Antithrombotic prophylaxis for surgery-associated venous thromboembolism risk in patients with inherited platelet disorders. The SPATA-DVT Study

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SUPPLEMENTAL METHODS

Study population

SPATA was a multicenter, international, retrospective observational study including patients with a definite diagnosis of IPD established according to well-defined laboratory and/or molecular genetic criteria[25-27] undergoing surgery [17]. IPDs were subdivided into inherited platelet number disorders (IPNDs), when low platelet count was the main phenotypic characteristic, and inherited platelet function disorders (IPFDs), when platelet dysfunction was the dominant phenotypic feature. Patients with acquired platelet disorders of any etiology were excluded [17].

In the current sub-study we included all the surgical procedures performed in patients for whom thromboprophylaxis should have been considered according to current guidelines, including major and minor invasive interventions[3, 11,28]. The decision to apply thromboprophylaxis was made by the attending physicians on an individual basis. Patients under 16 years of age were excluded due to the lower intrinsic VTE-risk in younger age[29, 30]. Major surgery was defined as any procedure in which a body cavity was entered, a mesenchymal barrier was crossed, a facial plane was opened, an organ was removed or normal anatomy was altered while minor invasive procedures were defined as any surgical procedure in which only skin, mucous membranes or superficial connective tissue were manipulated [17, 28]. Given the significant in situ thrombotic risk of central venous catheter insertion interventions [31], these were also considered in the analysis as minor procedures with high local thrombotic risk. Dental, ophthalmic, dermatological and endoscopic procedures and minor surgery not requiring immobilization were excluded.

Among the 829 surgical procedures included in the SPATA study, all those potentially amenable to thromboprophylaxis were identified [4] and the participating investigators were asked to review their records to extract additional data and, when data were not available in the records, to contact the surgeon who carried out the intervention or, when this was not possible, the patient or his/her relatives. A 48-item structured questionnaire on VTE-risk, thrombotic and bleeding events and antithrombotic prophylaxis had to be filled in for each at-risk procedure. Individual bleeding risk was estimated according to the type of IPD and previous individual bleeding history as assessed by the WHO-bleeding score [17].

The Institutional Review Board of the coordinating center approved this sub-study (CEAS Umbria, Italy, Approval n. 13138/18), each participating center complied with local ethical rules, and all patients or their legal representatives signed written informed consent.

Thromboembolic risk

VTE-risk associated with the individual surgical procedures was estimated using the Caprini Score [32], a validated method to predict VTE-risk based on clinical and laboratory parameters, such as type of intervention, comorbidities, previous VTE and thrombophilia, derived from a prospective study including patients undergoing general surgery [33]. The enrolled procedures were subdivided into four classes of risk depending on the Caprini score (very low risk: 0; low risk: 1-2; moderate risk: 3-4; high risk: ≥5). Surgical procedures were also classified according to procedure-related VTE-risk in three groups as suggested by the 2008 ACCP guidelines (low risk: minor surgery and interventions not requiring patient immobilization; moderate risk: abdominal, thoracic, gynecological and urological open surgery; high risk: hip or knee arthroplasty, hip fracture surgery, spinal cord injury and procedures associated with high bleeding risk)[3]. Both the Caprini and the procedure-related VTE-risk scores were centrally calculated based on the replies given by the participating investigators to the 48-item questionnaires.

Thrombotic outcomes

Thrombotic outcomes were defined as any symptomatic thrombosis (deep venous, including distal, and superficial) and/or pulmonary embolism occurring within one month after surgery. Diagnosis had to be confirmed using a validated method, including compression ultrasonography (CUS), phlebography, contrast enhanced computed tomography or ventilation/perfusion scintigraphy.

Supplementary table 1. Characteristics of patients and procedures according to the type of defect.

