SUPPLEMENTARY APPENDIX

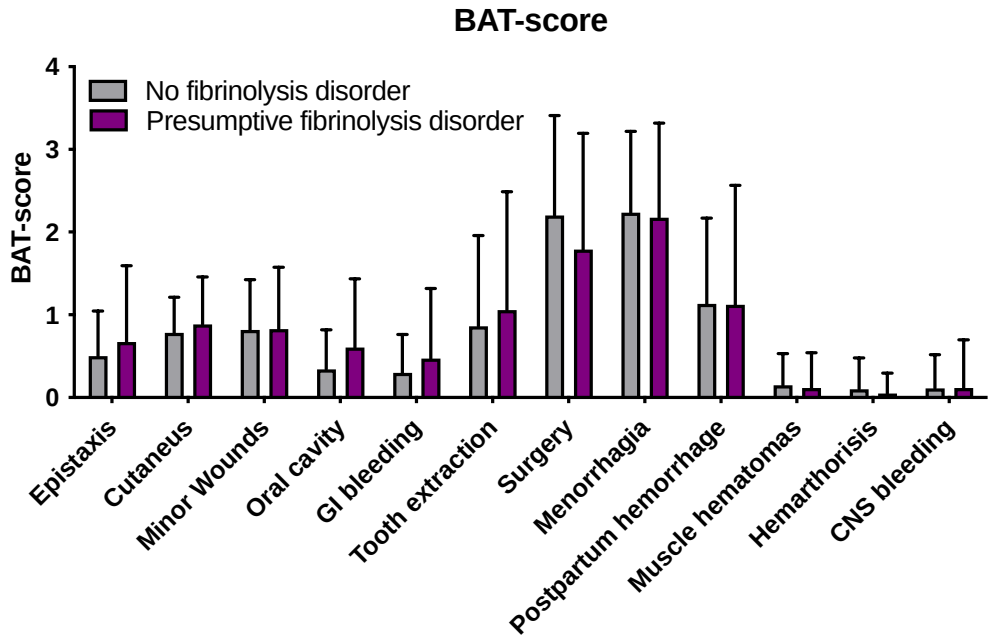
Fibrinolytic assays in bleeding of unknown cause: improvement in diagnostic yield

