Supplemental methods

Patient controls

40 pseudonymized patient controls were recruited from the laboratory routine of the Institute of Clinical Chemistry and Laboratory Medicine of the University Medical Center Mainz. The patients had all presented in January 2018 in one of the outpatient clinics of the University Medical Center Mainz; patients of the hematology outpatient clinic were excluded, as TTP patients and patients with von Willebrand disease (VWD) are affiliated there. Inclusion was conditional on the collection of citrated blood no longer than 4 hours ago and pre-existing analysis of the following parameters from the same date: PT, aPTT, fibrinogen, and a total blood count. PT, aPTT, fibrinogen, platelet count, and leukocyte count had to be within the laboratory's reference ranges, respectively. If C-reactive protein (CRP) was available, it also had to be within the reference range. The collective consisted of 26 women and 14 men aged between 14 and 80 years (mean ±standard deviation: 49 ±17 years).
The use of pseudonymized diagnostic rest material for the evaluation of diagnostic tests was approved by the Ethics Committee of the “Landesärztekammer Rheinland-Pfalz” and is part of the patient admission agreement (§ 14 Abs. 3) of the University Medical Center Mainz.

Healthy controls

Citrated plasma was obtained from 25 anonymized healthy controls. The study of healthy donors as controls for platelet disorders was approved by the Ethics Committee of the “Landesärztekammer Rheinland-Pfalz” (837.302.12; 25.07.12; 2018-13290_1; 27.07.2018).

Assays

All routine laboratory assays such as complete blood count, reticulocytes, schistocytes, creatinine, urea, ALAT, ASAT, total bilirubin, LDH, CRP, haptoglobin, creatine kinase (CK) and troponin I (TNI), coagulation screen (Quick, aPTT, fibrinogen, D-dimers), as well as testing for HIV, hepatitis B/ C were performed in the accredited (DIN-ISO 15.189) Institute of Clinical Chemistry and Laboratory Medicine of the University Medical Center, Mainz. Whole blood count was determined using ADVIA® 2120i Hematology system (Siemens); Schistocytes were counted visually using a light microscope (Leica); clinical chemistry parameters were measured using an Alinity (Abbott Diagnostics). Haemostatic parameters were measured using an ACL Top 750 coagulation analyzer (Instrumentation Laboratory/ Werfen Diagnostics).

ADAMTS13 inhibitor

ADAMTS13 inhibitor was detected by incubating a mixture of heat-inactivated patient plasma with pooled normal plasma (1:1; v:v) for 60 min at 37 °C and then measuring ADAMTS13 activity with the FRETS-VWF73 assay compared with heat-inactivated normal human plasma mixed 1:1 with normal human plasma[1-3]. Inhibition of 50% of ADAMTS13 activity of normal plasma by undiluted patient plasma was defined as 1 Bethesda unit per ml. An ADAMTS13 inhibitor was diagnosed when ≥0.5 BU/ml was found.

Supplemental Tables

Supplemental Tab. 1: Clinical data of 16 well documented acute iTTP episodes in 10 patients.

