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Management of patients with protein s deficiency: focus on clinical course and direct oral anticoagulants

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Abstract

Background Protein S (PS) is a cofactor of protein C (PC) which, when activated to activated PC (APC), mainly acts to degrade coagulation factor Va and VIIIa, and its deficiency may trigger an array of venous thromboembolic events (VTE); when unprovoked and life-threatening, these need indefinite anticoagulation. Direct oral anti coagulants (doac) are efficient drugs in therapy and prevention of VTE, although the optimal prophylactic doses in different conditions are not identified.

Methods General characteristics and clinical events of 33 PS deficient patients (7 uneventful, 10 carrying also other thrombophilic conditions) were recorded from their medical records. Patients suffering from VTE underwent LMWH/Fondaparinux therapy followed by a full dose of doac (apixaban or rivaroxaban) and then a reduced dose doac (apixaban and rivaroxaban).

Results Average, lowest and highest PS levels measured during follow-up were higher in male patients ($p=0.001$). The cumulative prevalence of patients taking drugs acting on central nervous system (opioids, antidepressants, antiepileptic, antimigraine, antipsychotic) was 33%. Three minor hemorrhages were observed during the full-dose and one during the reduced doac therapy, while 3 VTE (1 pulmonary embolism and 2 deep venous thrombosis) occurred exclusively during the reduced-dose doac therapy ($p=0.033$ Vs Full dose, 8.1 100patient/yr 95% CI 4–15). Compliance during the reduced-dose therapy was good according to the circulating levels of doac. In survival analysis, the only variable associated with VTE recurrence was PS deficiency combined with thrombophilic defects ($p=0.049$).

Conclusions Free PS deficiency affects the quality of life in many ways and a low dose doac in PS deficient patients is only partially effective in secondary prevention of VTE.

Keywords Protein S, Thrombophilia, Reduced-dose doac, Apixaban, Rivaroxaban, Prophylaxis, Incidence, Bleeding, Thromboembolic events, Antipsychotic drugs, Antidepressant drugs, Antiepileptic drugs, opioids

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Background

Thrombophilia consists of an increased risk of venous thromboembolic events (VTE) due to inherited, acquired, or environmental risk factors, acting either alone or combined [1]. Protein S (PS) is a vitamin K-dependent glycoprotein that serves as a cofactor for activated protein C (PC) in inactivating factors Va and VIIIa, therefore limiting the tenase and prothrombinase complexes formation and, consequently, reducing thrombin generation [2, 3]. Ancillary activities of PS are interaction/degradation of coagulation factors II, cofactor in activity of TFPI and direct inhibitor of FIXa [4].

The prevalence of PS deficiency is uncommon in the general population, with approximately 0.3–1.12% in unselected patients [5, 6] and 2–12% among thrombophilic patients with VTE [5, 7]. These figures refer to partial PS deficiency, since complete absence triggers neonatal purpura fulminans and is incompatible with life. The most common consequences of partial PS deficiency include superficial and deep venous thrombosis, especially in the lower limbs and pulmonary embolism [7–11] before the age of 50 [11–13].

Independent of the specific mutation detected, patients with free PS defect are considered at risk of recurrence of VTE [7, 9, 10] and, in the pre-doac era, lifelong antivitamin K therapy (INR range 2–3) was recommended in case of unprovoked life-threatening VTE [14, 15]. Doac have made more acceptable a therapy that should be continued for the whole life [16–21]. In patients with free PS deficiency in the range 50 to 70% (mild risk) and a venous thromboembolic event (VTE), after at least six months of full-dose doac (and in absence of guidelines), some authors suggest to shift from a full- to a reduced- doac dose. A clinical and laboratory monitoring of thrombotic and hemorrhagic events should accompany this dose reduction [21, 22]. Such a promising approach has been successfully validated only in atrial fibrillation, but its efficacy in PS deficiency has not been explored, yet. In the present retrospective study, medical records of PS deficient patients attending a Thromboembolic Diseases Center of an Italian teaching hospital were reviewed to ascertain the results of their management, particularly concerning the effects of reduced doac dose.

