-term monitoring strategy should be standardized. The neurological assessment should include the administration of neuropsychological tests, repeated annually, with the goal to detect and assess the trajectory of microvascular-related cognitive impairment. Depression management should combine counseling and, when necessary, appropriate medications. However, this management has to be personalized, taking into account patients' attitudes to these approaches [37].

9 | CONCLUSIVE REMARKS AND FUTURE DIRECTIONS

This updated overview of the state-of-the-art long-term cardiovascular and neurological complications in iTTP survivors clearly highlights how this disease is emerging as a paradigmatic model of chronic (not only acute) systemic microvascular dysfunction (Figure).

TTP can no longer be regarded solely as an acute and episodic disease; rather, it should be managed as a chronic condition requiring a multidisciplinary approach.

Cardiovascular risk factors and neuropsychological symptoms should be routinely screened and investigated in iTTP patients after

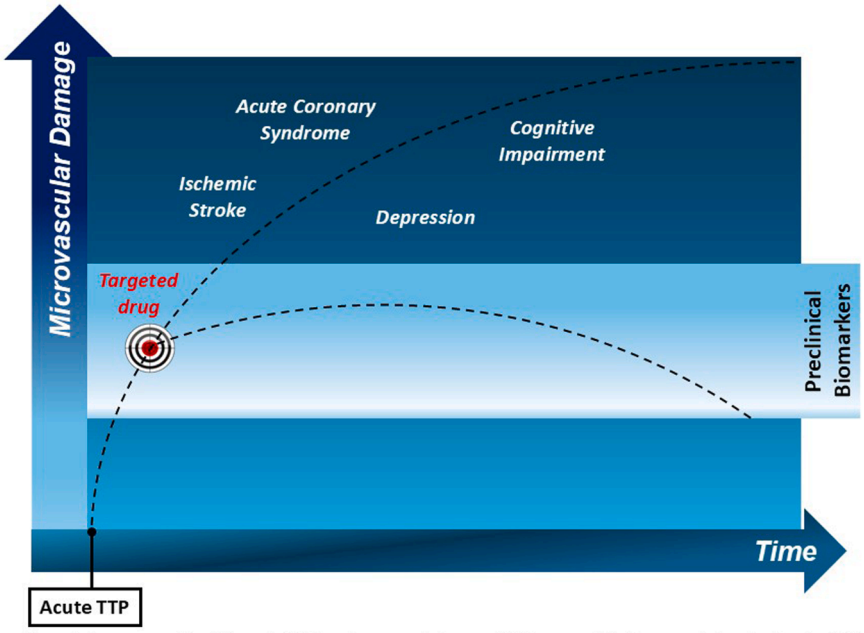

FIGURE Immune-mediated thrombotic thrombocytopenic purpura (iTTP) as a model of acute and chronic microcirculation dysfunction. After recovery from an acute immune-mediated TTP episode, a state of cumulative microvascular damage may persist and progress over time in an unpredictable trajectory. Novel preclinical multiomic biomarkers of microvascular damage could be useful to identify those patients at higher risk of major long-term cardiovascular and neurological complications who could benefit from preventive strategies able to modify the trajectory of the disease.

recovery from an acute episode through a comprehensive clinical assessment also includes neuropsychological tests, cardiovascular instrumental exams, and neuroimaging.

Despite growing evidence, several important questions remain unanswered: (i) the role of ADAMST-13 activity levels during remission; (ii) the role of antiplatelet agents, caplacizumab, and rituximab as preventive therapies for long-term cardiovascular and neurocognitive complications; (iii) the most appropriate timeline of cerebral MRI during clinical remission; (iv) the development and standardization of novel, diagnostic, noninvasive tools able to assess and monitor cardiac ischemic-related damage; (v) the identification of novel predictive phenotypes and omics biomarkers, both iTTP-related and unrelated, of long-term cardiovascular and neurological complications; and (vi) how integrating multiomics data (eg, phenotype and radiomics) with the final goal of a more personalized management.

To date, clinical practice for iTTP patients during remission is quite heterogeneous between reference centers and there are no shared guidelines concerning prevention of long-term complications. A task force within the scientific community aimed at the harmonization and standardization of the clinical approach during remission is needed to prevent long-term neurological and cardiovascular complications. This approach should include the most appropriate screening and monitoring tools (validated neuropsychological tests, novel biomarkers, instrumental exams, and pipelines for neuroimaging data acquisition and analysis) as well as effective preventive drugs.