Characteristics of the acute iTTP episode															
Pat.ID	**Age at acute episode [years]**	**Sex**	**Age at initial iTTP diagnosis**	**Number of previous acute episodes**	**Number of the current episode**	**Severity of the acute episode (clinical score[#])**	**Duration of the acute episode[+]**	**Start of the acute episode**	**Date of first TPE**	**Date of last TPE**	**Number of TPE sessions**	**Total volume of infused plasma during TPE**	**Daily predni-solone dose[*]**	**Rituximab**	**Other iTTP treatment**
011	63.5	f	53.8	4	5	moderate (2)	10	22.04.2017	11.05.2017	20.05.2017	8	20913ml	100mg	no	no
011	63.8	f		5	6	moderate (2)	9	09.08.2017	09.08.2017	17.08.2017	8	21674ml	75mg	no	no
011	64.0	f		6	7	moderate (2)	12	26.10.2017	26.10.2017	06.11.2017	8	21365ml	70mg	4x 375mg/m^2	3x RBC
015	25.2	f	12.3	3	4	laboratory abnormalities only (0)	12	09.01.2018	10.01.2018	21.01.2018	10	26632ml	no	3x 375mg/m^2	2x RBC
032	27.9	m	25.1	1	2	moderate (2)	15	29.12.2017	29.12.2017	12.01.2018	11	28609ml	100mg	no	no
032	28.5	m		2	3	moderate (2)	11	04.08.2018	04.08.2018	14.08.2018	9	25388ml	100mg	no	no
044	70.9	m	61.3	4	5	moderate (2)	13	25.01.2017	02.02.2017	06.02.2017	4	12400ml	40mg	4x 375mg/m^2	no
045	38.9	f	25.8	1	2	mild (1)	8	15.08.2017	15.08.2017	22.08.2017	7	18630ml	75mg	no	no
045	39.7	f		2	3	moderate (2)	11	15.06.2018	15.06.2018	25.06.2018	9	29703ml	80mg	no	no
063	32.2	f	17.5	11	12	mild (1)	11	08.08.2017	08.08.2017	18.08.2017	9	23455ml	100mg	no	no
063[P]	32.6	f		12	13	mild (1)	36	02.01.2018	19.01.2018	23.02.2018	15	39697ml	5mg	no	no
064	67.3	f	40.2	5	6	mild (1)	10	06.12.2017	06.12.2017	15.12.2017	8	21064ml	60mg	no	no
079	48.3	f	31.5	2	3	moderate (2)	16	02.12.2017	02.12.2017	18.12.2017	12	36726ml	75mg	no	no
079	48.6	f		3	4	mild (1)	13	21.03.2018	21.03.2018	02.04.2018	10	31496ml	75mg	4x 375mg/m^2	no
085	76.7	f	76.7	0	1	severe (3)	34	30.05.2018	03.06.2018	02.07.2018	29	86708ml	no	1[§] (stopped)	2x RBC
086	53.6	m	53.6	0	1	severe (3)	18	03.08.2018	03.08.2018	20.08.2018	15	unknown	100mg	no	2x RBC

[#]Clinical severity score for acute iTTP episodes[4]. [+]Days from 1st to last therapeutic plasma exchange (TPE). [*]Initial dose of Prednisolone (Decortin H) per day.

[§]Due to a complex focal seizure and fever, rituximab application was discontinued after 1st dose.

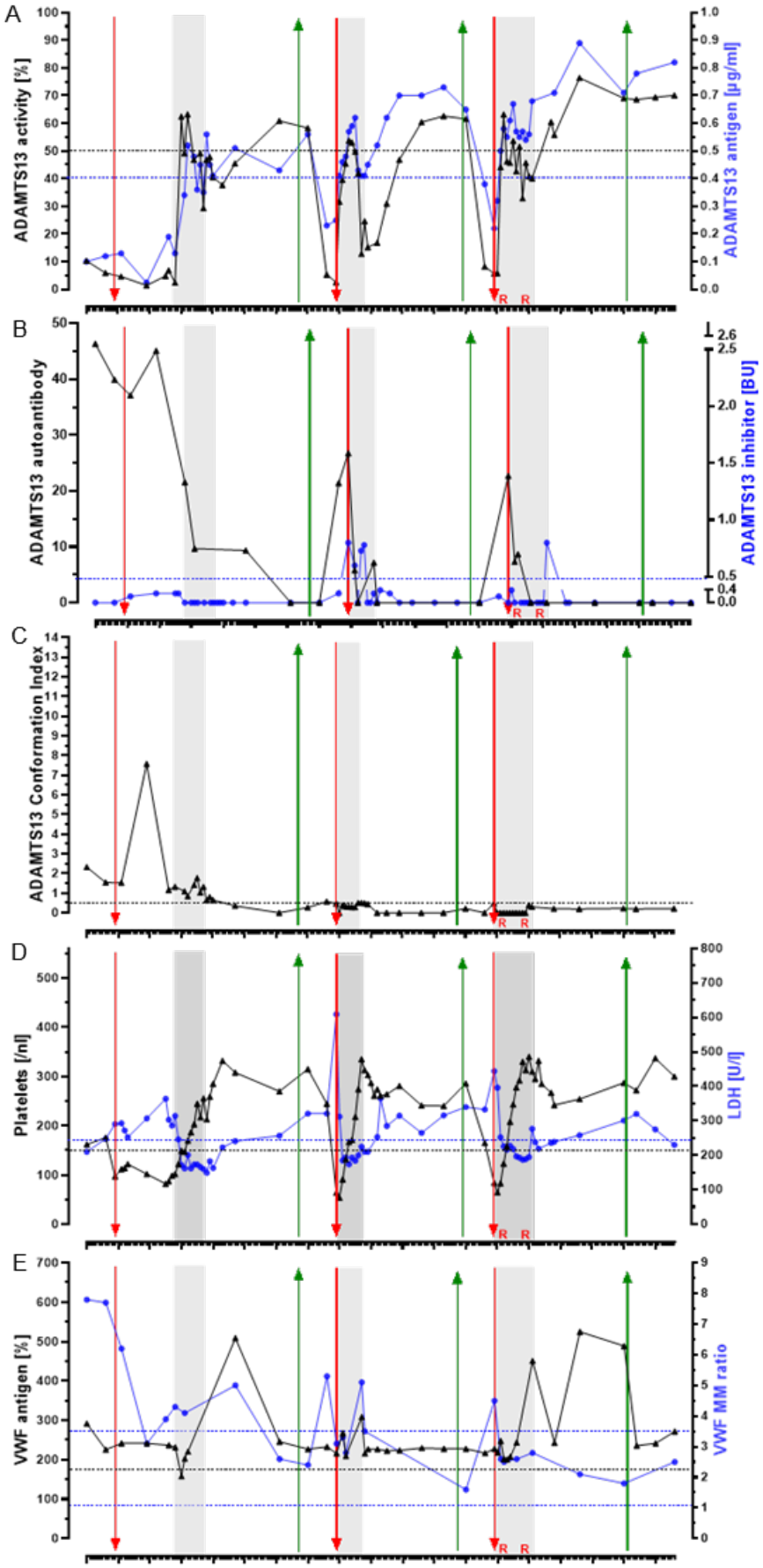
Pat.ID: patient identification, iTTP: autoimmune thrombotic thrombocytopenic purpura, TPE: therapeutic plasma exchange, RBC: red blood cell concentrate