Materials and methods

Patients

The review of 211 patients clinical records attending a secondary level Thromboembolic Diseases Center of an Italian University Hospital (Trieste, Italy) was carried out in order to select those patients with congenital PS deficiency. Patients that are referred to our outpatient clinics usually had previous VTE, are suspected of having an inheritable condition (because of young age at diagnosis, familial history of thrombophilia, recurrent or unprovoked deep venous thrombosis (DVT) in an unusual site, repeated miscarriages, and other conditions), and need diagnostic and therapeutic management. Clinical workout, carried out in due course, consisted of a physical examination, a clinical chemistry, blood cell count, and coagulation (see below) laboratory tests, a personal and family history collection, and therapy monitoring. All patients were asked to sign a written informed consent for the use of clinical data for scientific purposes (available in Supplementary Material) and only those fulfilling this condition were considered for the present analysis. The study has been carried out according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

Coagulation laboratory tests

All coagulation assays were performed on an ACL-TOP analyzer (Instrumentation Laboratory – Werfen, Bedford, MA USA) by means of reagents from the same manufacturer. Free Protein S (free PS) was evaluated with an immunoturbidimetric test (HemosIL free Protein S, Werfen, Bedford, MA, USA) and considering diagnostic values lower than 70% in men and 55% in women [23, 24]. The Lower Limit of Quantification (LLQ) was 7.3% free PS, with linearity of 11–150% free PS and maximum CV% of 2.8. The other tests were, activated PC resistance (HemosIL FV Leiden – APC Resistance V, Werfen, Bedford, MA, USA, containing FV deficient plasma), Antithrombin (AT, HemosIL Liquid Antithrombin, Werfen, Bedford, MA, USA, a chromogenic anti-FXa method, normal values > 78%), protein C (PC chromogenic test, Hemosil Protein C, Werfen, Bedford, MA, USA, normal values > 70%), FVIII (one stage coagulation test with HemosIL FVIII deficient plasma, Werfen, Bedford, MA, USA, normal values between 50 and 150%), FV Leiden R506Q (G1691A, Real-Time PCR), Prothrombin G20210A (rs1799963, Real-Time PCR) polymorphism, lupus anticoagulant with HemosIL dRVVT screen and confirm, (Werfen, Bedford, MA, USA) and Silica Clotting time (SCT) as LA sensitive APTT (HemosIL Silica Clotting time, Werfen, Bedford, MA, USA).

Doac were detected by assays calibrated against the specific anticoagulant: a chromogenic anti-Xa (HemosIL Liquid anti-Xa, Werfen, Bedford, MA, USA) for apixaban and rivaroxaban. All coagulation and Real-Time PCR tests were carried out at the certified Laboratories of Transfusion Medicine Department. Anti-phospholipid antibodies (anticardiolipin IgG and IgM, anti β2 glycoprotein 1 IgG and IgM) were detected with EliA Phadia assays (Thermo Fisher Scientific, Sweden) in the Core Lab of our local Healthcare Service. The timing of the determinations was set to avoid possible interference of the anticoagulant drug with the test, except for genetic testing, and 2 months apart (on average) from the acute

event [25]. The free PS determinations were also repeated in all patients after more than 4 weeks [25]. PROS genotyping was not carried out given the heterogeneous pattern of PROS mutations, the limited evidence of a real clinical difference among them, and the diagnostic criteria of ISTH [25]. To rule out the possibility of acquired PS deficiency, the test was repeated throughout follow-up so to exclude patients with severe liver disease.

Statistical analysis

Clinical and laboratory (anonymized) data have been transferred in a database for analysis. Data has been reported as median and interquartile for continuous variables or absolute number and prevalence (%) for dichotomous variables. Incidence of bleeding and VTE was calculated and expressed as the number of events/100 patient years, and years to observe one event. Additionally, for coagulation variables activated Thromboplastin Time (APTT), fibrinogen, D-dimer, Antithrombin, PC and PS, which were repeated over time, and are potentially linked to thromboembolic events; highest and lowest values recorded were included in the analysis. Comparisons of continuous variables in different categories have been carried out with non-parametric statistics: Mann Whitney or Friedman test for continuous variables) and with Chi Square test (χ^2) when appropriate. Survival analysis has been carried out with Kaplan Maier test. A P value < 0.05 has been considered statistically significant. The SPSS (21.0) software has been used for statistical analysis.

