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Haematologica 2019 [Epub ahead of print]

Citation: Francesco Paciullo, Loredana Bury, Patrizia Noris, Emanuela Falcinelli, Federica Melazzini, Sara Orsini, Carlo Zaninetti, Rezan Abdul-Kadir, Deborah Obeng-Tuudah, Paula Heller, Ana C. Glembotsky, Fabrizio Fabris, Jose Rivera, Maria Luisa Lozano, Nora Butta, Remi Favier, Ana Rosa Cid, Marc Fouassier, Gian Marco Podda, Cristina Santoro, Elvira Grandone, Yvonne Henskens, Paquita Nurden, Barbara Zieger, Adam Cuker, Katrien Devreese, Alberto Tosetto, Erica De Candia, Arnaud Dupuis, Koji Miyazaki, Maha Othman, and Paolo Gresele. Antithrombotic prophylaxis for surgery-associated venous thromboembolism risk in patients with inherited platelet disorders. The SPATA-DVT Study. Haematologica. 2019; 104:xxx
doi:10.3324/haematol.2019.227876

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

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ABSTRACT

Major surgery is associated with an increased risk of venous thromboembolism, thus the application of mechanical or pharmacologic prophylaxis is recommended. The incidence of venous thromboembolism in patients with inherited platelet disorders undergoing surgical procedures is unknown and no information on the current use and safety of thromboprophylaxis, particularly of low-molecular-weight-heparin in these patients is available. Here we explored the approach to thromboprophylaxis and thrombotic outcomes in inherited platelet disorders patients undergoing surgery at venous thromboembolism-risk participating in the multicenter SPATA study.

We evaluated 210 surgical procedures carried out in 155 patients with well-defined forms of inherited platelet disorders (venous thromboembolism-risk: 31% high, 28.6% intermediate, 25.2% low, 15.2% very low). The use of thromboprophylaxis was low (23.3% of procedures), with higher prevalence in orthopedic and gynecological surgeries, and was related to venous thromboembolism-risk. The most frequently employed thromboprophylaxis was mechanical and appeared to be effective, as no patients developed thrombosis, including patients belonging to the highest venous thromboembolism-risk classes. Low-molecular-weight-heparin use was low (10.5%) and it did not influence the incidence of post-surgical bleeding or of antihemorrhagic prohemostatic interventions. Two thromboembolic events were registered, both occurring after high venous thromboembolism-risk procedures in patients who did not receive thromboprophylaxis (4.7%).

Our findings suggest that venous thromboembolism incidence is low in patients with inherited platelet disorders undergoing surgery at venous thromboembolism-risk and that it is predicted by the Caprini score. Mechanical thromboprophylaxis may be of benefit in patients with inherited platelet disorders undergoing invasive procedures at venous thromboembolism-risk and low-molecular-weight-heparin should be considered for major surgery.

SUMMARY

- We evaluated the incidence of venous thromboembolism (VTE) and the use of thromboprophylaxis in patients with inherited platelet disorders (IPD) undergoing surgery
- VTE incidence is low in patients with IPD and is predicted by the Caprini score. Mechanical thromboprophylaxis may be of benefit and LMWH should be considered for major surgery
INTRODUCTION

Venous thromboembolism (VTE) is a severe and sometimes lethal complication of major surgery triggered by the release of pro-thrombotic substances from injured tissues, immobilization, medical comorbidities and favored by thrombophilia. It occurs in 20-25% of patients undergoing general surgery and in up to 60% of patients undergoing orthopedic surgery not receiving antithrombotic prophylaxis.

VTE can be largely prevented by the use of mechanical and/or pharmacologic antithrombotic prophylaxis. Mechanical thromboprophylaxis with compressive stockings or intermittent pneumatic compression devices reduces the risk of VTE by 64% and 60%, respectively, while pharmacologic thromboprophylaxis with low molecular weight-heparin (LMWH) reduces VTE risk by 75%, although it doubles the risk of major bleeding. A meta-analysis of clinical trials comparing mechanical vs pharmacologic thromboprophylaxis in general and orthopedic surgery found a 80% higher risk of DVT (including asymptomatic and distal DVT) among patients treated with mechanical thromboprophylaxis but a 57% lower risk of major bleeding. Moreover, a systematic review comparing intermittent pneumatic compression with elastic compressive stockings in surgical patients found a prevalence of deep vein thrombosis (DVT) of 2.9% in the first group and of 5.9% in the second. Recently, it has been observed that the addition of mechanical to pharmacologic thromboprophylaxis does not provide further benefit.