Supplementary figure

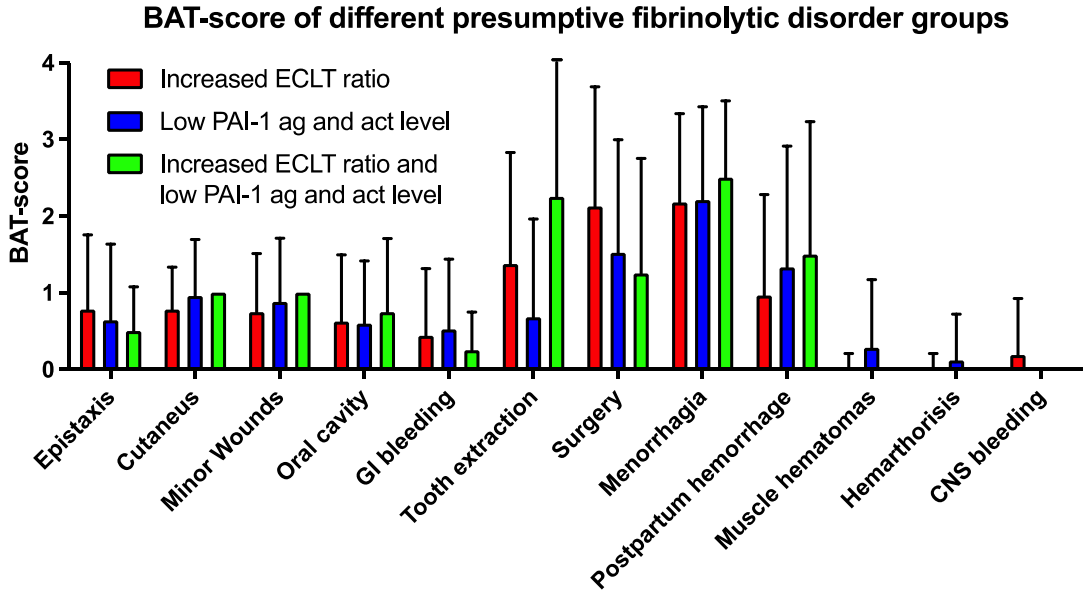
Supplementary tables

Supplementary figures

Supplementary figure 1: BAT score subcategories

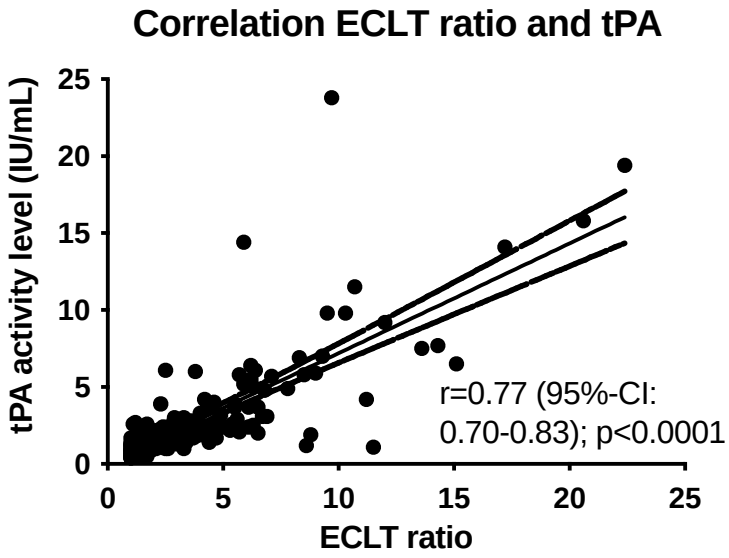


A. Subdivision of BAT-score according to symptoms, divided in patients without (grey) and with a presumptive fibrinolytic disorder (purple). Bar indicates mean, whiskers standard deviation.

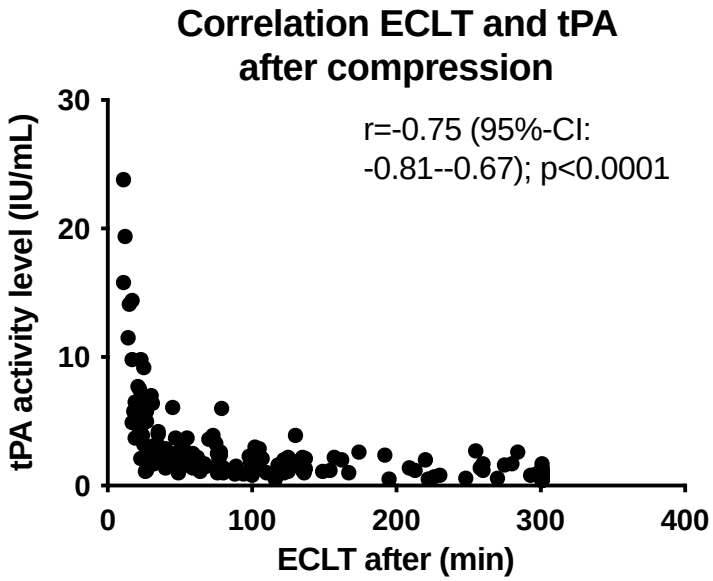


B. Subdivision of BAT-score according to symptoms, divided in patients with an increased ECLT ratio or low baseline ECLT (red), patients with a low PAI-1 ag and act level (blue), and patients with both a high ECLT ratio and low PAI-1 ag and act level (green). Bar indicates mean, whiskers standard deviation.