A better understanding of the pathogenic mechanisms underlying the risk of long-term cardiovascular and neurocognitive complications and related organ damage in iTTP patients at different stages of the disease could provide valuable insights into the systemic consequences of microvascular injury also in other diseases. This may help physicians and researchers improve their understanding of the role of microvascular dysfunction in common diseases in the general population with the identification of novel pathogenic pathways and therapeutic targets.

AUTHOR CONTRIBUTIONS

P.A. and E.I. performed the research on the literature and wrote the first draft of the manuscript. A.T., A.A., and F.P. carefully revised the manuscript.

DECLARATION OF COMPETING INTERESTS

P.A. received honoraria for participating as a speaker at educational meetings organized by Sanofi. F.P. has received honoraria for participating as a speaker at education meetings organized by Takeda and Sanofi, and she is a member of the scientific advisory boards of CSL Behring, BioMarin, Roche, Sanofi, Sobi, and Pfizer. The other authors do not have any conflicts of interest to disclose.

ORCID

Flora Peyvandi https://orcid.org/0000-0001-7423-9864

X

Pasquale Agosti @Pasquale_Agosti
Addolorata Truma @AddoloratoTruma
Flora Peyvandi @flora_peyvandi

REFERENCES

[1] Senarathna J, Pathak AP. Visualizing the microcirculation. *Microcirculation*. 2022;29:e12785. https://doi.org/10.1111/micc.12785

[2] Guven G, Hilty MP, Ince C. Microcirculation: physiology, pathophysiology, and clinical application. *Blood Purif*. 2020;49:143–50.

[3] Rizzoni D, Agabiti-Rosei C, Boari GEM, Muiesan ML, De Ciuceis C. Microcirculation in hypertension: a therapeutic target to prevent cardiovascular disease? *J Clin Med*. 2023;12:4892. https://doi.org/10.3390/jcm12154892

[4] Alexander Y, Osto E, Schmidt-Trucksäss A, Shechter M, Trifunovic D, Duncker DJ, Aboyans V, Bäck M, Badimon L, Cosentino F, De Carlo M, Dorobantu M, Harrison DG, Guzik TJ, Hoefer I, Morris PD, Norata GD, Suades R, Taddei S, Vilahur G, et al. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovasc Res*. 2021;117:29–42.

[5] Goligorsky MS. Glomerular microcirculation: implications for diabetes, preeclampsia, and kidney injury. *Acta Physiol (Oxf)*. 2023;239:e14048. https://doi.org/10.1111/apha.14048

[6] Maneta E, Aivalioti E, Tual-Chalot S, Emini Veseli B, Gatsiou A, Stamatelopoulos K, Stellos K. Endothelial dysfunction and immunothrombosis in sepsis. *Front Immunol*. 2023;14:1144229. https://doi.org/10.3389/fimmu.2023.1144229

[7] Singh A, Bonnell G, De Prey J, Buchwald N, Eskander K, Kincaid KJ, Wilson CA. Small-vessel disease in the brain. *Am Heart J Plus*. 2023;27:100277. https://doi.org/10.1016/j.ahjo.2023.100277

[8] Feuer DS, Handberg EM, Mehrad B, Wei J, Bairey Merz CN, Pepine CJ, Keeley EC. Microvascular dysfunction as a systemic disease: a review of the evidence. *Am J Med*. 2022;135:1059–68.

[9] Mazini B, Dietz M, Maréchal B, Corredor-Jerez R, Prior JO, Dunet V. Interrelation between cardiac and brain small-vessel disease: a pilot quantitative PET and MRI study. *Eur J Hybrid Imaging*. 2023;7:20. https://doi.org/10.1186/s41824-023-00180-7

[10] Højstrup S, Hansen KW, Talleruphuus U, Marner L, Galatius S, Rauf M, Bjerking LH, Jakobsen L, Christiansen EH, Bouchelouche K, Christensen H, Prescott EIB. Coronary microvascular disease assessed by 82-rubidium positron emission tomography myocardial perfusion imaging is associated with small vessel disease of the kidney and brain. *J Am Heart Assoc*. 2023;12:e028767. https://doi.org/10.1161/JAHA.122.028767

[11] Nowroozpoor A, Gutterman D, Safdar B. Is microvascular dysfunction a systemic disorder with common biomarkers found in the heart, brain, and kidneys? - a scoping review. *Microvasc Res*. 2021;134:104123. https://doi.org/10.1016/j.mvr.2020.104123

[12] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2486–95.