The risk of VTE associated with surgery changes according to a series of variables. The American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines classify surgical interventions into three VTE-risk categories depending on the type of procedure. Individual VTE-risk can be estimated more accurately based on patient characteristics and risk factors using appropriate scores, one of the most widely used of which is the “Caprini score” which subdivides patients into four risk categories.

The incidence of VTE in patients with inherited platelet disorders (IPDs) undergoing surgical procedures at VTE-risk is unknown, and no clinical trials or large case series have ever been reported, although several reports suggest that these patients may not be protected from thrombosis, especially when considering that some prophylactic antihemorrhagic treatments currently used in these patients for the preparation to surgery, like platelet transfusions or rFVIIa, increase VTE-risk.
Moreover, no systematic studies on the use of thromboprophylaxis in patients with IPDs undergoing surgery have been carried out, and no information on the safety of the prophylactic administration of LMWH to IPD patients is available, although isolated reports on the safe administration of anticoagulants to IPD patients have been published\textsuperscript{20-24}. Recently, the large retrospective, multicenter SPATA study evaluated bleeding complications and management of surgery in patients with IPD\textsuperscript{17}. In the present study we evaluated the approach to thromboprophylaxis adopted for the IPD patients undergoing surgery at VTE-risk participating in the SPATA study. In particular, we aimed to assess current clinical decisions on VTE prevention, to estimate postoperative VTE risk and to evaluate the association between the use of mechanical or pharmacologic thromboprophylaxis and clinical VTE incidence and surgical bleeding in IPD.

**METHODS**

**Study population**

In the current sub-study we included all the surgical procedures performed in patients enrolled in the SPATA study according to well-defined laboratory and/or molecular genetic criteria\textsuperscript{17,25-27} for whom thromboprophylaxis should have been considered according to current guidelines, including major and minor invasive interventions\textsuperscript{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\textsuperscript{29,30}. Surgery definitions were previously reported\textsuperscript{17}. Given the significant in situ thrombotic risk of central venous catheter insertion interventions\textsuperscript{31}, these were also considered in the analysis as minor procedures with high local thrombotic risk.

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\textsuperscript{17}.

The Institutional Review Board of the coordinating center approved this sub-study (CEAS Umbria, Italy, Approval n. 13138/18).

For further details see the Supplemental Data.

**Thromboembolic risk**
VTE-risk associated with the individual surgical procedures was estimated using the Caprini Score\textsuperscript{32,33}. The enrolled procedures were subdivided into four classes of risk depending on the Caprini score. Surgical procedures were also classified according to procedure-related VTE-risk in three groups as suggested by the 2008 ACCP\textsuperscript{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. Further details are in the Supplemental Data.

**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. For details see Supplemental Data.

**Bleeding outcomes**

Previous bleeding history was assessed using the World Health Organization (WHO) bleeding assessment scale (WHO-BS)\textsuperscript{34}, while excessive bleeding occurring after surgery and the rate of success of emergency treatment of post-surgical bleeding were classified as previously described\textsuperscript{17}. Additionally, data about the need of blood transfusion after surgery were collected. Participating investigators were asked to provide informations about bleeding outcomes occurred both during and immediately after hospitalization for surgery.

The outcome of emergency treatment of excessive post-surgical bleeding was classified as successfully controlled, not responsive to treatment or re-bleeding\textsuperscript{17}.

**Statistical analysis**

As this was a pilot, exploratory study without any a-priori test hypothesis, we did not perform a formal sample study analysis. Variables not normally distributed were reported as medians and interquartile ranges (IQRs), and differences were tested using the Mann–Whitney U test or the Kruskal–Wallis analysis of variance (ANOVA) test. Data are shown as medians and interquartile ranges (IQRs). Categorical variables were analysed using the Chi-square test. A Cochrane-Armitage test of trend was used to evaluate the correlation between dichotomous and ordinal variables. Logistic regression analysis was performed to identify predictors of excessive post-surgical bleeding, of heparin use, of the need for anti-hemorrhagic interventions and of the success of post-surgical bleeding management. All analyses were performed using SPSS version 22.0 (IBM
RESULTS