Results

Baseline observation

General characteristics of the patients, divided according to the number of coagulation defects diagnosed (i.e. isolated PS deficiency or combined with other defects), are reported in Table 1. Anthropometric, general characteristics, and comorbidities of patients were not different according to the number of thrombophilia-associated genetic defects. One third of our population took drugs acting on the central nervous system (namely antiepileptic, antipsychotic, antidepressant and antimigraine, and opioids). The different drugs or mental disturbances were evenly spread in our population. PS levels were tested at least twice (range 2–5) throughout the follow-up.

Free PS antigen, measured throughout the observation, was higher in male (64 IQR 60–68) than in female patients (51 IQR 45–57, $p = 0.001$) for all measurements at all times. Given the variability in PS values over time, we compared also highest and lowest values within each patient. The pattern was maintained considering lowest (63, IQR 60–65 and 49, IQR 40–52 in male and female patients, $p < 0.001$) and highest values (65, IQR 61–71 and 52, IQR 45–60 in male and female patients, respectively, $p = 0.001$). Plasma levels of coagulation factors altered in these patients have been specified in Table 2, and divided by the specific trait.

Acute treatment

Nineteen patients, who had an acute clinical event (VTE) right before or during the observation at the Center, underwent treatment with Enoxaparin (range 4000–16000 IU/die) or Fondaparinux (range 2.5–7.5 mg/die) according to the clinical conditions, after ruling out high-risk antiphospholipid syndrome. The duration of this therapy was 3 to 6 months because other professionals had prescribed it. Subsequently, the majority of these patients underwent a full-dose of doac therapy (apixaban 5 mg BID or rivaroxaban 20 mg once a day) [17–19]. The type and dose of the doac was customized, based on the pharmacokinetics of the drug, body weight, mental status, or personal preferences, and kidney and liver function of the patient. An initial diagnostic workup was completed within the first two months of treatment. Other patients did not require treatment, either because they were asymptomatic or because they were observed after the acute phase.

During the full-dose treatment, 3 episodes (hematuria, hemorrhoid and gum bleeding) of minor bleedings were reported by 3 male patients (2 of them had preexisting urologic conditions). No VTE were recorded in any of the patients taking full dose doac. The time spent in full dose was of 12 months, on average. At 3 and 6 months, when deep vein recanalization occurred or embolism symptoms/signs improved or disappeared, apixaban was reduced from 5 to 2.5 mg BID and rivaroxaban from 20 to 10 mg/once a day, monitoring compliance with plasma levels of doac [26–28]. The main results are reported in Table 1 and abnormal plasma levels of coagulation factors or genetic testing results are detailed in Table 2.

Follow-up during doac treatment

All twenty patients with a reduced-dose of doac attended the follow-up examinations. During the observation, one minor post-traumatic bleeding and three VTE occurred in these 20 subjects with a full-dose doac (two DVT and one PE). The three patients with VTE were carriers of FV Leiden, FII rs 1,799,963, and FVIII 186%, respectively ($p = 0.07$ for χ^2 test of events in combined Vs isolated defects). Within patients with VTE relapses, only the occurrence of combined accredited genetic defects (FV Leiden or FII rs 1,799,963) accounted for an earlier relapse (Kaplan Maier analysis $p = 0.049$, Fig. 1).