[13] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2496–502.

[14] Coppo P, Bubenheim M, Benhamou Y, Völker L, Brinkkötter P, Kühne L, Knöbl P, Mingot-Castellano ME, Pascual-Izquierdo C, de la Rubia J, Del Rio Garma J, Chaturvedi S, Masias C, Mazepa M, Zheng XL, Sinkovits G, Réti M, Patriquin CJ, Pavenski K, Boechat T, et al. Caplacizumab use in immune-mediated thrombotic thrombocytopenic purpura: an international multicentre retrospective Cohort study (The Capla 1000+ project). *EClinicalMedicine*. 2025;82:103168. https://doi.org/10.1016/j.eclinm.2025.103168

[15] Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, Lämmle B, Matsumoto M, Pavenski K, Sadler E, Sarode R, Wu H, International Working Group for Thrombotic Thrombocytopenic Purpura. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost*. 2017;15:312–22.

[16] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. Good practice statements (GPS) for the clinical care of patients with thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2020;18:2503–12.

[17] Truma A, Mancini I, Agosti P, Artoni A, Giannotta JA, Ferrari B, De Leo P, Peyvandi F. Main features of ischemic stroke in patients with acute immune-mediated thrombotic thrombocytopenic purpura. *Thromb Res*. 2024;243:109151. https://doi.org/10.1016/j.thromres.2024.109151

[18] Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med*. 1998;339:1585–94.

[19] Seidizadeh O, Cairo A, Mancini I, George JN, Peyvandi F. Global prevalence of hereditary thrombotic thrombocytopenic purpura determined by genetic analysis. *Blood Adv*. 2024;8:4386–96.

[20] Selvakumar S, Liu A, Chaturvedi S. Immune thrombotic thrombocytopenic purpura: Spotlight on long-term outcomes and survivorship. *Front Med (Lausanne)*. 2023;10:1137019. https://doi.org/10.3389/fmed.2023.1137019

[21] Adeyemi A, Razakariasa F, Chiorean A, de Passos Sousa R. Epidemiology, treatment patterns, clinical outcomes, and disease burden among patients with immune-mediated thrombotic thrombocytopenic purpura in the United States. *Res Pract Thromb Haemost*. 2022;6:e12802. https://doi.org/10.1002/rth2.12802

[22] George JN. Thrombotic thrombocytopenic purpura: from 1972 to 2022 and beyond. *Semin Thromb Hemost*. 2022;48:926–36.

[23] Deford CC, Reese JA, Schwartz LH, Perdue JJ, Kremer Hovinga JA, Lämmle B, Terrell DR, Vesely SK, George JN. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood*. 2013;122:2023–9. quiz 2142.

[24] George JN. TTP: long-term outcomes following recovery. *Hematology Am Soc Hematol Educ Program*. 2018;2018:548–52.

[25] Sukumar S, Brodsky M, Hussain S, Yanek L, Moliterno A, Brodsky R, Cataland SR, Chaturvedi S. Cardiovascular disease is a leading cause of mortality among TTP survivors in clinical remission. *Blood Adv*. 2022;6:1264–70.

[26] Upreti H, Kasmani J, Dane K, Braunstein EM, Streiff MB, Shanbhag S, Moliterno AR, Sperati CJ, Gottesman RF, Brodsky RA, Kickler TS, Chaturvedi S. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood*. 2019;134:1037–45.

[27] Vesely SK. Life after acquired thrombotic thrombocytopenic purpura: morbidity, mortality, and risks during pregnancy. *J Thromb Haemost*. 2015;13:S216–22.

[28] Brodsky MA, Sukumar S, Selvakumar S, Yanek L, Hussain S, Mazepa MA, Braunstein EM, Moliterno AR, Kickler TS, Brodsky RA, Cataland SR, Chaturvedi S. Major adverse cardiovascular events in survivors of immune-mediated thrombotic thrombocytopenic purpura. *Am J Hematol*. 2021;96:1587–94.

