RESEARCH LETTER

Unfavorably altered fibrin clot properties are associated with recurrent venous thromboembolism in patients following post--discharge events

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Introduction Venous thromboembolism (VTE) involving the presence of deep vein thrombosis (DVT), pulmonary embolism (PE), or both is more prevalent among older patients (>40 years of age).[1] It is often associated with previous hospitalization or nursing home stay, which together constitute up to 60% of overall VTE incidents.[1] Given the fact that VTE-related sudden death could be the first symptom,[2] timely and adequate thromboprophylaxis with heparins in hospitalized patients is strongly recommended. In the past, as much as 40% of the patients who met the criteria of the American College of Chest Physicians did not receive prophylaxis.[3] On the other hand, about 1% of patients experience VTE despite in--hospital thromboprophylaxis.[4]

There is uncertainty concerning risk factors for VTE recurrence in acutely ill patients who experienced VTE following discharge from hospital. In 2019, Wójcik et al[5] reported that characteristics of fibrin clots, such as clot lysis time (CLT), maximum rate of increase in D-dimer levels during clot degradation (D-D_{rate}), clot permeability, and the length of lag phase of fibrin formation, are unfavorably altered in individuals with post-discharge VTE despite pharmacological thromboprophylaxis, and their clot phenotype is similar to that observed in patients following an unprovoked VTE. The prothrombotic plasma fibrin clot phenotype conditioned by both genetic and environmental factors has been demonstrated to increase the risk of recurrent DVT and PE.[6,7]

The objective of the current report was to determine whether a more prothrombotic clot phenotype (defined by decreased porosity and lysability with increased density of fibrin clots) is characteristic of patients with recurrent VTE who had a history of post-discharge VTE after hospitalization for an acute disease and stopped anticoagulation.

Patients and methods In this case-control study patients were recruited at the John Paul II Hospital, Krakow, Poland, between October 2010 and June 2017. The design of the study was published previously.[5] In the current report, we assessed 2 age- and sex-matched groups of 48 adult patients who experienced VTE within 4 weeks of discharge from internal medicine wards. Exclusion criteria comprised age above 65 years, recent acute cardiovascular events, severe diseases (eg, cancer, end-stage kidney disease), and current anticoagulation. We compared follow-up data of the failed thromboprophylaxis group (acutely ill patients who developed post-discharge VTE despite thromboprophylaxis with low-molecular--weight heparins during the index hospital stay) and the non-thromboprophylaxis group (acutely ill patients without such thromboprophylaxis who experienced VTE within 4 weeks of discharge) reported previously.[5] Causes of the index hospitalization included: exacerbation of asthma or chronic obstructive pulmonary disease, pneumonia, exacerbation of chronic heart failure, and relapse of rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, and others). Detailed patient characteristics, definitions of comorbidities, and VTE risk factors were provided previously.[5]

After at least 3 months of anticoagulation, blood samples were collected while off anticoagulation for coagulation assays. To characterize

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the fibrin clot phenotype, hydrostatic pressure-based fibrin clot permeation (K_s) was performed, together with lysis assays using various concentrations of recombinant tissue plasminogen activator (CLT, $D\text{-}D_{rate}$, and maximum values of D-dimer released from clots [$D\text{-}D_{max}$]), turbidity measurements for fibrin polymerization (lag phase of the turbidity curve and maximum absorbance at 405 nm [ΔAbs_{max}]), and peak thrombin generation using calibrated automated thrombography, as described in detail previously.[5] Moreover, we determined plasma D-dimer, fibrinogen, and C-reactive protein (CRP) levels.

Follow-up visits were performed on a 6-month basis (a visit at the center or telephone contact with a patient or a family member) until April 2020. All the study participants stopped anticoagulation after at least 3 months since the index post-discharge event. Documented provoked and unprovoked recurrent VTE while off anticoagulation defined as described previously[5] were recorded.

This study was approved by the Jagiellonian University Ethics Committee (1072.6120.136.2018), and all relevant guidelines and regulations were followed.

All study participants provided written informed consent.

Statistical analysis Continuous variables were presented as mean (SD) or median (interquartile range [IQR]), as appropriate. The normality of distribution of variables was determined using the Shapiro–Wilk test. Categorical variables were reported as numbers and percentages. The χ^2 test or the Fisher exact test was implemented to compare the categorical variables, as appropriate. Differences in the continuous variables between the groups were assessed using the Mann–Whitney test. A *P* value below 0.05 was considered significant.

Results Median duration of the follow-up after anticoagulation cessation was 40 months (IQR, 38–42), with no difference between the groups ($P = 0.22$). Among the patients who experienced postdischarge VTE despite thromboprophylaxis, recurrent VTE occurred in 10 cases (20.8%; 7.24 per 100 patient-years), including 7 unprovoked events and 4 PE episodes (isolated PE, n = 1). In the patients who had post-discharge VTE and did not receive thromboprophylaxis during the hospital stay, as few as 3 individuals were diagnosed with recurrent VTE (6.3%; 1.91 per 100 patient-years), including 2 provoked VTE events with 2 concomitant PE episodes, and the risk of recurrent VTE was significantly lower than in the other group ($P = 0.035$). None of the recurrent episodes was related to the hospitalization for acute medical condition. No fatalities were recorded.