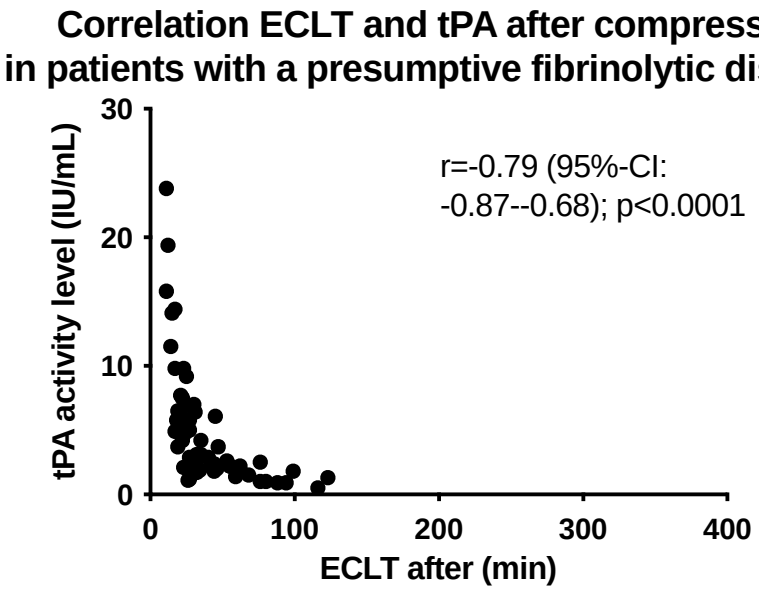
Supplementary figure 2: Correlation of euglobulin clot lysis time and tPA activity level



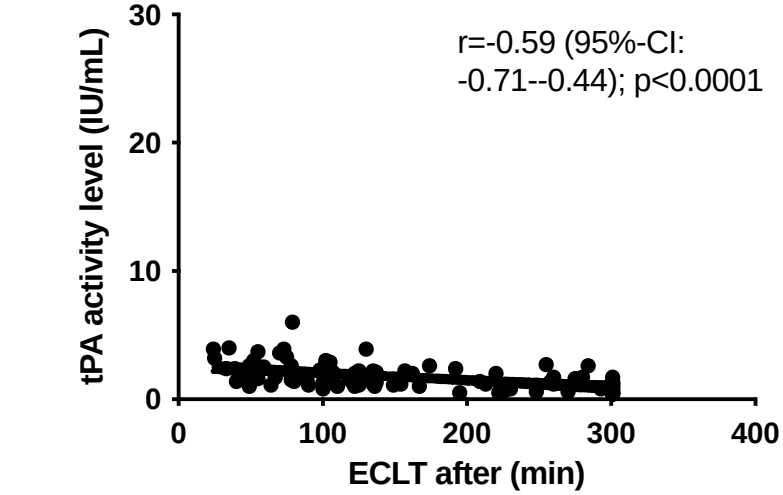
A. Correlation between ECLT ratio and tPA concentration after venous compression.



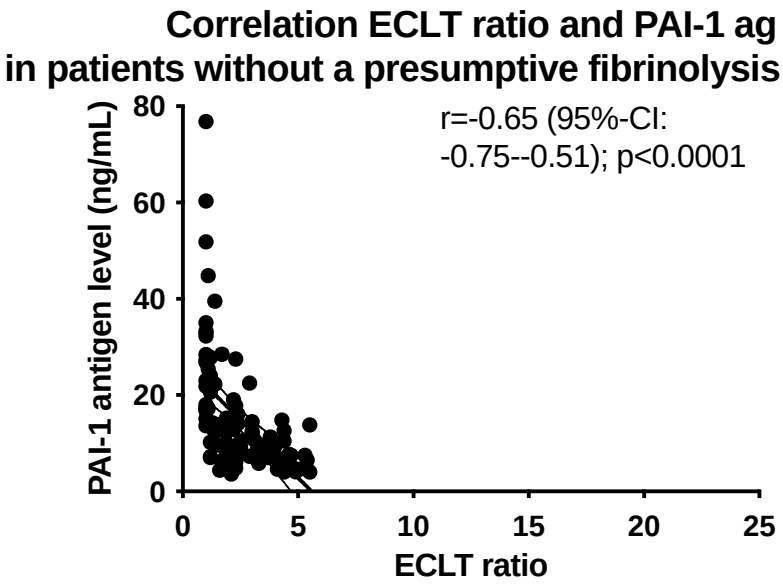
B. Correlation between ECLT and tPA activity level after venous compression in all patients.