[29] Chaturvedi S, Yu J, Brown J, Wei A, Selvakumar S, Gerber GF, Moliterno AR, Streiff MB, Kraus P, Logue CM, Yui JC, Naik RP, Latif H, Lanzkron SM, Braunstein EM, Brodsky RA, Gottesman RF, Lin DD. Silent cerebral infarction during immune TTP remission: prevalence, predictors, and impact on cognition. *Blood*. 2023;142:325–35.

[30] Yu J, Brown J, Meade J, Gerber GF, Streiff MB, Kraus P, Merrill S, Pishko AM, Yui J, Naik RP, Brodsky RA, Lin DD, Chaturvedi S. Progressive silent cerebral infarction is associated with stroke and persistent cognitive impairment in iTTP survivors. *Blood Adv*. 2025;9:5945–53.

[31] Kennedy AS, Lewis QF, Scott JG, Kremer Hovinga JA, Lämmle B, Terrell DR, Vesely SK, George JN. Cognitive deficits after recovery

from thrombotic thrombocytopenic purpura. *Transfusion*. 2009;49:1092–101.

[32] Lewis QF, Lanneau MS, Mathias SD, Terrell DR, Vesely SK, George JN. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009;49:118–24.

[33] Cataland SR, Scully MA, Paskavitz J, Maruff P, Witkoff L, Jin M, Uva N, Gilbert JC, Wu HM. Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura. *Am J Hematol*. 2011;86:87–9.

[34] Han B, Page EE, Stewart LM, Deford CC, Scott JG, Schwartz LH, Perdue JJ, Terrell DR, Vesely SK, George JN. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. *Am J Hematol*. 2015;90:709–14.

[35] Falter T, Schmitt V, Herold S, Weyer V, von Auer C, Wagner S, Hefner G, Beutel M, Lackner K, Lämmle B, Scharrer I. Depression and cognitive deficits as long-term consequences of thrombotic thrombocytopenic purpura. *Transfusion*. 2017;57:1152–62.

[36] Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. *Thromb Res*. 2017;151:51–6.

[37] Terrell DR, Tolma EL, Stewart LM, Shirley EA. Thrombotic thrombocytopenic purpura patients' attitudes toward depression management: a qualitative study. *Health Sci Rep*. 2019;2:e136.

[38] Riva S, Mancini I, Maino A, Ferrari B, Artoni A, Agosti P, Peyvandi F. Long-term neuropsychological sequelae, emotional wellbeing and quality of life in patients with acquired thrombotic thrombocytopenic purpura. *Haematologica*. 2020;105:1957–62.

[39] Alwan F, Mahdi D, Tayabali S, Cipolotti L, Lakey G, Hyare H, Scully M. Cerebral MRI findings predict the risk of cognitive impairment in thrombotic thrombocytopenic purpura. *Br J Haematol*. 2020;191:868–74.

[40] Holmes S, Podger L, Bottomley C, Rzepa E, Bailey KMA, Chandler F. Survival after acute episodes of immune-mediated thrombotic thrombocytopenic purpura (iTTP)—cognitive functioning and health-related quality of life impact: a descriptive cross-sectional survey of adults living with iTTP in the United Kingdom. *Hematology*. 2021;26:465–72.

[41] Falter T, Böschen S, Schepers M, Beutel M, Lackner K, Scharrer I, Lämmle B. Influence of personality, resilience and life conditions on depression and anxiety in 104 patients having survived acute autoimmune thrombotic thrombocytopenic purpura. *J Clin Med*. 2021;10:365.

[42] Graciaa S, Adeagbo S, Fong G, Rollins M, McElfresh P, Zerra PE, Bennett C, Josephson CD, Briones M, Fasano RM, Chonat S. Clinical features and neurological outcomes in pediatric immune-mediated thrombotic thrombocytopenic purpura: a report from a large pediatric hematology center. *Pediatr Blood Cancer*. 2022;69:e29992. https://doi.org/10.1002/pbc.29992

[43] Kelley RA, Cheney MK, Martin CM, Cataland S, Quick LB, Keller S, Vesely SK, Llaneza AJ, Khawandanah MO, Journeycake JM, Panepinto JA, Terrell DR. Health following recovery from immune thrombotic thrombocytopenic purpura: the patient's perspective. *Blood Adv*. 2023;7:1813–22.

