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Major adverse cardiovascular events in immune-mediated thrombotic thrombocytopenic purpura during clinical remission

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For original, deidentified data, please contact the corresponding author.

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Authorship Contributions

F. Peyvandi conceived and designed the study, including the original concept of investigating microcirculation in TTP within the framework of the PNC and Excellence project. P. Agosti contributed to the study design, performed data analysis and wrote the manuscript. F. Boggio performed data collection. F. Peyvandi and P. Agosti critically revised the manuscript for important intellectual content. All authors carefully revised the manuscript and approved the final version of the manuscript.

Conflict of Interest Disclosures

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There is a growing evidence of a higher than expected prevalence of several long-term adverse health issues in patients with immune-mediated thrombotic thrombocytopenic purpura (iTTP). Among them, major adverse cardiovascular events (MACE) have to be mentioned [1-6]. Data on MACE incidence during clinical remission in iTTP patients are still scarce and stem from two studies enrolling patients from US iTTP cohorts. In a study of 137 cases, 13% had an ischemic stroke (IS) during remission over a median follow-up of about 3 years; in 52/137 patients ADAMTS13 activity level below 70% was associated with an increased risk of IS [7]. In another study of 181 patients over a median follow-up of 7.6 years, 28.6% experienced a MACE (18.2% IS) [8]. In both studies the MACE rates (particularly the rate of IS) were significantly higher than the expected, even higher than the rates reported in cohort studies including patients at high or very high cardiovascular risk [8]. Pertaining to the main risk factors, in the study by Brodsky et al, age, ethnicity and diabetes mellitus were associated with MACE, whereas the predictive role of ADAMTS13 activity levels during remission was not confirmed [8].

The present study aims to evaluate the incidence of MACE during remission in a large Italian cohort of iTTP patients and to report the main related risk factors.

MACE was defined as a composite endpoint of ACS or IS. ACS was defined as the occurrence of ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) or unstable angina. IS was defined based on the evidence of new ischemic lesion(s) on neuroimaging.

In this retrospective cohort study, patients surviving a first acute iTTP episode occurred after January 2002 and referred at least once to the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (Milan) were followed-up for at least six months up to the date of MACE or the last follow-up date or the study end date (December 31, 2022), whichever occurred first.

Cases with a history of IS or ACS and those lost to follow-up before 2012 were excluded, as well as those without clear data on MACE or lacking data on cardiovascular risk factors.

Age, sex, ethnicity, time of observation, disease history (e.g. number of TTP episodes), traditional cardiovascular risk factors and concomitant autoimmunity were retrospectively obtained from medical records.

For each patient, a cardiovascular risk category was assessed according to the European Society of Cardiology (ESC) guidelines [9].

A descriptive analysis was performed. We estimated the incidence proportion and the annual/monthly incidence rate. The analyses were performed by JMP Pro18 (SAS Institute Inc. Cary, NC, USA). Written informed consent from all subjects and approval by Ethics Committee have been obtained, in accordance with the Helsinki Declaration.

Among 266 outpatients referred at our center at least once and followed up for at least 6 months and with no history of MACE before TTP onset, 232 cases were eligible after exclusion of those without clear data on MACE.

Among these patients, 8 (3.4%) had at least one MACE during a median follow-up of 6.3 years, with a 10-year MACE incidence rate of 4.8%. The median age at the time of MACE was 56 years (IQR, 44-69). A total number of 11 MACE was recorded (in the 8 patients), including 3 ACS, 7 symptomatic IS and 1 silent IS. All these MACE occurred during clinical remission, in the absence of clinical or laboratory signs of iTTP clinical relapse. Two cases had 2 and 3 MACE, respectively. In particular, a woman presented IS 11 months after the fourth TTP episode at age 31; thereafter she presented ACS and IS at 22 and 25 months after the seventh TTP episode, respectively. The other patient had IS at ~19 years after the first TTP episode (at age 51) and ACS at ~21 years after the first TTP episode.

The main features of iTTP patients with and without MACE during remission are shown in Table 1. In cases presenting with MACE there was a higher proportion of males (50% vs 24%), whereas the median age was similar. In the whole sample the prevalence of the traditional atherogenic risk factors was low-moderate and the most common cardiovascular risk factor was smoking (67%). No patients with MACE occurring during remission had diabetes mellitus nor chronic kidney disease. Almost

two thirds of cases without history of MACE were overweight or obese, this proportion being lower (33%) in cases with MACE. Hypertension and hyperlipidemia were slightly less prevalent in cases without MACE (23.3% and 16.5%, respectively).

MACE occurred at a median time of 95 months (IQR: 66-141) after the first iTTP episode. Among the 6 iTTP patients with detailed data on the clinical manifestations of their first TTP episode, neurological or cardiovascular clinical signs and symptoms were present in half of them.

ADAMTS13 activity at the time of MACE for 3 out of 8 patients were 50%, 54% and 12%, respectively. Although regular ADAMTS13 monitoring during remission prior to MACE was not available, in 6 out of 8 patients at least one ADAMTS13 measure was available within the two years before and/or after MACE. Among these, two patients showed persistently reduced ADAMTS13 activity (more than two evaluations below the lower limit of the normal range, <45%), two patients had only a single available ADAMTS13 measure which was <45%, the remaining two patients had ADAMTS13 activity within normal range throughout.