Patient characteristics

Out of the 829 surgical procedures included in the SPATA study, 210 carried out in 133 patients met the inclusion criteria, 132 of which were performed in females (63.8%), with 31 patients undergoing more than one procedure. Of these interventions, 110 (52.4%) were carried out in 66 patients with 14 different forms of IPFD, and 100 (47.6%) in 67 patients with 7 different forms of IPND (Supplementary Table 1). Median age at surgery was 45 years (IQR 29-56; min 17, max 88). Two patients (0.9%), aged 19 and 26 years undergoing one procedure each, were heterozygous carriers of FV Leiden mutation, although it should be considered that no systematic search for thrombophilic genetic mutations was made in the enrolled population; 11 procedures (5.2%) were performed in patients with a history of malignancy (median age 55 years, IQR 52-79), and 4 (1.9%) in patients with chronic obstructive pulmonary disease (COPD) (median age 51 years, IQR 42-59). Sixty-five interventions (31%) were performed in patients with a Caprini score ≥ 5, 60 (28.6%) in patients with a score between 3 and 4, 53 (25.2%) in patients with a score between 1 and 2, and 32 (15.2%) in patients with a score of 0. Median age was 32 years (IQR: 20-49) for patients with a score of 0, 35 (IQR 27-46) for patients with a score of 1-2, 46 (IQR 32-60) for patients with a score of 3-4, and 52 (IQR 41-61) for patients with a score ≥5. Sixty-one interventions (29%) (32 in patients with IPFD and 29 in patients with IPND) were low-risk, 114 (54%) (55 in patients with IPFD and 59 in patients with IPND) were intermediate-risk, and 35 (17%) (23 in patients with IPFD, 12 in patients with IPND) were high-risk.3 In low-risk procedures, the median age was 49 years (IQR 33-58), in intermediate-risk 37 years (IQR 28-53), and in high-risk 53 years (IQR 33-62).

Type of surgery and antithrombotic prophylaxis

Seventy-two procedures were abdominal (34.3%), 55 gynecological (26.2%), 41 orthopedic (19.5%), 14 urological (6.7%), 10 cardiovascular (4.8%), 9 thoracic (4.3%), 6 neurosurgical (2.9%), and 3 spine surgeries (1.3%). Ninety interventions were major surgery (43%) while the other 120 procedures (57%) were minor invasive interventions followed by immobilization for ≥ 24 hours. The oldest group of patients were those undergoing urological interventions (median age 58 years), while the youngest patients underwent gynecological surgery (median age 36 years).
Malignancy was most frequent in patients undergoing thoracic surgery (Table 1). Of the overall 210 surgical procedures, 89% were elective and 11% urgent.

The Caprini score was higher in patients undergoing cardiovascular interventions and lower for abdominal interventions (Table 1).

Out of 210 surgical procedures, 49 (23.3%) were managed with thromboprophylaxis; of these 27 (55.1%) were managed with mechanical thromboprophylaxis alone, using either compression stockings (26 procedures) or intermittent pneumatic compression (one procedure), 19 (38.8%) with LMWH alone, and 3 (6.1%) with both methods (mechanical and pharmacologic).

Of the 49 interventions managed with thromboprophylaxis, 13 were orthopedic (26.0%), 12 gynecological (24.5%), 7 abdominal (14.3%), 7 thoracic (14.3%), 7 urological (14.3%) and 3 neurospinal (6%). LMWH prophylaxis was adopted in 22% of the orthopedic procedures, 12.7% of gynecological, 11% of thoracic, 11% of neurospinal surgery, 7.1% of urological and 4.2% of abdominal (Table 1, Figure 1). The two patients carriers of FV Leiden mutation were both at intermediate VTE-risk and had a low WHO-BS (0 and 2, respectively). They both underwent gynecological surgery without thromboprophylaxis and did not develop VTE. Patients with a history of malignancy were all classified at intermediate VTE-risk, and their median WHO-BS was 2. In these patients, heparin was used in 4 procedures mechanical thromboprophylaxis in 5 and no prophylaxis in 2. No VTE was recorded in this population (Supplementary table 2).