IPFD	Number of procedures (%)	Age median (IQR)	WHO-BS bleeding score median (IQR)	Platelet count at surgery ($x10^9$/L) median (IQR)	Caprini class median (IQR)	Procedure-related VTE risk median (IQR)	Thrombo prophylaxis (%)	LMWH (%)	Mechanical (%)	Any excessive post-surgical bleeding (%)
α2-adrenergic receptor defect	2 (1.8)	58 (58-59)	1 (1-1)	163.2(162-163.2)	3 (3-3)	1 (1-1)	0	0	0	0
Combined □/□ granule deficiency	1 (0.9)	43	2 (2-2)	NA	4	1	1 (100)	0	1 (100)	1 (100)
Bernard-Soulier Syndrome (biallelic)	11 (10)	53 (46-56)	3 (2-3)	60 (35.6-66.5)	4 (2-4)	2 (1-2)	0	0	0	7 (63)
Collagen receptors defect	2 (1.8)	47 (38-47)	2 (2-2)	58 (58-58)	2 (2-3)	2.5 (2-3)	2 (100)	2 (100)	1 (50)	0
CalDAG-related platelet disorder	1 (0.9)	NA	3	NA	3	2	1	1 (100)	0	0
Delta granule deficiency	20 (18.2)	50 (30-57)	3(1-3)	NA	3(2-3)	2 (2-3)	13 (65)	1 (5)	12 (60)	2 (10)
Gray platelet syndrome	6 (5.5)	60 (28-69)	2 (2-2)	NA	2 (1-3)	2 (2-2)	2 (33)	1(16.7)	1 (16.7)	2 (33)
Glanzmann thrombasthenia	33 (30)	49 (37-60)	3 (1-3)	185(142-212.5)	3 (2-4)	2 (1-2)	5 (15)	4 (12.1)	1 (3)	10 (30)
Glanzmann thrombasthenia variant form	5 (4.5)	32 (21-38)	2 (2-3)	NA	2 (2-3)	2 (1-2)	0	0	0	1 (20)
Hermansky–Pudlak syndrome	2 (1.8)	52 (52-52)	2 (2-2)	197.5 (194-197.5)	4 (4-4)	2 (1-2)	0	0	0	1(50)
P2Y12 deficiency	3 (2.7)	NA	2 (2-2)	NA	2 (1-2)	2 (2-2)	0	0	0	0
Primary secretion defect	18 (16.4)	37 (28-59)	3(2-3)	245 (194-245)	2 (3-2)	3(3-3)	12 (67)	1 (5.6)	11 (61)	5 (27)
Platelet-type Von Willebrand Disease	4 (3.6)	31 (23-58)	3 (3-3)	180 (112-180)	1 (1-1)	2 (2-2)	1 (25)	1 (25)	0	2 (50)
Scott syndrome	1 (0,9)	43	NA	NA	3	1	0	0	0	0
Thromboxane A2 receptor defect	1 (0.9)	24	2	NA	4	1 (1-1)	0	0	0	0
Total	110	48 (31-57)	4 (3-4)	145 (59 -200)	2 (1-4)	1 (1-2)	38 (34.5)	12 (10.9)	27 (24.5)	31 (14.7)

IPND	Number of procedures (%)	Age, median (IQR)	WHO-BS, median (IQR)	Platelet count at surgery (x 10^9/L), median (IQR)	Caprini class, median (IQR)	Procedure-related VTE risk median (IQR)	Thrombo prophylaxis (%)	LMWH (%)	Mechanical (%)	Any excessive post-surgical bleeding (%)
ACTN1-related thrombocytopenia	5 (5)	54 (19-64)	2 (1-2)	NA	3 (2-3)	1 (1-2)	0	0	0	0
ANKRD26-related thrombocytopenia	32 (32)	44 (29-56)	1 (0-2)	NA	3 (2-4)	2 (1-2)	1 (3.1)	1 (3.1)	0	4(12.5)
Familial platelet disorder and predisposition to acute myelogenous leukemia	4 (4)	26 (21-57)	2 (0-2)	NA	2 (1-3)	2 (2-3)	1 (25)	1 (25)	1 (25)	3 (75)
Bernard-Soulier Syndrome (monoallelic)	26 (26)	40 (31-56)	0 (0-2)	120 (120-782.5)	2 (1-4)	2 (2-2)	3 (11)	3 (11.5)	0	4 (15.4)
MYH9-related disease	30 (30)	37 (25-50)	2 (1-2)	39.5 (34.5-92.5)	3 (2-4)	2(1-2)	4 (13.3)	3 (10)	1 (3.3)	8 (26.7)
TRPM7 channel defect	1(1)	34	0	8	4	2 (2-2)	1	1 (100)	1 (100)	0
TUBB1-related thrombocytopenia	1(1)	33	2	88	3	1 (1-1)	1	1 (100)	0	0
X-linked thrombocytopenia	1(1)	26	2	NA	2	2 (2-2)	0	0	0	0
Total	100	41 (26-54)	3(1-3)	88 (40-120)	2(1-3)	2 (1-2)	11	10	3	19