Notably, the incidence proportion of ischemic stroke (IS) in iTTP patients was higher than expected, in comparison with a large Italian population study (n=132,598) with a similar age and sex distribution [10] [7/232 (3%) vs 0.8%]. Conversely, the rate of ACS was lower in our cohort [1/232 (0.4%) vs 1.9%], even when including the ACS events occurring in patients with history of IS (3/232, 1.3%). However, these comparisons should be interpreted with caution. Indeed, the two studies have different observation time periods (median follow-up of 6.3 years in the present study vs lifelong in the cross-sectional survey by Santoro et al). Notably, except for smoking, the prevalence of all the other cardiovascular risk factors in our subsample of patients with MACE was lower than that reported by Santoro et al among those patients with history of cardiovascular diseases (CVDs) (Table 2).

In our Italian cohort of patients with iTTP a MACE rate of 3.4% was observed during clinical remission over a median follow-up of 6.3 years, with a 10-year incidence rate of 4.8%. After

stratification for age at onset, the 10-year MACE incidence rates were as follows: 5/157 over a median follow-up of 6.9 years (4.2%) in patients aged<50 years, 2/70 over a median follow-up of 5.2 years (4.6%) in those aged 50-69 years, and 1/5 over a median follow-up of 3.8 years (41%) in those aged ≥70 years. According to the ESC guidelines [9], these rates are higher than those observed in the general population and are consistent with a population at high cardiovascular risk. In particular, for patients aged ≥70 years, a rate higher than 15% is considered indicative of a very high CVD risk. Therefore, in our cohort patients with elderly-onset iTTP (i.e. ≥70 years of age) appear to be at much higher risk of developing MACE during remission.

Despite the elevated rates of MACE we observed, the prevalence of traditional cardiometabolic risk factors in the overall cohort was low to moderate; this suggests that the observed rates exceed those expected based on the traditional atherogenic risk factors and the standard risk scores [e.g. Systematic Coronary Risk Estimation 2 (SCORE-2)]. This finding is consistent with a previous study showing that standard cardiovascular risk models do not properly predict MACE risk in iTTP survivors [10]. Therefore, iTTP itself appears to be the major independent risk factor for MACE during remission. Consistently, when comparing the main features of iTTP patients with and without MACE, the risk of MACE seemed to be unrelated to the prevalence of the main cardiometabolic risk factors. Moreover, except for smoking, all the other main traditional cardiovascular risk factors were less prevalent in the present cohort of iTTP cases than in a general Italian population (Santoro et al) [11]. All these findings appear to support a major role of microvascular dysfunction (cumulative microvascular injury) more than atherosclerosis progression in iTTP patients who developed long-term cardiovascular complications during clinical remission [7,12]. We postulate that in addition to the acute ischemic injury caused by microvascular thrombosis during the acute episode, during clinical remission a state of subclinical vasculopathy may lead to a cumulative vascular injury and persistent organ damage. Such cumulative vascular injury, together with chronic inflammation and

VWF/ADAMTS13 imbalance, may in turn be the main cause of the increased incidence of MACE during clinical remission.

This research hypothesis is consistent with the significantly increased observed rate of IS at variance with the ACS rate. Indeed, ACS is known to be more related to atherogenic risk factors than IS that has a more heterogeneous etiology [13].

Regarding the lower MACE rates we observed in comparison with that reported by Brodsky et al [8], this is not surprising, considering the very higher prevalence of cardiometabolic risk factors in the Afro-American ethnicity. It must be noticed that the study of Brodsky et al was a prospective cohort study in contrast to the present retrospective study. Moreover, the definition of ACS used by Brodsky et al was different from our study because in addition to fatal and non-fatal MI they also included cardiac revascularizations.

This study has several limitations. First, the retrospective nature of data collection, leading to several missing data and no detailed information on the cardiovascular risk factors and events. Several variables were available only in a subsample; however, as being representative of the whole cohort, this does not affect our findings. Regular ADAMTS13 testing during remission was unavailable before MACE and thus it was not possible to estimate its predictive role on MACE. Conclusions are in some parts limited by the small size of the group with MACE, especially when data are also missing for a part of patients. However, the work provides interesting results for practitioners who manage these patients.

These preliminary results underline the urgent need of a multidisciplinary scientific effort aimed at understanding the role of microvascular cumulative organ damage in iTTP patients during remission.