Of the procedures at high VTE-risk according to the Caprini risk stratification (n=65), thromboprophylaxis was adopted in 22 (33.8%) (LWMH in 14, mechanical in 6, and both in two) with no VTE events, while in 43 it was not adopted. Regarding procedures at intermediate VTE-risk (n= 60), thromboprophylaxis was used in 15 (25%) (mechanical in 11 and pharmacologic in 4), while of the procedures at low VTE-risk (n=53) thromboprophylaxis was used in 10 (18.9%) (9 mechanical, 1 both mechanical and pharmacologic), and of the procedures at very low VTE-risk (n=32), thromboprophylaxis was used in only 2 patients (6.2%) (1 mechanical, 1 pharmacologic). According to the procedure-related VTE-risk stratification, 35 high-risk procedures, 114 intermediate-risk and 61 low-risk, were performed. Thromboprophylaxis was adopted in 42% (nine pharmacologic and six mechanical) of the high-risk procedures, in 21% (six pharmacologic, 15 mechanical and three both) of the intermediate-risk and in 16.4% (four pharmacologic and six mechanical) of the low risk procedures. The choice of using LMWH, was significantly associated with the Caprini risk class (p< 0.001 and p= 0.002 respectively) (Supplementary Table 3) and with the procedure-related VTE-risk class (p= 0.007 and p= 0.009, respectively) (Figure 2A). The use of
thromboprophylaxis with LMWH was similar between elective and urgent procedures: 10.2% vs 13% respectively (p=ns).

Older age also independently predicted the use of pharmacologic thromboprophylaxis. In fact, LMWH-treated patients were significantly older (median age: 67 vs 42 years; p< 0.01) and had a higher median Caprini score (8 vs 4; p < 0.01) than non-treated patients (Table 2). Additionally, history of cancer was more frequent in heparin users than in non-users (18% vs 3.2%, p=0.018). On the contrary, neither the WHO-BS nor gender distribution (both in IPFD and IPND) were significantly associated with LMWH use.

Mechanical prophylaxis was applied with graduated compression stockings in 30 procedures (14%) and with intermittent pneumatic compression in 1 procedure (0.47%), while pharmacologic prophylaxis was undertaken with enoxaparin in 18 procedures (8%), tinzaparin in 1 (0.47%), dalteparin in 1 (0.47%), and in two cases (0.95%) type was not specified. Enoxaparin was administered at a median dose of 4000 IU/day (IQR 2000-5000 IU/day) for a median duration of 15 days (IQR 7-18), starting on the day of surgery. The use of LMWH, as well as the use of any thromboprophylaxis, increased over time during the observation period covered by the study (LMWH: OR 2.5; 95% Cis 1.31-4.96; any thromboprophylaxis: OR 1.4; 95% Cis 0.98-2.08) (Figure 3).

Thromboprophylaxis (pharmacologic and/or mechanical) was more common in patients with IPFD compared with those with IPND (34.5% vs 11% p<0.01) due to the greater use of mechanical thromboprophylaxis in the former (24% vs 3%; p<0.01), even if there was no difference in VTE-risk between the two groups. LMWH was administered in 10% of procedures carried out in patients with IPND (10 procedures), and in 10.9% of those carried out in patients with IPFD (12 procedures).

None of the patients affected by biallelic Bernard Soulier syndrome (bBSS) (n=11) and Glanzmann thrombasthenia (n=5) received pharmacologic thromboprophylaxis. This finding probably reflects the perception that the VTE-risk of these patients is low, as suggested by previous reports and fear of bleeding. In IPND, LMWH was neither administered in patients with ACTN1-related thrombocytopenia (n=5) nor in the only patient with X-linked thrombocytopenia (Supplementary Table 1). Median platelet count of the overall IPD population before surgery was 158 x 10^9/L (IQR: 120-287 x 10^9/L) in procedures followed by LMWH vs 120 x 10^9/L (IQR: 8-163) in those where LMWH was not administered (p= n.s).

**Thrombotic outcomes**
Two thromboembolic events were recorded (0.95% of all interventions), both occurring in patients who did not receive thromboprophylaxis (3.5% of non-prophylaxed procedures). One was a pulmonary embolism (PE) in a bBSS patient who underwent mitral valve surgery, the other a femoral DVT in a Glanzmann thrombasthenia (GT) patient occurring after the placement of a central venous femoral catheter for blood transfusions. Both patients were at high VTE-risk (Caprini score 12 and 8, respectively), had received prophylactic platelet transfusions before the invasive procedure, and had suffered excessive post-procedural bleeding prompting red blood cell transfusions. The patient suffering from PE was a 56-year-old obese woman affected by COPD. She was then treated with therapeutic dose enoxaparin, but died in hospital from septic shock, disseminated intravascular coagulation and acute respiratory distress syndrome. The patient suffering from DVT was a 60-year-old woman and she was then treated with therapeutic dose enoxaparin for three months, without bleeding complications and with complete resolution of the femoral thrombosis. Both patients had previously undergone major elective surgery without thromboprophylaxis and without thrombotic complications. When dividing the included surgeries according to procedure-related VTE risk, in two of 35 high-risk procedures (0.7%, both IPFD) a VTE event occurred, while in 114 intermediate-risk procedures and 61 low-risk procedures no VTE occurred.