Supplemental Tab. 2: Comorbidities in 10 patients with 16 well documented acute iTTP episodes.

Characteristics of the patients with an acute episode during observation time									
Pat.ID	**Age at end of study [years]**	**Number of all acute episodes at the end of observation time**	**BMI**	**Arterial hyper-tension**	**Type 2 Diabetes mellitus**	**Ischemic stroke**	**Myocardial infarction**	**others**	**Smoking**
011	64.8	6	26.4	Yes	No	2 (1993/ 1994)	1 (2008)	Atrial fibrillation Hyperlipoproteinemia Osteoporosis	No
015	25.8	4	24.6	No	No	No	No	Hashimoto thyreoiditis Psoriasis	No
032	28.6	3	24.5	No	No	No	No	Sarcoidosis	No (since 2015)
044	72.3	5	28.1	Yes	Yes	2 (2002/ 2007)	No	PAOD Scheuermann`s disease Renal insufficiency 3	No (since 2002)
045	39.8	3	28.0	No	No	No	No	Coeliac disease Lipedema	No
063	33.2	13	32.0	No	No	No	No	Epilepsy	Yes
064	68.0	6	23.4	Yes	No	No	No	Hashimoto thyreoiditis	No
079	48.9	4	35.9	No	No	No	No	Cholecystectomy	No
085	76.9	1	26.6	Yes	No	No	No	Rheumatoid arthritis	No
086	53.7	1	27.8	No	No	No	No	Chronic pain Diverticulosis	Yes