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Table 1. Main features of our cohort of iTTP patients, with and without MACE occurring during clinical remission

Variables	iTTP patients with MACE N=8	iTTP patients without MACE N=224
Age at the first TTP episode, years, median (IQR)	44 (31-58)	41 (30-52)
<50 years, n (%)	5 (62.5)	152 (67.9)
50-69 years, n (%)	2 (25)	68 (30.4)
≥70 years, n (%)	1 (12.5)	4 (1.8)
Female sex, n (%)	4 (50)	171 (76.3)
White ethnicity, n (%)	8 (100)	217 (96.9)
Time of observation, months, median (IQR)	95 (66-141)	73 (40-116)
Number of iTTP episodes, median (IQR)	1 (1-2)	1 (1-3)
concomitant autoimmune disease, n (%)[1]	1 (12.5)	24 (18)
overweight/obesity, n (%)[2]	2 (33.3)	55 (60.4)
current/former smoker, n (%)[3]	4 (66.7)	64 (66.7)
type 2 diabetes, n (%)[4]	0	11 (8.3)
hypertension, n (%)[5]	2 (28.6)	31 (23.3)
hyperlipidemia, n (%)[6]	2 (28.6)	22 (16.5)

[1]available in 8/8 (MACE) and 133/224 (No MACE); [2]available in 6/8 (MACE) and 91/224 (No MACE); [3]available in 6/8 (MACE) and 96/224 (No MACE); [4]available in 7/8 (MACE) and 133/224 (No MACE); [5]available in 7/8 (MACE) and 131/224 (No MACE); [6]available in 7/8 (MACE) and 131/224 (No MACE).

Age was recorded at the onset of the first TTP episode and, for patients with MACE, also at the time of MACE. Hypertension, hyperlipidemia and type 2 diabetes were recorded as self-reported or in case of chronic use of antihypertensive, lipid-lowering or anti-diabetic medications. Overweight and obesity were defined when body mass index (BMI) was equal to or greater than 25 kg/m^2 and 30

kg/m^2. Current smokers were those who smoked at least a cigarette per day or had stopped smoking for less than one year, former smokers who had stopped smoking for at least one year.

For the comparison on concomitant autoimmunity and cardiovascular risk factors we could consider only a subsample in the frame of those without MACE (i.e., those with disease onset and referral to our Center after 2012, n=133/224), because only these cases had available information on these variables. For patients with MACE, concomitant autoimmunity and cardiovascular risk factors were recorded at the closest time visit before MACE (or before the first MACE for cases with 2 or more MACE). For patients with no MACE, concomitant autoimmunity and cardiovascular risk factors were recorded both at the time of first TTP episode and at the last follow-up date, when available (in the context of patients with onset and referral to our Center after 2012). Each condition or risk factor was considered present if recorded in at least one of the two times.

Abbreviations: ACS, acute coronary syndrome; iTTP, immune-mediated thrombotic thrombocytopenic purpura; IQR, interquartile range; IS: ischemic stroke; MACE, major adverse cardiovascular events.

Table 2. MACE rates and main features of patients with MACE within our cohort and in two selected cohorts from the US and Italian population.

	Our cohort n=232	**Brodsky et al cohort* n= 181**	**Santoro et al cohort** n= 132,598**
Population	iTTP patients (Italy)	iTTP patients (US)	General population (Italy)
Study design	cohort study	cohort study	cross-sectional
Median follow-up, years	6.3	7.6	Lifelong
MACE incidence proportion, %	3.4	28.6	Not available
IS incidence proportion, %	3	18.2	0.8
ACS incidence proportion, %	0.4	12.2***	1.9
	Patients with MACE in our cohort n=8	**Patients with MACE in Brodsky et al* n=43**	**Patients with CVDs in Santoro et al** n=6545**
white ethnicity, %	100	32.6	95
female sex, %	50	74.4	43
age at enrolment, years, median (IQR) [1]	44 (31-58)	45 (34-53)	range: 18-69
overweight/obesity, %[2]	33.3	55.8[3]	61.1
current/former smoking, %[2]	66.7	not available	56.9
type 2 diabetes, %[3]	0	53.5	18.6
hypertension, %[3]	28.6	74.4	55.9
hyperlipidemia, %[3]	28.6	51.2	44.2
chronic kidney disease, %[3]	0	41.9	Not applicable
concomitant autoimmune disease, %	12.5	14	Not applicable

*Brodsky MA et al. Am J Hematol. 2021 [8]; **Santoro V et al. Ann Ist Super Sanita. 2022 [11].

***including non-fatal MI (12/181), fatal MI (1/181) and cardiac revascularization (9/181).

[1] For iTTP patients (our cohort and Brodsky et al), age at the first TTP episode onset was considered.

[2]available in 6/8 patients; [3]available in 7/8 patients; [4]referred to obesity.

For the patients with more than one MACE, these rates were estimated including only the first occurring MACE.

In the study by Santoro et al, authors used data from the Italian cross-sectional Behavioural Risk Factor Surveillance System PASSI (2015-2018). Information on CVDs were retrieved by asking the interviewees if a physician had ever diagnosed or con-firmed any of the following: (i) myocardial infarction, cardiac ischaemia or coronary disease; (ii) other heart diseases such as heart failure or valvulopathy; (iii) stroke or cerebral ischaemia.

Abbreviations: ACS: acute coronary syndrome; CVDs: cardiovascular diseases (myocardial infarction, cardiac ischemia or coronary disease; other diseases such as heart failure or valvulopathy; stroke or cerebral ischemia); IQR: interquartile range; MACE: major adverse cardiovascular event.