Bleeding outcomes

The percentage of patients who suffered from excessive bleeding after surgery was not significantly different in LMWH users compared with non-users (4/22: 18.2% vs 46/188: 25.8%, p=0.5) and no significant difference in bleeding duration after surgery was found between heparin users and non-users (Table 2). The rate of excessive bleeding was instead significantly higher in urgent (45.5%) than in elective (22.5%) procedures (p<0.05).

Also the need of post-surgical blood transfusions did not differ between heparin users and non users (18% vs 19%, p=0.51) as well as the use of post-surgical anti-hemorrhagic interventions. In 57 cases emergency treatment of post-surgical bleeding was required (27.1%), with platelet transfusions administered in 38 procedures, anti-fibrinolytic agents in 9, DDAVP in 1, recombinant FVII in 1, other not specified treatment in 6, and combination therapy with anti-fybrinolytic and DDAVP in 2. Thromboprophylaxis did not predict the need of post surgical anti-hemorrhagic intervention while the bleeding history did (Supplementary table 4). Finally, heparin use was not significantly
associated with the rate of success of emergency treatment of excessive post-surgical bleeding, although percentages of cases with treatment failures were numerically higher in LMWH users than in non-users (19% vs 7%; OR 2.05, CI: 0.496-8.536, p=0.321) (Table 2, Supplementary table 5). Preoperative prophylactic prohemostatic treatment was adopted in 125 procedures (59%), in 78 with platelet transfusions, in 9 with anti-fibrinolytic agents, 6 with DDAVP, 3 with activated recombinant FVII and 3 with a not-specified agent, in 12 with anti-fibrinolytic agents and DDAVP, in 6 with platelet transfusions, anti-fibrinolytic and DDAVP in combination, in 4 with platelet transfusions and anti-fibrinolitics in combination, in 2 with platelet transfusions and DDAVP in combination, in 1 with antifibrinolytic agents and a not-specified agent combination, in 1 with platelet transfusions and not-specified agent combination. Thromboprophylaxis with LMWH was adopted in 10 procedures (11.8%) not managed with preoperative prohemostatic prophylaxis and in 12 (9.6%) of those managed with preoperative thromboprophylaxis (p=0.651).

**DISCUSSION**

Our data show that the current use of thromboprophylaxis in patients with IPD undergoing surgery at VTE-risk is low, probably due to fear of bleeding complications and to the belief that these patients are protected from VTE. In the general population the prevalence of pharmacologic thromboprophylaxis use has been estimated to be 17.7% in neurosurgery, 27% in abdominal surgery, 50% in gynecological surgery, 52% in cardiovascular surgery, 67% in urological surgery, 91% in orthopedic surgery, and 98% in thoracic surgery, while in our IPD population it was 0% in cardiovascular surgery, 9% in abdominal surgery, 11% in neuro and spinal surgery, 21.8% in gynecological surgery, 31.7% in orthopedic surgery, 50% in urological surgery, and 77% in thoracic surgery. In IPD patients, as expected, the most frequently employed thromboprophylaxis was mechanical, principally with elastic compression stockings. In otherwise healthy subjects undergoing general and orthopedic surgery the use of compression stockings was shown to exert a significant protective effect against VTE compared with no stockings (9% vs 21%, OR 0.35, 95% CI: 0.28-0.43) In our IPD population this approach seemed to be effective, as no patients using post-surgery elastic compression stockings developed thrombosis, including patients at high risk based on the Caprini score.