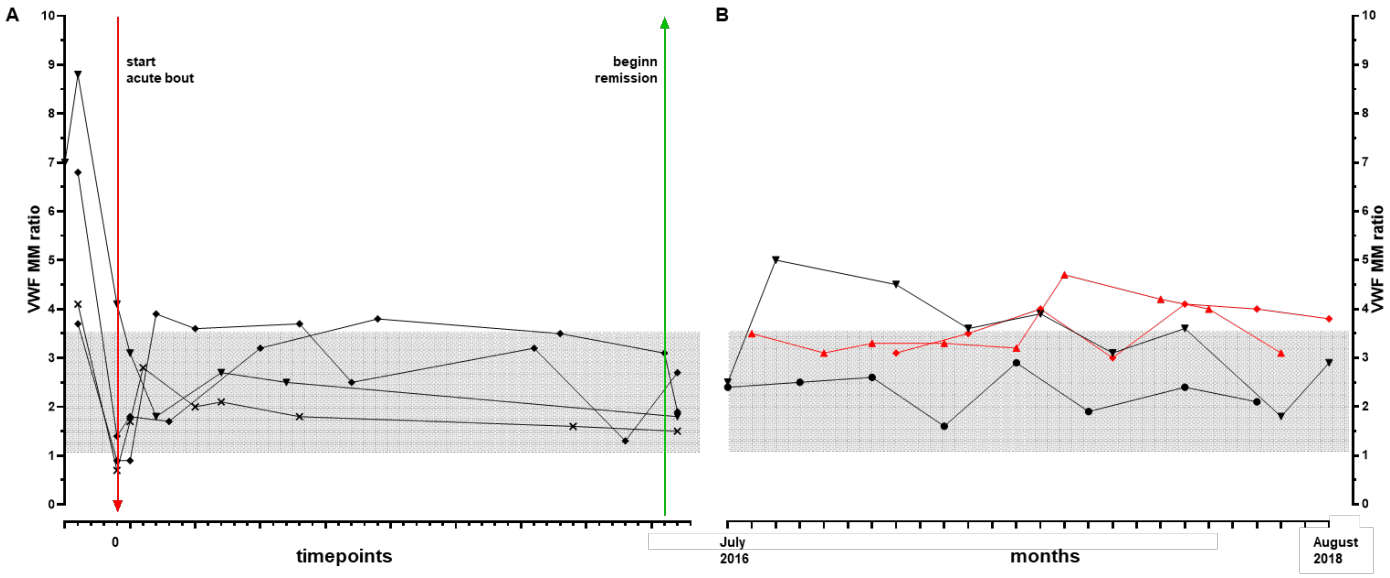
Pat.ID: patient identification, iTTP: autoimmune thrombotic thrombocytopenic purpura, BMI: Body mass index, PAOD: peripheral artery occlusive disease