Compliance and efficacy, of the therapy were analyzed through doac concentrations, when appropriate. The timing of the sampling reflected the pharmacokinetics of the drug: at 1 hour (9 measurements) the mean peak value was 154 ± 78 ng/mL and at 13 hours (11 measurements)

Table 1 Main characteristics of the patients according to the thrombophilic condition observed. Routine coagulation tests are the earliest available (i.E at the beginning of follow-up)

	PS deficiency only	Combined defects†	P
Number & Sex (M/F)	11/12 (23)	5/5 (10)	0.838
INDEX Events			
No event*	5	2	0.075
SVT	3	0	
DVT (+ portal thrombosis) †	10	5	
PE	5	4	
Age at trigger event (years)	61(46–75)	64 (44–70)	0.915
Events > 50 y of age	18 (75%)	6 (75%)	0.849
Months in Follow-up	26.5 (20–34)	33 (27.5–48.5)	0.078
BMI	24.3 (22–30.9)	25.3 (22.7–26.5)	0.994
BMI > 30	6	1	0.398
Drugs n			
No doac	6**	2	0.916
Apixaban (reduced and full therapy)	13	4	
Rivaroxaban (reduced and full therapy)	1/0	0/1	
Combined therapies	6	0	
Antihypertensive drugs	10	1	0.779
Hormones	16	8	0.626
Supplements @	7	5	0.146
Gastrointestinal	8	2	0.806
Metabolic (diabetes, hyperuricemia/gout)	6	2	0.876
Lipid lowering drugs	9	1	0.038
Central nervous system drugs#	8	3	0.641
NSAID + Opioids	5	3	0.418
Cortisone (asthma)	3	1	1.0
INR (Ratio)	1.03 (1–1.07)	1.06 (1–1.12)	0.735
APTT (Ratio)	1.06 (0.92–1.12)	1.06 (0.97–1.19)	0.417
Fibrinogen (mg/dL)	382 (334–398)	283 (228–345)	0.139
D-dimer (ng/mL FEU)	774 (533–1096)	469 (239–1290)	0.353

Legend. Combined therapies = patients who switched from one doac to another one. Combined defects are patients with PS deficiency plus at least one of the following: factor V Leiden, Prothrombin mutation, low-risk Anti-phospholipid antibodies, FVIII > 200%, low PC, and/or low AT. † One patient experienced 1 DVT plus 1 PE. Hormones: thyroid hormones, oral hormone replacement therapy, Gastrointestinal: proton pump Inhibitors, Ursodeoxycholic acid, lactulose pancreatic enzymes, NSAID = non-steroidal anti-inflammatory drug, PS = protein S, PC = protein C, FVIII = Coagulation factor VIII; AT = Antithrombin, INR = International Normalized Ratio, APTT = activated prothrombin time, SVT = Superficial vein thrombosis, VTE = venous thromboembolic events, PE = pulmonary embolism, DVT = Deep Venous Thrombosis, LMWH = low molecular weight heparin, FPX = fondaparinux. Coagulation methods are as follows: Antithrombin (AT, with chromogenic substrate, normal values > 78%), Free Protein S with immunoturbidimetric test, protein C (PC chromogenic test, normal values > 70%), FVIII (normal values between 50 and 150%), FV Leiden R506Q (G1691A, Real-Time PCR) and Prothrombin G20210A (rs1799963, Real-Time PCR) polymorphisms, FEU = fibrinogen equivalent unit

P= X^2 test or Mann Whitney test as appropriate

*diagnosis made during: screening, >1.000 ng/mL FEU D-dimer, investigation during pregnancy/infertility/subfertility

#major antidepressants, anticonvulsants, antipsychotic, against migraine

@ iron, vitamins, *n*-3 polyunsaturated fatty acids

** 5 asymptomatic + 1 patient with DVT refused the therapy

the mean levels were 73 ± 39 ng/mL. The ICSH (International Council for Standardization in Haematology) 2021 [29] and EHRA (European Heart Rhythm Association) 2021 [30] found levels within 59–302 ng/mL and 22–177 ng/mL at 1 and 13 hours, respectively, during doac therapy. Therefore, the compliance of the patients can be confirmed since all the measurements, except two, were within the range. The results of the observation are reported in Table 3. Laboratory values measured during the therapy are described in Table 4.

The only significant differences in coagulation markers during the follow-up were an increase in AT and a reduction of FVIII. These modifications have been observed throughout years of follow-up with the same doac treatment.