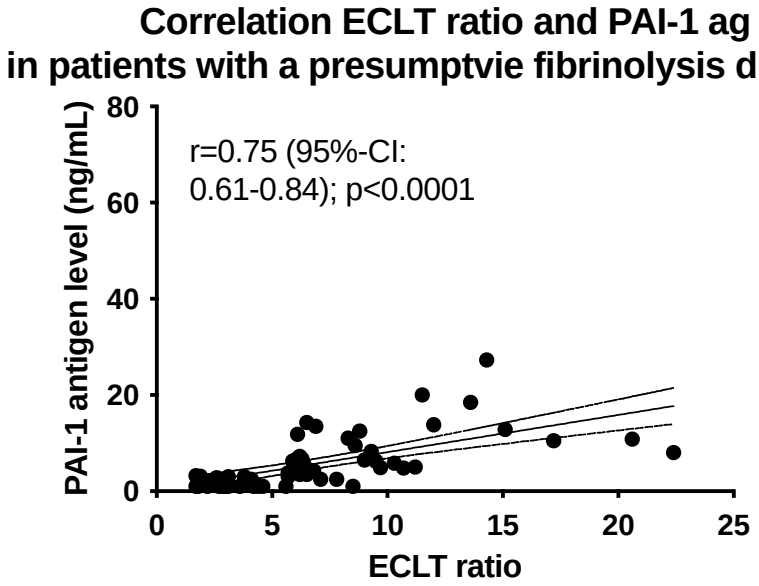
C. Correlation between ECLT and tPA concentration after venous compression in patients with a presumptive fibrinolytic disorder.