[44] Azoulay E, Souppart V, Kentish-Barnes N, Benhamou Y, Joly BS, Zafrani L, Joseph A, Canet E, Presne C, Grall M, Zerbib Y, Provot F, Fadlallah J, Mariotte E, Urbina T, Veyradier A, Coppo P. Post-traumatic stress disorder and quality of life alterations in survivors of immune-mediated thrombotic thrombocytopenic purpura and atypical hemolytic and uremic syndrome. *J Crit Care*. 2023;76:154283. https://doi.org/10.1016/j.jcrc.2023.154283

[45] Hannan F, Hamilton J, Patriquin CJ, Pavenski K, Jurkiewicz MT, Tristao L, Owen AM, Kosalka PK, Deoni SCL, Théberge J, Mandzia J, Huang SHS, Thiessen JD. Cognitive decline in thrombotic thrombocytopenic purpura survivors: the role of white matter health as assessed by MRI. *Br J Haematol*. 2024;204:1005–16.

[46] Mulas O, Efficace F, Costa A, Baldi T, Zerbini F, Mantovani D, Morelli E, Perra D, La Nasa G, Caocci G. Long-term health-related quality of life and mental health in patients with immune thrombotic thrombocytopenic purpura. *Ann Hematol*. 2024;103:2523–31.

[47] Boothby AB, Evans MD, Yang S, Sukumar S, Scott JG, Terrell DR, Cataland S, Mazepa M. Multicenter prospective pilot study identifying thrombomodulin as a potential biomarker for neurocognitive outcomes in immune thrombotic thrombocytopenic purpura. *J Clin Med*. 2025;14:694.

[48] Little DJ, Reese JA, Vesely SK, George JN. Increased urinary albumin excretion following recovery from thrombotic thrombocytopenic purpura due to acquired ADAMTS13 deficiency. *Am J Kidney Dis*. 2014;64:317–8.

[49] Shaw RJ, Dutt T. Mind and matter: the neurological complications of thrombotic thrombocytopenic purpura. *Br J Haematol*. 2022;197:529–38.

[50] Sonneveld MA, Kavousi M, Ikram MA, Hofman A, Rueda Ochoa OL, Turecek PL, Franco OH, Leebeek FW, de Maat MP. Low ADAMTS-13 activity and the risk of coronary heart disease—a prospective cohort study: the Rotterdam Study. *J Thromb Haemost*. 2016;14:2114–20.

[51] Sonneveld MA, de Maat MP, Portegies ML, Kavousi M, Hofman A, Turecek PL, Rottensteiner H, Scheiflinger F, Koudstaal PJ, Ikram MA, Leebeek FW. Low ADAMTS13 activity is associated with an increased risk of ischemic stroke. *Blood*. 2015;126:2739–46.

[52] Sonneveld MA, Franco OH, Ikram MA, Hofman A, Kavousi M, de Maat MP, Leebeek FW. von Willebrand factor, ADAMTS13, and the risk of mortality: the Rotterdam study. *Arterioscler Thromb Vasc Biol*. 2016;36:2446–51.

[53] Wieberdink RG, van Schie MC, Koudstaal PJ, Hofman A, Witteman JC, de Maat MP, Leebeek FW, Breteler MM. High von Willebrand factor levels increase the risk of stroke: the Rotterdam study. *Stroke*. 2010;41:2151–6.

[54] Bongers TN, de Maat MP, van Goor ML, Bhagwanbali V, van Vliet HH, Gómez García EB, Dippel DW, Leebeek FW. High von Willebrand factor levels increase the risk of first ischemic stroke: influence of ADAMTS13, inflammation, and genetic variability. *Stroke*. 2006;37:2672–7.

[55] Bongers TN, de Bruijne EL, Dippel DW, de Jong AJ, Deckers JW, Poldermans D, de Maat MP, Leebeek FW. Lower levels of ADAMTS13 are associated with cardiovascular disease in young patients. *Atherosclerosis*. 2009;207:250–4.

[56] Zhao BQ, Chauhan AK, Canault M, Patten IS, Yang JJ, Dockal M, Scheiflinger F, Wagner DD. von Willebrand factor-cleaving protease ADAMTS13 reduces ischemic brain injury in experimental stroke. *Blood*. 2009;114:3329–34.

[57] Fujioka M, Hayakawa K, Mishima K, Kunizawa A, Irie K, Higuchi S, Nakano T, Muroi C, Fukushima H, Sugimoto M, Banno F, Kokame K, Miyata T, Fujiwara M, Okuchi K, Nishio K. ADAMTS13 gene deletion aggravates ischemic brain damage: a possible neuroprotective role of ADAMTS13 by ameliorating postischemic hypoperfusion. *Blood*. 2010;115:1650–3.