During the observation of a female patient, an anorexic young woman with PE after two uneventful pregnancies, the PS apparently returned to normality (free protein S 92%) after 6 months of nutritional and antithrombotic therapy. Such a recovery has been attributed to an acquired PS deficiency likely due to malnutrition. In

Table 2 Abnormal plasma levels of coagulation factors or genetic testing results in the study population according to the type of thrombophilic condition. The timing of dosage was at least 2 months after the acute event or at the beginning of follow-up, for patients without VTE. Data are median and, in parenthesis, interquartile values when observations were > 3, or individual values in the remaining categories

Thrombophilia	n	Free PS (%)	FVL	FIIm	PC (%)	AT (%)	APL	FVIII (%)
Free PS only	23	50 (45–61)						
+ high FVIII	3	53, 56, 64						208, 225, 238
+ FVL	1	37	X					
+ FIIm	2	54, 68		X				
+ low PC + high FVIII	1	50			60			250
+ FVL + high FVIII	1	47	X					230
+low PC+ low AT+FVL	1	61	X		52	64		
+ low risk APL	1	61					23	

Legend: Free PS = free Protein S, FVL = heterozygote factor V Leiden, FIIm = heterozygote prothrombin mutation rs 1,799,963, PC = protein C, AT = Antithrombin, APL = low-risk Anti-phospholipid antibodies (anti-cardiolipin IgG 23 U/mL, reference values: negative < 10, borderline 10–40, positive >40), FVIII = factor VIII

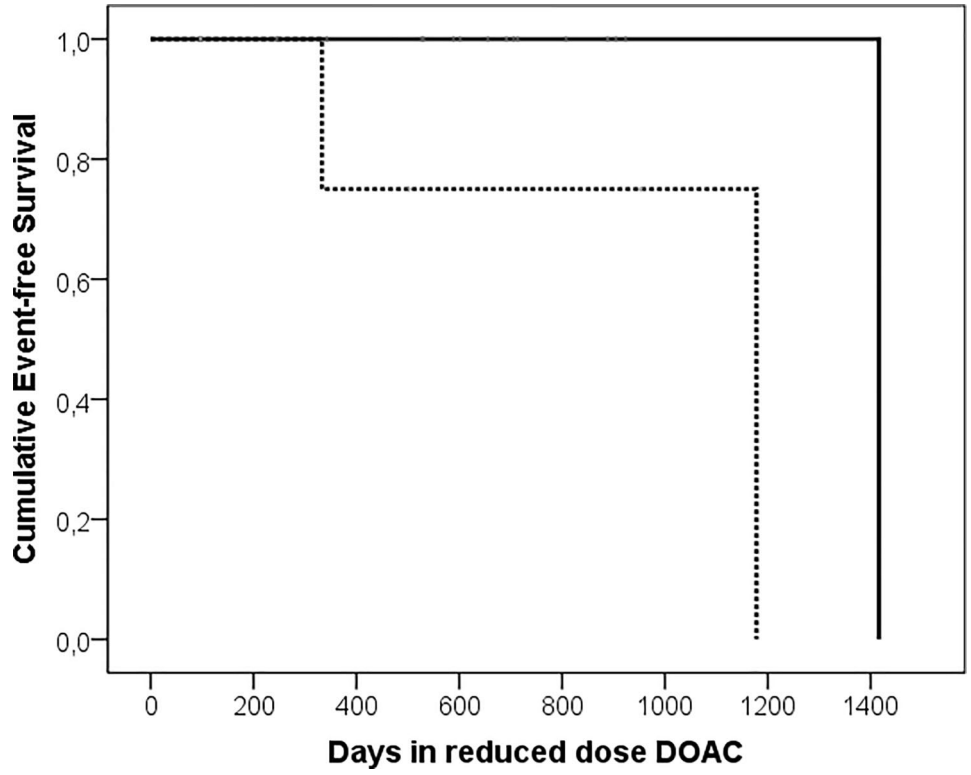

Fig. 1 Event-free survival curve of VTE relapse during reduced-dose doac. Legend: solid line: PS deficiency + FVIII 186% (one patient), dotted line: combined defects: PS deficiency + FV Leiden R506Q or prothrombin G20210A (two patients). Kaplan Maier curve, $p = 0.049$