D. Correlation between ECLT and tPA concentration after venous compression in patients without a fibrinolytic disorder.

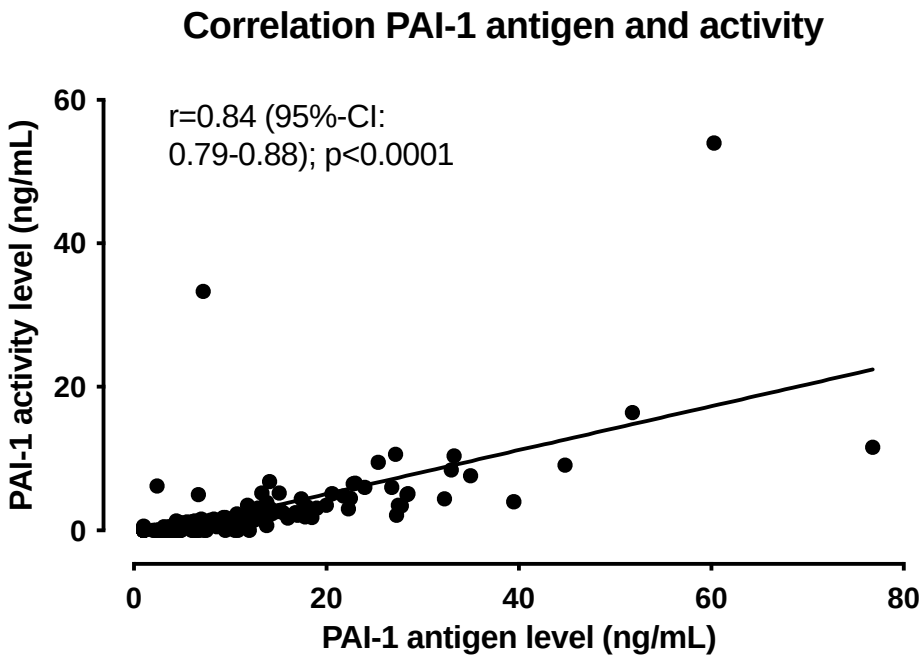


E. Correlation between ECLT ratio and PAI-1 antigen in patients without a fibrinolytic disorder.

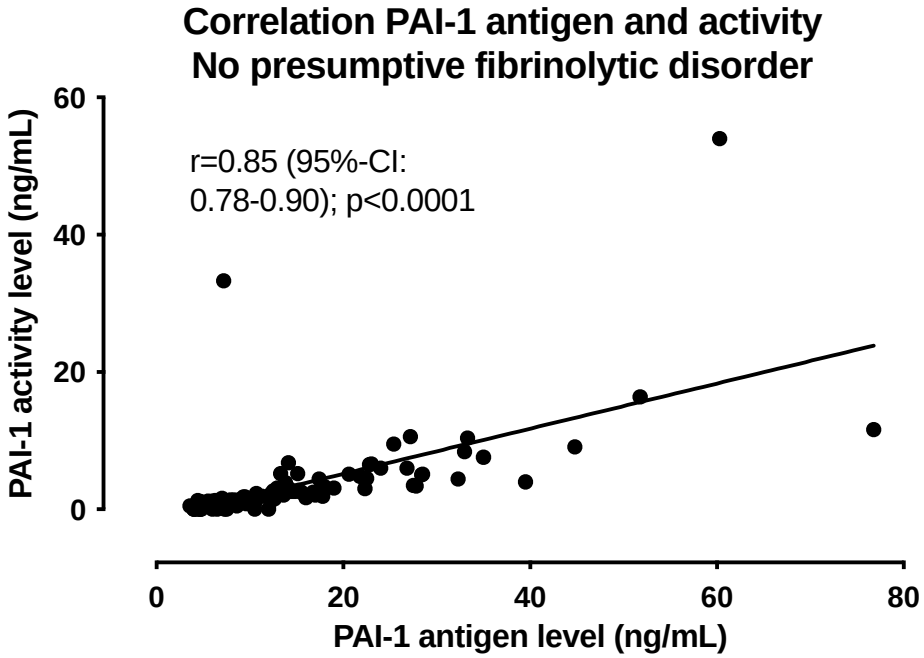


F. Correlation between ECLT ratio and PAI-1 antigen in patients with a presumptive fibrinolytic disorder.

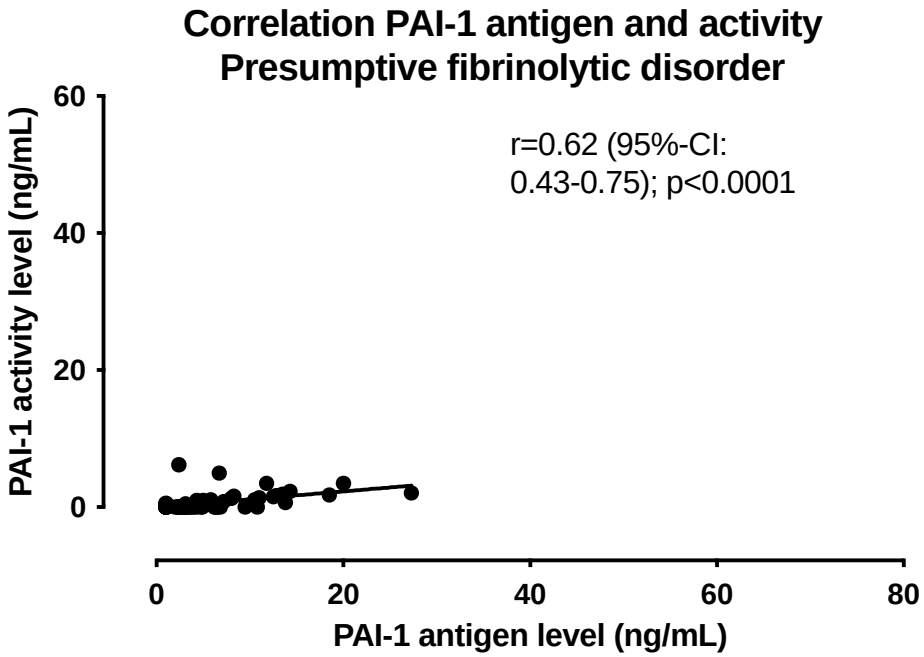
Supplementary figure 3: Correlation between PAI-1 antigen and PAI-1 activity