Supplemental Figures

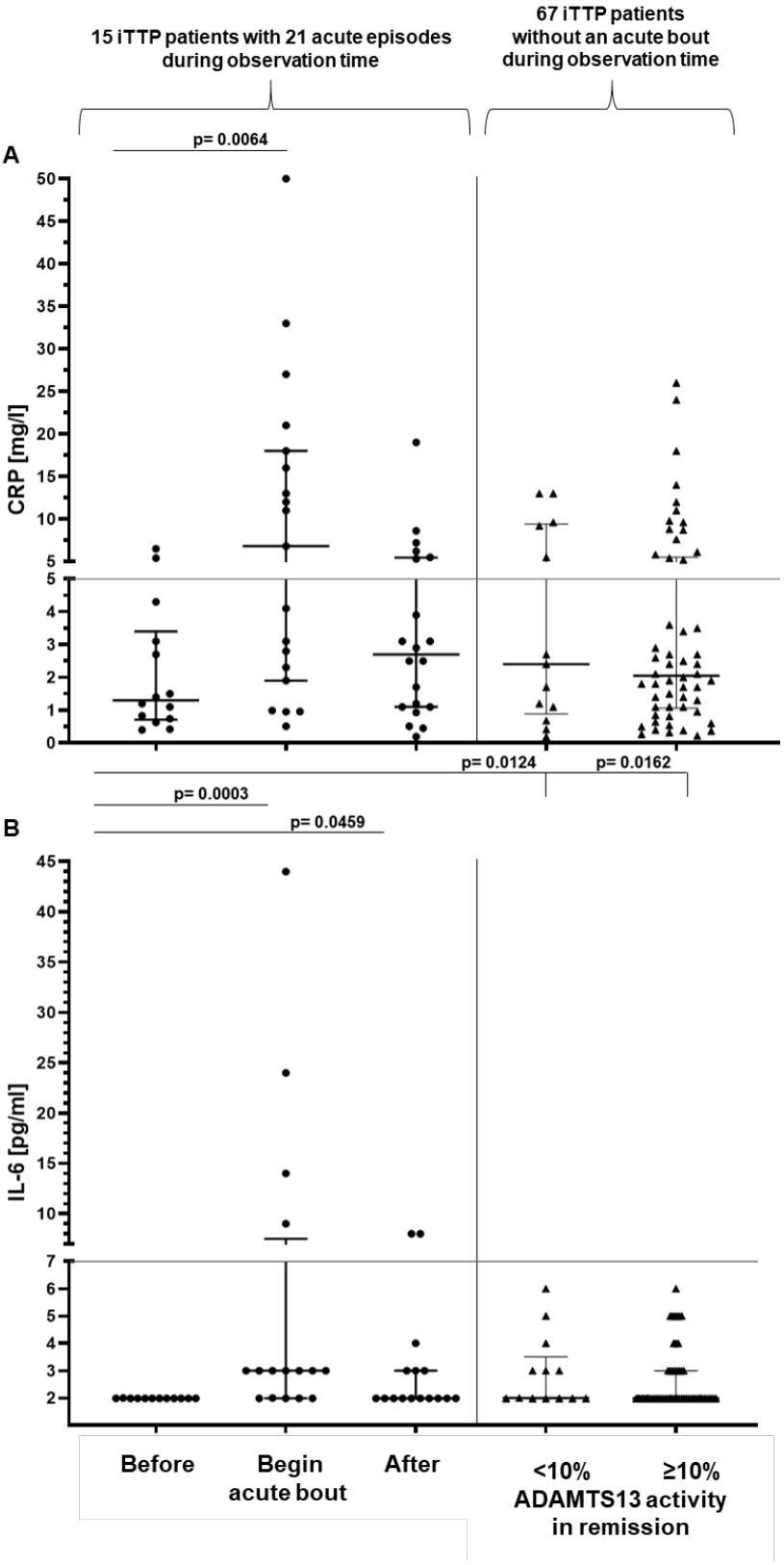


Supplemental Fig. 1: Course over time of iTTP markers in one exemplary patient with three acute iTTP episodes during study period. Time axis on the abscissa**.** Prednisolone, given during TPE periods is not

shown. „R“ denotes rituximab application. The red arrows mark the onset of acute episodes, the green arrows the onset of remission after acute episodes. The period of TPE is highlighted in gray. (A) The dotted lines indicate the lower limits of reference ranges. (B) The blue dotted line indicates the upper limit of reference range. (C) The dotted line indicates the upper limit of normal. (D) The dotted lines indicate the lower limit for platelet count and the upper limit for LDH. (E) The dotted lines indicate the upper and lower limits for VWF multimer (MM) ratio and upper limit for VWF antigen, respectively.



Supplemental Fig. 2: Course of VWF multimer (MM) ratio. (A) VWF MM ratio before, during and after four exemplary acute episodes in different patients shown by different symbols (×, ▼, ♦, ●). Timepoints between episode onset (red arrow) and remission (green arrow) represent days. (B) VWF MM ratio in four exemplary iTTP patients in continuous remission during the whole study period. Two patients with constant ADAMTS13 activity <10% are shown by red symbols (▲, ♦), two patients with ADAMTS13 activity >10% in black symbols (●, ▼). Months on the abscissa from study start in July 2016 until study end in August 2018. The reference range for VWF MM ratio is highlighted in gray.



Supplemental Fig. 3: CRP (A) and IL-6 (B) in 82 iTTP patients with and without acute episodes during the study period. The left panel in A and B, respectively, shows CRP and IL-6 before (n=14), at the beginning (n=16) and in remission after the acute episodes (n=20) of the acute episodes. The right panel gives these parameters in iTTP patients in constant remission, grouped according to ADAMTS13 values <10% (n=13) and ≥10% (n=54). The gray horizontal lines mark the upper limits of the CRP and IL-6 reference ranges, respectively.

Supplemental References:

1. Kokame K, Nobe Y, Kokubo Y, Okayama A, Miyata T. FRETS-VWF73, a first fluorogenic substrate for ADAMTS13 assay. *Br J Haematol*. 2005;129(1):93-100.
2. Kremer Hovinga JA, Mottini M, Lammle B. Measurement of ADAMTS-13 activity in plasma by the FRETS-VWF73 assay: comparison with other assay methods. *J Thromb Haemost*. 2006;4(5):1146-1148.
3. Froehlich-Zahnd R, George JN, Vesely SK, et al. Evidence for a role of anti-ADAMTS13 autoantibodies despite normal ADAMTS13 activity in recurrent thrombotic thrombocytopenic purpura. *Haematologica*. 2012;97(2):297-303.
4. Falter T, Herold S, Weyer-Elberich V, et al. Relapse Rate in Survivors of Acute Autoimmune Thrombotic Thrombocytopenic Purpura Treated with or without Rituximab. *Thromb Haemost*. 2018;118(10):1743-1751.