tandem with PS reduction, this patient had also increased factor VIII activity at the first observation (>250%) and PC reduction (lowest measured value 60%). The increase of FVIII in association with PS reduction was previously observed also by other authors [31]. In this patient, the combined doac treatment and nutritional intervention allowed for an increase in 8 kg body weight gain (from 27 to 35), and a BMI from 10.54 to 13.67 associated with a complete recovery of these abnormalities (PS 89%, PC 78%, and factor VIII 93.1%), and it was not possible to stablish the relative role of doac and nutrition on her recovery. Ten months after doac suspension, nutritional intervention is effective in maintaining a fair nutritional status (weight 39 kg and BMI 15) and normal coagulation balance (normalized free PS, PC and D-dimer).

The patients without VTE (5 with isolated PS deficiency and 2 with combined defects) did not undergo to doac treatment.

Table 3 Epidemiology of the patients according to the therapy. The different treatment patterns are specified in the left part of the table. On the right part, is reported the prevalence and incidence of the bleeding and VTE observed during each specific treatment

Pattern of the different treatments										Months	Bleedings		VTE	
											N/event 100 pt yr	Years for 1 event	N/event 100 pt yr	Years for 1 event
LMWH/FPX	*	X	X	X	X					53	0/0	0	0/0	0
F D doac		X		X		X	X			238	3/15	6.6	0/0	0
R D doac		X			X	X		X		450	1/2.7	37	3/8.1 (95% C.I. 4–15)	12.3
N	8	10	1	2	5	4	2	1			$\chi^2 = 0.26$		$\chi^2 = 0.033$	

Legend. Months: cumulative duration of the therapy. VTE = venous thromboembolic events, 100 pt/yr = events observed in 100 patient/years, LMWH/FPX = Low molecular weight heparin/Fondaparinux, F D doac = full dose apixaban or rivaroxaban, R D doac = reduced dose apixaban or rivaroxaban, χ^2 test P value in the comparison of thrombotic and bleeding events between F D and R D doac; * a PS deficient pregnant woman (diagnosed before pregnancy) was treated with prophylactic LMWH

Discussion

Some results stem from the observation of this group of PS-deficient patients. Namely, a) a vast majority of first VTE occur after 50 years of age, b) one third of them take drugs functioning on the central nervous system, c) male patients have higher free PS values than female patients, d) a reduced-dose of doac offers a suboptimal protection from DVT/PE in spite of plasma levels of doac within range during follow-up, and e) all VTE relapses occurred in patients with another thrombophilic condition.

The first observation is that three out of four patients studied in the present observation had their first event after 50 years of age and more than half of them would not have been candidates to inherited thrombophilia screening according to the current guidelines [10–13, 32, 33]. Lifestyle improvements in the last 30 years, e.g. reduction of smokers, improved physical activity and vegetable consumption [34–36] are making western population healthier and, particularly in this area, the number of centenarians is increasing [37, 38]. These changes might explain the delayed occurrence of VTE in western population. Another factor to consider is that handling of some hemocoagulation tests (namely PC and PS) have become easier after the doac therapy replaced warfarin, which is known to decrease protein C and protein S levels [39].

Beyond carrying PS deficiency, 33% of our population also had presence of other thrombophilia markers. This is consistent with other reports [40–43], even if the prevalence of the single genetic defects can widely vary [44, 45]. All the studies agree that patients with combined defects have a higher probability of VTE. Even in a small number of observations, our study confirms that VTE relapses in reduced doac patients with combined defects and, above all, that a reduced-dose of doac is not protective in these patients.