In the general population, the risk of surgery-associated VTE in patients not undergoing thromboprophylaxis is strongly dependent on the Caprini score, with an incidence lower than 0.5% when the score is 0, 3% when the score is 1-2, 5% when the score is 3-4, and ≥ 6% when the score
is $\geq 5^{11,33,40}$. In our IPD population not receiving thromboprophylaxis, no VTE was observed in patients with a Caprini score $< 5$, while in patients with a Caprini score $\geq 5$, symptomatic VTE occurred in 4.7% of the procedures. These data could suggest that the incidence of surgery-associated symptomatic VTE is indeed lower in patients with IPD that in healthy controls, at least when the Caprini score is not high. The ACCP guidelines classify surgical interventions in three groups depending on the risk of developing VTE: low risk (<10%), including minor surgery and interventions not requiring patient immobilization, moderate risk (10-40%), including gynecological and urological open surgery, and high risk (risk up to 80%), including hip or knee arthroplasty, hip fracture surgery, spinal cord injury and procedures associated with high bleeding risk $^3$. In our IPD patients, in the high-risk group $^3$ 58% of the procedures (21 interventions) were performed without prophylaxis and 9.5% of these were followed by VTE, while no VTE events were observed in moderate or low-risk procedures carried out without thromboprophylaxis. Of the two thromboembolic events recorded, one was observed in a GT patient undergoing a femoral vein catheter insertion and the other in a bBSS patient undergoing mitral valve surgery, both with a high individual VTE-risk (Caprini score of 8 and 12, respectively) and not receiving any thromboprophylaxis. Interestingly, the latter is, to our knowledge, the first case of VTE described in a bBSS patient. Pharmacologic thromboprophylaxis with LMWH was adopted in only 10% of all surgical procedures at VTE-risk in our IPD population. The use of thromboprophylaxis with LMWH increased over the observation period covered by the study, reflecting the increased awareness of the thrombotic risk of surgical procedures and of the efficacy of pharmacologic thromboprophylaxis. When heparin thromboprophylaxis was applied, its use did not seem to be guided by the assessment of the individual bleeding risk, but rather by the thromboembolic risk. Indeed, the Caprini score was strongly and independently associated with heparin use in our case series. No VTE was observed in patients undergoing LMWH prophylaxis, including in those belonging to the highest VTE-risk categories according to both the Caprini and procedure-related VTE scores.

LMWH use was neither associated with an increased rate of excessive post-surgical bleeding nor with enhanced need for post-surgical antihemorrhagic intervention. Also the use of preoperative anti-hemorrhagic prophylaxis was similar in patients treated or not with LMWH. Thus, our results could suggest that thromboprophylaxis with LMWH may be safer than anticipated in IPD patients. On the other hand, it should be pointed out that although LMWH did not significantly affect the success rate of emergency treatment of post-surgical bleeding, a numerically higher number of
insucces ses was observed in patients treated with LMWH. Thus, caution should be taken when deciding about LMWH use for IPD patients, especially for those at higher bleeding risk (e.g. more severe forms and/or patients with higher WHO bleeding scores). The use of post-surgical thromboprophylaxis with LMWH and the rate of VTE were similar between elective and urgent procedures, while the rate of excessive post-surgical bleeding was higher in urgent than in elective procedures, as expected.

Our study has several limitations. First, we only looked for symptomatic VTE, thus the incidence of total VTE may have been significantly underestimated due to the lack of a systematic instrumental diagnostics search of these events during post-surgical follow-up. Indeed, no calf or distal vein thrombosis was reported and the latter could have been overlooked, due to the low clinical expressivity and difficulty of diagnosis. However, possible underestimation of distal DVT may not significantly diminish the clinical relevance of our observations because untreated distal DVT is associated with a low risk of proximal propagation and PE. Second, the retrospective nature of our study does not allow for definitive conclusions about the impact of heparin use on bleeding in patients with IPD. However, the collection of hemorrhagic post-surgical events was the main aim of our study and great emphasis was given to careful evaluation of their occurrence. Moreover, the observational multicenter nature of our study, as already observed for other registries of populations with VTE, allowed us to gather a large patient series in an area difficult to explore with clinical trials, like subjects at high bleeding risk. Indeed, interventional clinical trials generally exclude patients at bleeding risk, limiting the generalizability of the evidence. Registries have been helpful for improving our understanding of the epidemiology, pattern of care and outcomes in such patient subgroups.