A. Correlation of PAI-1 antigen level and PAI-1 activity level for all patients included in the study.

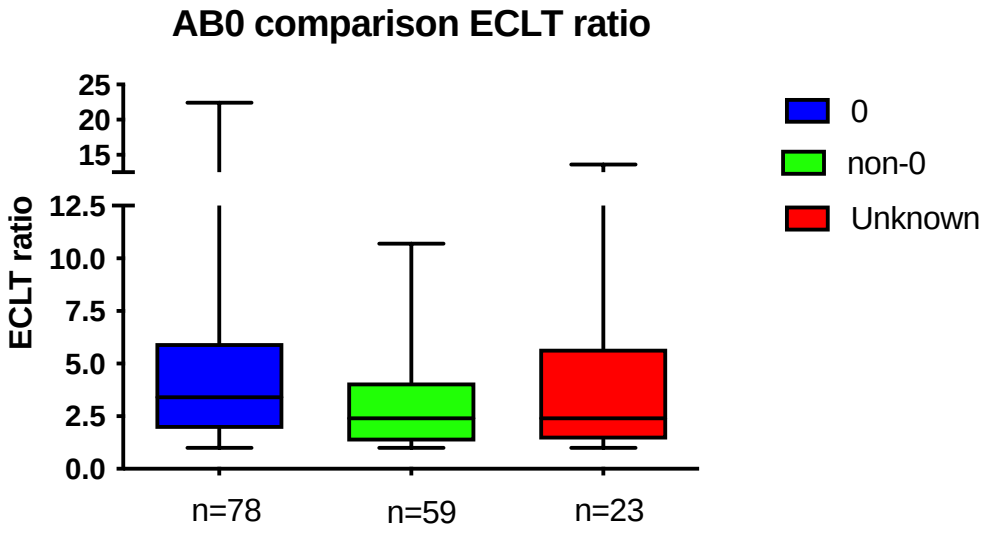


B. Correlation of PAI-1 antigen level and PAI-1 activity level for patients without a fibrinolytic disorder.

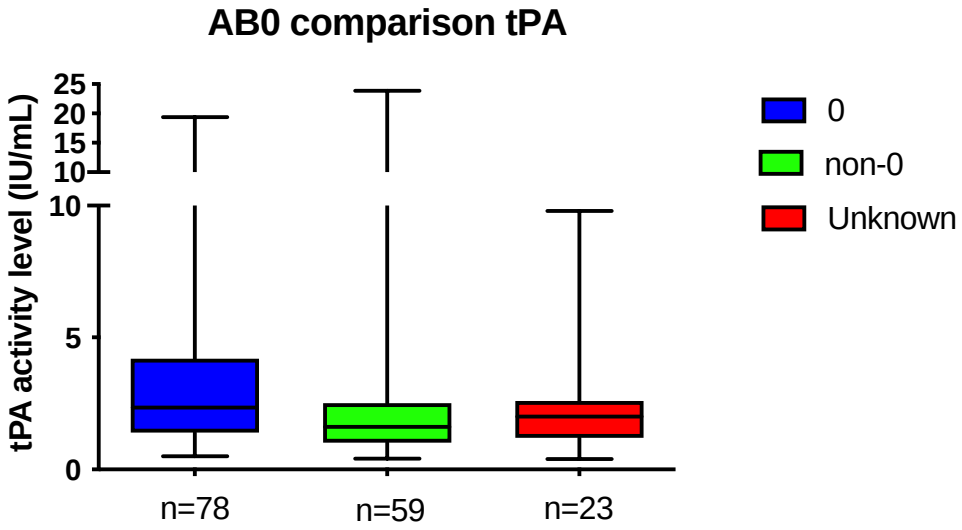


C. Correlation of PAI-1 antigen level and PAI-1 activity level for patients with a presumptive fibrinolytic disorder.

Supplementary figure 4: ECLT ratio and tPA according to blood group



A. Euglobulin clot lysis time ratio divided according to blood group (0, non-0 and unknown blood group).



B. Tissue plasminogen activator divided according to blood group (0, non-0 and unknown blood group).

Supplementary tables

Supplementary table 1: Clinical characteristics per subgroup of fibrinolytic disorder

	Presumptive fibrinolytic disorder (n=63)	**High ECLT ratio (n=34)**	**Low PAI-1 ag and act (n=25)**	**High ECLT ratio and low PAI-1 ag and act (n=4)**
Age, median (extremes)	38 (15-78)	57 (15-78)	33 (17-61)	30 (17-58)
Female, n (%)	55 (87)	28 (82)	23 (92)*	4 (100)
BAT-score, mean (SD)	9.8 (3.5)	9.9 (3.2)	9.4 (4.0)	11 (4.1)
Epistaxis	0.6 (0.9)	0.8 (1.0)	0.5 (0.9)	0.5 (0.6)
Cutaneous	0.9 (0.6)	0.8 (0.6)	1.0 (0.7)	1.0 (0.0)
Minor wounds	0.8 (0.8)	0.8 (0.8)	0.9 (0.8)	1.0 (0.0)
Oral cavity	0.6 (0.8)	0.6 (0.9)	0.6 (0.8)	0.8 (1.0)
GI bleeding	0.5 (0.9)	0.4 (0.9)	0.5 (0.9)	0.3 (0.5)
Tooth extraction	1.1 (1.5)	1.4 (1.5)	0.7 (1.3)	2.3 (2.2)
Surgery	1.8 (1.5)	2.1 (1.6)	1.5 (1.5)	1.3 (1.5)
Menorrhagia*	2.2 (1.2)	2.2 (1.2)	2.2 (1.2)	2.5 (1.0)
Post-partum hemorrhage*	1.2 (1.5)	1.0 (1.3)	1.3 (1.6)	1.5 (1.7)
Muscle hematomas	0.1 (0.6)	0.0 (0.2)	0.3 (0.9)	0.0 (0.0)
Hemarthrosis	0.1 (0.4)	0.0 (0.2)	0.1 (0.6)	0.0 (0.0)
CNS bleeding	0.1 (0.5)	0.2 (0.7)	0.0 (0.0)	0.0 (0.0)
Use of anticoagulants, number (%)	2 (3)	1 (3)	1 (4)	-
Use of NSAIDs, number (%)	1 (2)	-	1 (4)	-
* Bleeding scores of male patients were described as missing data, except for the male patient who was in a transgender trajectory, originating from female.				