Our patients with PS deficiency also suffer conditions not apparently linked to thrombophilia: even excluding patients taking opioids and one case of mental anorexia, which was not treated with antipsychotic drugs, about one patient out of three takes on regular bases drugs interfering with central nervous system activity. No category of drugs or related conditions prevailed over the others. Such a prevalence is much higher of that observed in a recent report from the Italian Medicines Agency (less than 10%) [46]. The most likely explanation of this surprising result is that PS is an activator of tyrosine kinase receptors (TAM), namely Tyro3 and Mertk [47], which mediates neurological development [48], protects Blood Brain Barrier [49] and prevents brain injury [50]. Specifically, in cortical neurons of mice, PS activates intracellular signaling by activating the phosphatidylinositol 3-kinase (PI3K)–Akt pathway [50] through Tyro3 and PS ligation to Mertk stimulates phagocytic activity of

Table 4 Laboratory values according to the therapy

	LMWH/FPX	FD doac	RD doac	P
INR (Ratio)	1.03 (1.00–1.07)	1.10 (1.08–1.38)	1.19 (1.03–1.40)	0.077
APTT (Ratio)	1.12 (1.05–1.14)	1.15 (1.05–1.17)	1.06 (0.98–1.1)	0.175
Fibrinogen (mg/dL)	361 (252–382)	331 (309–405)	393 (344–477)	0.102
D-dimer (ng/mL FEU)	731 (330–1290)	489 (298–680)	528 (367–957)	0.865
AT (%)	89 (82–99)	102 (97–123)	104 (91–112)	0.040
PC (%)	106 (97–119)	121 (106–126)	108 (100–117)	0.261
Free PS (%)	62 (49–68)	57 (51–63)	57 (51–70)	0.927
Factor VIII (%)	200 (169–215)	75 (68–117)	152 (128–166)	0.031

Legend. LMWH/FPX = Low molecular weight heparin/Fondaparinux, F D doac = full dose doac, R D doac = reduced dose doac, *p* = Significance of Friedman test. INR = International Normalized Ratio, APTT = activated prothrombin time, FEU = fibrinogen equivalent unit

subventricular zone neural stem-like cells [51]. The overall effect is to ensure anti-inflammatory and efferocytosis activity. While animal and in vitro experiments have well documented the effect of PS on TAM (mainly Tyro3 and Mertk) and neurologic development, human studies have reported only sporadic occurrence of low PS activity in neuro-psychiatric patients with frontotemporal dementia [48], headache [52], and schizophrenia [53, 54]. To the best of our knowledge, this is the first report of such a high prevalence of this class of drugs in PS deficient patients. Future studies should be planned to observe how PS affects both episodic and long-term mental dysfunction, as well as recovery from injury.

Higher PS plasma values have been measured in men than in women, particularly in general Eastern populations [55–57]. Rather than the inhibitory effect of hormones in fertile women [56] the reason of such a pattern, with a decrease in older man [57], is more likely that PS is expressed in various organs and, among them, the testis [58, 59]. This marginal but measurable testicular aliquot of PS could match the progressive loss of efficiency of this organ and explain both the higher level in young men and its reduction over time seen in Miyata's work [57]. The advanced age of our population, with 87% of our male population being 50 years old or older, might have obscured the relationship between PS and age (data not reported). Nevertheless, our study adds that such a difference between genders is observed also in a population of the PS deficiency and, particularly, that fluctuations over time do not modify such a gap. The general management of VTE usually consists in treating patients immediately with low molecular weight or unfractionated heparin, or Fondaparinux, followed by a therapeutic dose of warfarin or doac for three to six months, with the latter being preferable for long-term anticoagulation [15, 16, 19], if the bleeding risk is not excessive. The decision to administer anticoagulation therapy after these three, six months or indefinitely, depends on whether the thrombosis was provoked or unprovoked [60–62], and if it was life threatening or not [15, 63–65]. Indefinite anticoagulation is recommended for patients with an unprovoked thromboembolic event or having a strong family history of VTE [15, 63–65]. Unless a patient is diagnosed with triple antiphospholipid positive syndrome (for which warfarin treatment is mandatory), the choice of the anticoagulant drug for VTE of an unknown origin is empiric, given that the final (clinical, instrumental, and/or laboratory) diagnosis is achieved weeks after beginning therapy. In general, doac is preferred over Warfarin based on the patient's choice, compliance, potential drug-food interactions, the risk of falling, and in cases of INR lability [19, 21, 22]. After completion of the acute treatment of VTE, the reduced-dose of doac has gained popularity given the substantial equivalence with a full dose treatment, as evidenced by two independent metanalysis [66, 67]. Only the study of Ibrahim and Coworkers reports the efficacy in thrombophilia referring to the REMOVE and EINSTEIN CHOICE study. The metanalysis shows that, despite the low number of VTE, the use of a reduced dose of doac is associated with a higher risk of recurrent VTE. Our findings are in agreement with those of Ibrahim and identify patients with combined genetic defects as those at higher risk of a recurrence. In our observation, three thromboses and one minor bleeding were recorded during the reduced-dose of doac. The low number of observations hinders a multivariate analysis concerning the factors determining the relapse of VTE in a reduced-dose doac. In a univariate analysis, the only variable weakly linked to an earlier recurrence of VTE was combined thrombophilia: namely, one FV Leiden, one FII rs179963 and the third, although not universally accepted as a VTE risk factor, high FVIII levels (238%) [68]. It could be speculated that PS reduced activity can synergize with FV Leiden [69, 70], rs1799963 [71, 72] and high levels of FVIII [67] in determining the VTE risk, given that PS has a spectrum of protein C dependent (anti FV and FVIII) and independent (anti FII) anticoagulant activities. The interaction between inherited defects in determining the VTE risk could be far more complex than imagined, grouping defects according to the interference of coagulation control pathways, e.g. PS reduced activity with increased expression of one of its (pre)