Third, our study has a relatively small sample size and it involves a rather heterogeneous population undergoing a wide range of interventions performed over a fairly broad time period, thus limiting the strength of our results compared with studies carried out in the general population, especially when subgroup analyses are concerned. Although this is true, a case series of over 200 procedures carried out in rare-disease patients is not negligible in this clinical context, if one considers that phase III studies on LMWH prophylaxis in high-risk surgery and trauma have included between 100 and 440 patients.

Despite the above limitations, to the best of our knowledge this is the first study which explored VTE-risk of surgical procedures in a large series in patients with IPD, and our results may represent
the starting point for an evidence-based approach to the antithrombotic management of these subjects.

CONCLUSIONS

Our findings suggest that VTE incidence is low in patients with IPD undergoing at risk surgery. Moreover, among IPD subjects as well as in the general population, patients at high VTE-risk may be identified by the Caprini score. Our data also suggest that mechanical thromboprophylaxis may be of benefit in patients with IPD undergoing invasive procedures at VTE-risk and that LMWH should be considered for major surgery. Prospective studies are required to further clarify the impact of pharmacologic thromboprophylaxis on VTE and bleeding complications in patients with IPD undergoing surgery.

ACKNOWLEDGEMENTS

This study was promoted by the Scientific Working Group on Thrombocytopenias and Platelet Function Disorders of the European Hematology Association (EHA).

LB and EF were supported by a scholarship grant from Fondazione Umberto Veronesi. This study was supported in part by a Telethon grant (GGP15063) to PG. NB holds grants from FIS-FONDOS FEDER (CP14/00024 and PI15/01457).

The authors thank Dr. Giuseppe Guglielmini for help with statistical analysis, Prof. Marco Cattaneo (Università degli Studi di Milano, Italy), Prof. Christian Gachet (University of Strasbourg, France), Dr. Alessandro Pecci, Drs. Davide Rancitelli, Silvia Ferrari and Irene Bertozzi (University of Padua, Italy) and Dr. Giovanni Favuzzi (IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy) for their contribution to the study.

We thank Dr. Rino Migliacci (Division of Internal Medicine, Ospedale della Valdichiana "S. Margherita", Cortona, Italy) and Prof. Carlo Balduini (Department of Internal Medicine, IRCCS Policlinico S. Matteo Foundation, University of Pavia, Italy) for the critical reading of the manuscript.

CONFLICT OF INTEREST DISCLOSURE

The authors declare non conflict of interest.
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Table 1. IPD patient characteristics according to type of surgery

|                          | Abdominal surgery (N 72) | Gynecological surgery (N 55) | Orthopedic surgery (N 41) | Urological surgery (N 14) | Cardiovascular surgery (N 10) | Thoracic surgery (N 9) | Neuro/spinal surgery (N 9) |
|--------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|-------------------------------|-----------------------|--------------------------|
| Age in years, median (IQR) | 47 (29-57)               | 36 (29-45)                  | 42 (24-58)               | 58 (45-70)               | 54 (52-65)                    | 37 (28-58)           | 40 (16-76)               |
| Females, N (%)           | 38 (54.2)                | 55 (100)                    | 22 (53.7)                | 3 (21.4)                 | 6 (60)                        | 2 (22)                | 3 (30)                   |
| Platelet count before surgery ($\times 10^9$/L), median (IQR) | 120 (65-175)             | 56 (34-162.5)               | 139 (103-191.5)          | 75 (5-90)                | 60 (425-94)                   | NA                    | NA                       |
| Malignancy, N (%)        | 1 (1.4)                  | 2 (3.6)                     | 1 (2.4)                  | 1 (7.1)                  | 2 (20)                       | 3 (33)                | 1 (11)                   |
| WHO bleeding score, median (IQR) | 2 (1-4)              | 2 (1-2)                     | 2 (1-3)                  | 2 (1-3)                  | 3 (1-3)                       | 2 (1-3)              | 3 (2-4)                  |
| Caprini score, median (IQR) | 2 (1-4)               | 3 (2-5)                     | 4 (2-7)                  | 3 (2-4)                  | 7 (3-8)                       | 2 (1-5)              | 2 (0-8)                  |
| Caprini class risk, median (IQR) | 1 (1-2)              | 2 (1-3)                     | 2 (1-2)                  | 2 (1-2)                  | 4 (3-4)                       | 2 (1-4)              | 2 (1-4)                  |
| Use of thromboprophylaxis, N (%) | 7 (9)                | 12 (21.8)                   | 13 (31.7)                | 7 (50)                   | 0                             | 7 (77)               | 3 (30)                   |
| Mechanical thromboprophylaxis, N (%) | *5 (6.9)          | *7 (12.7)                    | 4 (9.7)                  | 6 (42.9)                 | 0                             | 6 (66)               | 2 (22)                   |
| LMWH thromboprophylaxis, N (%) | 3 (4.2)                | 7 (12.7)                    | 9 (22)                   | 1 (7.1)                  | 0                             | 1 (11)               | 1 (11)                   |
| Preoperative antihemorrhagic prophylaxis, N (%) | 34 (62.5)             | 27 (49.1)                   | 25 (62)                  | 9 (64.3)                 | 7 (70)                        | 5 (55)               | 7 (77)                   |
| Any excessive post-surgical bleeding, N (%) | 22 (30)                | 42 (76.5)                   | 5 (12.5)                 | 2 (14.3)                 | 6 (60)                        | 3 (33)               | 4 (44)                   |