BAT: bleeding assessment tool; GI: gastro-intestinal; CNS: central nervous system; NSAID: non-steroidal anti-inflammatory drug; VWD: von Willebrand disease.

Supplementary table 2: Results of coagulation analysis in all included patients.

	Reference range	No fibrinolytic disorder (n=97)*	Presumptive fibrinolytic disorder (n=63)*
Thrombocytopathy			
Aggregation disorder, number (%)		14 (14)	17 (28)
1 agonist defect		7 (8)	9 (16)
2 agonists defects		4 (5)	5 (7)
3 or more agonist defects		3 (3)	3 (5)
Receptor disorder, number (%)			
GPIIIa disorder, number (%)		1 (1)	1 (2)
Activation marker disorder, number (%)		6 (6)	1 (2)
GPIIb/IIIa (PAC-1) disorder, number (%)		3 (3)	1 (2)
GP53 disorder, number (%)		2 (2)	-
P-selectin disorder, number (%)		1 (1)	-
ADP in platelets in nmol/10^8 platelets , mean (SD)	2.5-5.6	4.2 (1.0)	4.2 (0.9)
ADP in thrombocytes lowered, number (%)		1 (1)	-
PF4 in platelets in ug/10^9 platelets, mean (SD)	0.9-1.7	1.2 (0.2)	1.3 (0.5)
PF4 in thrombocytes lowered, number (%)		3 (3)	1 (2)
BTG in platelets in IU/10^9 platelets, mean (SD)	17.4-32.8	26.9 (5.0)	27.1 (6.2)
BTG in platelets lowered, number (%)		1 (1)	-
Von Willebrand disease			
Ristocetin activity in %, mean (SD)	> 50	91 (39)	87 (34)
Ristocetin activity lowered, number (%)		5 (5)	4 (7)
Von Willebrand factor antigen in %, mean (SD)	> 50	100 (44)	97 (43)
Von Willebrand factor antigen lowered, number (%)		5 (5)	4 (7)
Collagen binding capacity in %, mean (SD)	> 64	100 (46)	97 (42)

Collagen binding capacity lowered, number (%)		10 (12)	10 (22)
Von Willebrand factor multimers reduced, number (%)		-	1 (3)
Secondary hemostasis			
PT in seconds, mean (SD)	12.0-15.0	13.8 (1.3)	14.4 (2.3)
PT elevated, number (%)		3 (3)	5 (8)
APTT in seconds, mean (SD)	26.0-34.0	31.7 (3.3)	31.7 (3.0)
APTT elevated, number (%)		11 (11)	6 (10)
Factor VIII in %, mean (SD)	> 60	114 (41)	111 (38)
Fibrinogen in mg/l, mean (SD)	1600-3200	3376 (659)	3093 (772)
Other factor deficiencies (per patient)		Factor II 63%	Factor II 42%; Factor IX 69%; Factor XI 54%; Factor XII 54%
		Factor V 60%	Factor VII 50%
		Factor XI 53%; Factor XII 68%	Factor IX 67%; Factor XII 64%
		Factor IX 51%; Factor XII 54%	
* Not all tests are performed in all patients, therefore the percentage can change per test			