WHO-BS: World Health Organization bleeding assessment scale; *LMWH*: low molecular weight heparin; *IPFD*: inherited platelet function disorders, *IPND*: inherited platelet number disorders; *NA*: not applicable, missing data

Supplementary table 2. Characteristics of patients with FV Leiden mutation and cancer

	F V Leiden	**Malignancy**
N (% of total)	2 (0.9)	11 (5.2)
Age median (IQR)	26	59 (55-72)
Mechanical tromboprophylaxis N (%)	0 (0)	5 (45)
LMWH thromboprophylaxis N (%)	0 (0)	4 (36)
Pro-hemostatic preoperatory prophylaxis N (%)	1 (50)	6 (54.5)
Type of surgery N (%)		
Orthopedic	0 (0)	1 (9.1)
Abdominal	0 (0)	1 (9.1)
Cardiovascular	0 (0)	2 (18.1)
Gynecological	2 (100)	2 (18.1)
Neuro/spine surgery	0 (0)	1 (9.1)
Thoracic	0 (0)	3 (27.2)
Urological	0 (0)	1 (9.1)
Post-surgical hemorrhage N (%)	0 (0)	3 (27)

Supplementary table 3. Logistic regression analysis of parameters associated with LMWH use.

	OR	CI	***P* value**
Gender (female)	0.587	0.117-2.950	0.518
Age	1.053	1.007-1.100	**0.023**
Caprini class of risk			**0.002**
Very low risk	0.169	0.016-1.733	0.134
Low risk	0.066	0.007-0.608	**0.016**
Moderate risk	0.060	0.011-0.330	**0.001**
High risk	1		
Obesity	0.617	0.129-2.958	0.546
Surgery			0.680
Orthopedic	1		
Abdominal	0.152	0.027-0.869	**0.034**
Cardiovascular	-	-	-
Gynecological	1.543	0.253-9.416	0.638
Neuro/spine surgery	0.161	0.005-4.295	0.295
Thoracic	0.286	0.015-5.566	0.408
Urological	0.298	0.020-4.396	0.378
WHO-BS			0.505
WHO 0	0.086	0.005-1.435	0.088
WHO 1	0.870	0.162-4.671	0.871
WHO 2	0.543	0.090-3.263	0.504
WHO 3	-	-	-
WHO 4	1		

LMWH: low molecular weight heparin; *WHO-BS:* World Health Organization bleeding assessment scale. Surgey risk: VTE class of risk according to surgery.

Supplementary table 4. Logistic regression analysis of the parameters associated with the need of emergency treatment of post-surgical bleeding

	OR	**CI**	***P* value**
LMWH use	0.737	0.236-2.302	0.599
WHO Bleeding score			**0.002**
WHO 0	0.054	0.005-0.636	**0.020**
WHO 1	0.620	0.129-2.2969	0.549
WHO 2	0.283	0.064-1.250	0.096
WHO 3	1.239	0.288-5.327	0.773
WHO 4	1		
Gender (female)	1.210	0.564-2.596	0.625
IPFD vs IPND	1.070	0.448-2.554	0.879
Any preoperative antihemorrhagic prophylaxis	1.556	0.631-3.836	0.337

LMWH: low molecular weight heparin; *IPFD:* inherited platelet function disorders; *IPND:* inherited platelet number disorders; *WHO-BS:* World Health Organization bleeding assessment scale.

Supplementary table 5. Logistic regression analysis of predictors of unsuccessful control of bleeding

	OR	**CI**	***P* value**
LMWH use	2.057	0.496-8.536	0.321
WHO-BS			0.904
WHO 0	-	-	-
WHO 1	0.298	0.020-4.447	0.380
WHO 2	0.407	0.036-4.567	0.466
WHO 3	0.551	0.051-6.001	0.625
WHO 4	1		
Gender (female)	0.355	0.114-1.101	0.625
IPFD vs IPND	6.760	1.139-40.123	0.879
Any prophylaxis	0.524	0.127-2.170	0.337
Caprini class of risk			0.449
Very low risk	1		
Low risk	0.403	0,049-3,320	0,398
Moderate risk	0.944	0.143-6.205	0.952
High risk	1.597	0.277-9.209	0.601

Logistic regression. *LMWH*: low molecular weight heparin; *IPFD:* inherited platelet function disorders; *IPND:* inherited platelet number disorders; *WHO-BS:* World Health Organization bleeding assessment scale.