substrates like prothrombin in rs1799963 variant [71, 72]. In such a scenario, future research should identify a screening tool to expand our in vivo knowledge of the complex interactions of these genetic defects and avoid potentially life-threatening VTE. Further research should also address the efficacy of reduced doac doses in other inheritable and acquired thrombophilia.

The effect of full anti-Xa doac therapy on INR, AT and FVIII are known and depend on the type of doac and on its interference with the assay, but the effects of the reduced doses remain to be reported. Given the low number of cases, reduced and full doac doses have a similar pattern on these coagulation markers. Therefore, none of them can be used as a marker of VTE relapse. The low number of patients, the retrospective design of the study and its monocentric setting have to be acknowledged among the major limitations of the present report. Also, the availability of a Xa-independent laboratory coagulation tests would have given a more precise picture of the effects of doac.

In conclusion, PS has coagulation and non-coagulation activities, and its deficiency deeply affect the quality of life of these patients. The high risk of VTE appears to cover the adult lifespan and its clinical management should consider the lowest possible risk of bleeding and recurrence. A reduced-dose of doac are effective in reducing the bleeding rate, and in prevention of thrombotic recurrence, it seems effective only in patients with isolated PS deficiency.

Abbreviations

PROS1	Protein S gene
PS	Protein S
PC	Protein C
FVIII	Coagulation factor VIII
AT	Antithrombin
SVT	Superficial vein thrombosis
VTE	Venous thromboembolic events
PE	Pulmonary embolism
DVT	Deep venous thrombosis
LMWH	Low molecular weight Heparin
FONDA	Fondaparinux
Doac	Direct oral anticoagulant
BID	Twice a day (Bis In Die).

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by N. A. and N. F. The first draft of the manuscript was written by N. A., F. G. Di G. and N. F. and all authors commented on previous versions of the manuscript. Conceptualization: G. B.; Methodology: T.K., P. P., M. C., G. C., I. G., P. La R., M. La R.; Formal analysis and investigation: N. A., P. V., T.K., E. P., M. Z., F. P.; Writing - original draft preparation: N. A., F. G. Di G. and N. F.; Funding acquisition: G. B.; Supervision: G. B. and N. F.

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Data availability

Concerning database availability, our data are obtained from a limited population with one/two/three rare diseases, and sharing the databases might allow the identification of a patient, thus infringing the privacy rights. However, the databases are available from the authors upon reasonable request and with permission of the local healthcare authority ASUGI.

Declarations

Ethics approval and consent to participate

This research study was conducted retrospectively from data obtained for clinical purposes. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Each of the patients involved in the study signed written informed consents. A template of the two forms is enclosed in "Supplementary Material".

Consent for publication

Each of the patients involved in the study signed written informed consents. A template of the two forms is enclosed in "Supplementary Material".

Competing interests

The authors declare no competing interests.

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