[58] Khan MM, Motto DG, Lentz SR, Chauhan AK. ADAMTS13 reduces VWF-mediated acute inflammation following focal cerebral ischemia in mice. *J Thromb Haemost*. 2012;10:1665–71.

[59] Nakano T, Irie K, Hayakawa K, Sano K, Nakamura Y, Tanaka M, Yamashita Y, Satho T, Fujioka M, Muroi C, Matsuo K, Ishikura H, Futagami K, Mishima K. Delayed treatment with ADAMTS13 ameliorates cerebral ischemic injury without hemorrhagic complication. *Brain Res*. 2015;1624:330–5.

[60] Xu H, Cao Y, Yang X, Cai P, Kang L, Zhu X, Luo H, Lu L, Wei L, Bai X, Zhu Y, Zhao BQ, Fan W. ADAMTS13 controls vascular remodeling by modifying VWF reactivity during stroke recovery. *Blood*. 2017;130:11–22.

[61] Gandhi C, Ahmad A, Wilson KM, Chauhan AK. ADAMTS13 modulates atherosclerotic plaque progression in mice via a VWF-dependent mechanism. *J Thromb Haemost*. 2014;12:255–60.

[62] Jin SY, Tohyama J, Bauer RC, Cao NN, Rader DJ, Zheng XL. Genetic ablation of Adamts13 gene dramatically accelerates the formation of early atherosclerosis in a murine model. *Arterioscler Thromb Vasc Biol*. 2012;32:1817–23.

[63] Wolters FJ, Boender J, de Vries PS, Sonneveld MA, Koudstaal PJ, de Maat MP, Franco OH, Ikram MK, Leebeek FW, Ikram MA. Von Willebrand factor and ADAMTS13 activity in relation to risk of dementia: a population-based study. *Sci Rep*. 2018;8:5474.

[64] Hanas JS, Hocker JRS, Vannarath CA, Lerner MR, Blair SG, Lightfoot SA, Hanas RJ, Couch JR, Hershey LA. Distinguishing Alzheimer's disease patients and biochemical phenotype analysis using a novel serum profiling platform: potential involvement of the VWF/ADAMTS13 axis. *Brain Sci*. 2021;11:583.

[65] Cao Y, Xu H, Zhu Y, Shi MJ, Wei L, Zhang J, Cheng S, Shi Y, Tong H, Kang L, Lu L, Luo H, Yang X, Bai X, Wang R, Ma Y, Wang Y, Wang Z, Zhong K, Zhao BQ, et al. ADAMTS13 maintains cerebrovascular integrity to ameliorate Alzheimer-like pathology. *PLoS Biol*. 2019;17:e3000313. https://doi.org/10.1371/journal.pbio.3000313

[66] Shao B, Hoover C, Shi H, Kondo Y, Lee RH, Chen J, Shan X, Song J, McDaniel JM, Zhou M, McGee S, Vanhoorelbeke K, Bergmeier W, López JA, George JN, Xia L. Deletion of platelet CLEC-2 decreases GPIbα-mediated integrin αIIbβ3 activation and decreases thrombosis in TTP. *Blood*. 2022;139:2523–33.

[67] Shao B, Nusrat S, George JN, Xia L. Aspirin prophylaxis for hereditary and acquired thrombotic thrombocytopenic purpura? *Am J Hematol*. 2022;97:E304–6.

[68] Jestin M, Benhamou Y, Schelpe AS, Roose E, Provôt F, Galicier L, Hié M, Presne C, Poullin P, Wynckel A, Saheb S, Deligny C, Servais A, Girault S, Delmas Y, Kanouni T, Lautrette A, Chauveau D, Mousson C, Perez P, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. *Blood*. 2018;132:2143–53.

[69] Dupuy H, Lazaro E, Machelart I, Viallard JF, Coppo P, Rivière E. Rituximab prevents stroke recurrences in atypical chronic immune-mediated thrombotic thrombocytopenic purpura. *TH Open*. 2018;2:e407–10.

[70] Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Angelantonio ED, Franco OH, Halvorsen S, Richard Hobbs FD, Hollander M, Jankowska EA, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for Cardiovascular Disease Prevention in Clinical Practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Rev Esp Cardiol (Engl Ed)*. 2022;75:429.