*IPD:* inherited platelet disorders; *IQR:* interquartile range; *LMWH:* low molecular weight heparin; *NA:* not available; *:* in some procedures both mechanical and LMWH thromboprophylaxis was employed
Table 2. Differences between surgical procedures carried out with or without LMWH thromboprophylaxis.

|                                | LMWH use (N=22) | LMWH non use (N=188) | P value |
|--------------------------------|-----------------|----------------------|---------|
| **Age, median (IQR)**          | 67 (79-55)      | 42 (25-54)           | 0.01    |
| **Females, N (%)**             | 14 (63.6)       | 120 (63.8)           | n.s.    |
| **Platelet count before surgery x 10^9/L, median (IQR)** | 158 (120-287) | 120 (8-163)          | n.s.    |
| **IPFD, N (%)**                | 12 (54.5)       | 98 (52.1)            | n.s.    |
| **COPD, N (%)**                | 2 (9.1)         | 2 (1.1)              | n.s.    |
| **Malignancy, N (%)**          | 4 (18.4)        | 7 (3.2)              | 0.018   |
| **WHO bleeding score, median (IQR)** | 2 (0.75-3)  | 2 (1-3)              | n.s.    |
| **Caprini score, median (IQR)** | 8 (5-12)       | 4 (2-6)              | 0.02    |
| **Caprini class, median (IQR)** | 4 (3-4)        | 3 (2-4)              | 0.01    |
| **Preoperative antihemorrhagic prophylaxis, N (%)** | 12 (54.5)      | 113 (60.1)           | n.s.    |
| **Any excessive post-surgical bleeding, N (%)** | 4 (18.2)       | 46 (25.8)            | n.s.    |
| **Treatment of post-surgical bleeding, N (%)** | 6 (28.6)       | 49 (27.2)            | n.s.    |
| **Post-surgical bleeding duration, hours, median (IQR)** | 6 (4-8)        | 6 (1-6)              | n.s.    |
| **Failure of post-surgical bleeding control, N (%)** | 4 (19)         | 13 (7)               | n.s.    |
| **Thrombosis, N (%)**          | 0               | 2 (1)                | n.s.    |

IQR: interquartile range, COPD: chronic obstructive pulmonary disease, IPFD: inherited platelet function disorders, IPND inherited platelet number disorders; LMWH: low molecular weight heparin.
FIGURE LEGENDS

Figure 1. Use of thromboprophylaxis in different types of surgery in the IPD population.

Figure 2. Use of LMWH in IPD patients according to VTE risk classes. Use of LMWH in IPD patients according to A) Caprini VTE class risk and B) procedure related VTE-risk (* p<0.01 vs high-risk).

Figure 3. Use of thromboprophylaxis according to date of surgery (*p<0.01 vs 2010-2017). Procedures carried out ≤ 1980 were 7 (3.3% of total).
Figure 3

% of procedures treated with thromboprophylaxis

Date of surgery

- Any prophylaxis
- LMWH prophylaxis

- before 1980
- 1980-2000
- 2000-2010
- 2010-2017

*
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\textsuperscript{25-27} undergoing surgery \textsuperscript{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 \textsuperscript{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\textsuperscript{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\textsuperscript{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 \textsuperscript{17,28}. Given the significant in situ thrombotic risk of central venous catheter insertion interventions \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 postsurgical 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

| Characteristics                                      | 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 preoperative 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. Surgery 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**    |     |             |         |
| 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.