As shown in TABLE 1, in both groups, the individuals who experienced recurrent VTE did not differ from the remaining study participants in terms of demographics, clinical characteristics, and comorbidities or the use of statin and aspirin, with one exception, that is, the patients with recurrent VTE from the non-thromboprophylaxis group were on average 9 years older than the others. Regarding laboratory investigations following the index post-discharge VTE event, the patients with recurrent VTE in both groups tended to have higher D-dimer levels than the others, without any difference in CRP levels. Increased fibrinogen and peak thrombin concentrations were found solely in those with recurrent VTE from the failed thromboprophylaxis group. Interestingly, the patients with recurrent VTE in the failed thromboprophylaxis and non-thromboprophylaxis groups had a more prothrombotic plasma fibrin clot phenotype, as reflected by lower K_s, indicating more compact fibrin networks (TABLE 1). Additionally, there were some intragroup differences in fibrin properties related to VTE recurrence. Turbidity analysis showed that only in the failed thromboprophylaxis group, fibrinogen-adjusted lag phase was shorter and ΔAbs_{max} was higher among the patients who had recurrent VTE. However, longer CLT was observed in the patients with recurrent VTE in the non-thromboprophylaxis group, while in the failed thromboprophylaxis group a similar trend was of borderline significance.

Discussion To our knowledge, this study is the first to show that prothrombotic fibrin clot characteristics, including reduced clot permeability, are linked to VTE recurrence in patients with a history of hospitalization for acute disease and post-discharge VTE, and the unfavorable features are more pronounced in those who experienced the post-discharge event despite in-hospital thromboprophylaxis. These findings expand our knowledge regarding the relationship between the structure and function of fibrin clots and VTE.

The rate of recurrent VTE in the failed thromboprophylaxis group in our study was relatively high, with unprovoked episodes in the majority of cases. It was similar to that reported for nonanticoagulated middle-aged patients after an unprovoked VTE. In those individuals, the risk of recurrent VTE was 10% in the first year after treatment, 15% after 2 years, and 25% after 5 years.[8] This indicates that patients following post-discharge VTE in whom thromboprophylaxis fails in the first month post hospitalization represent a high-risk group that require not only close clinical surveillance, but also possibly extended or indefinite secondary prevention to reduce a substantial recurrent VTE risk.

The results of fibrin clot assessment suggest that reduced clot permeability, a key measure of the clot structure, is characteristic of patients at risk of recurrent VTE regardless of the use of pharmacological thromboprophylaxis during the index hospitalization, which is in line with our previous studies on other patient populations.[9-11] Notably, the difference in this parameter was still present after adjustment for fibrinogen, which is the most potent fibrin clot modulator. Fibrin

TABLE 1 Baseline characteristics of patients with recurrent vs nonrecurrent venous thromboembolism who experienced post-discharge venous thromboembolism after hospitalization for an acute disease

Variable	Recurrent VTE despite thromboprophylaxis (n = 10)	No recurrent VTE after thromboprophylaxis (n = 38)	*P* value	Recurrent VTE without thromboprophylaxis (n = 3)	No recurrent VTE without thromboprophylaxis (n = 45)	*P* value
Age, y	53 (47–59)	52 (48–58)	0.85	64 (58–64)	55 (50–60)	0.047
Male sex, n (%)	5 (50)	25 (66)	0.47	0	25 (56)	0.10
Body mass index, kg/m^2	29.4 (24.8–32.6)	27.3 (24.8–29.6)	0.35	28.4 (28.4–36.2)	26.7 (25.4–27.7)	0.053
Duration of anticoagulation, mo	3.5 (3–6)	4 (3–5)	0.75	3 (3–5)	4 (3–5)	0.46
Cause of acute hospitalization, n (%)						
COPD/asthma	2 (20)	17 (45)	0.28	0	15 (33)	0.54
Heart failure	4 (40)	12 (32)	0.71	3 (100)	16 (36)	0.056
Rheumatic disorders	4 (40)	10 (26)	0.45	0	14 (31)	0.55
Risk factors and comorbidities, n (%)						
Current smoking	1 (10)	14 (37)	0.14	0	18 (40)	0.28
Hypertension	4 (40)	13 (34)	0.73	0	13 (29)	0.55
Diabetes	2 (20)	6 (16)	0.67	0	0	–
Oral contraceptives or HRT at the index event[a]	2 (20)	7 (18)	0.99	0	7 (16)	0.99
Family history of VTE	1 (10)	12 (32)	0.25	2 (67)	5 (11)	0.052
Factor V Leiden	2 (20)	5 (13)	0.63	0	4 (9)	0.99
Prothrombin 20210A mutation	0	1 (3)	0.99	0	0	–
Medications used during follow-up, n (%)						
Aspirin	2 (20)	8 (21)	0.99	0	3 (7)	0.99
Statin	3 (30)	16 (42)	0.72	0	6 (13)	0.99
Compression therapy	7 (70)	29 (76)	0.69	1 (33)	23 (51)	0.99
Laboratory investigations at baseline						
hsCRP, mg/l	3.14 (1.60–7.49)	2.47 (1.41–5.85)	0.63	3.42 (0.70–3.59)	1.71 (1.15–2.24)	0.46
D-dimer, ng/ml	361 (291–405)	278 (202–342)	0.054	390 (302–452)	279 (233–324)	0.053
Fibrinogen, g/l	3.99 (2.93–4.71)	2.97 (2.53–3.80)	0.02	2.45 (2.37–3.59)	2.64 (2.42–3.45)	0.66
Peak thrombin, nM	319 (267–397)	252 (211–339)	0.03	269 (204–319)	212 (190–249)	0.25
K_s, 10^{-9} cm^2	5.85 (5.30–6.00)	6.80 (6.30–7.70)	0.008	5.5 (5.0–6.3)	7.6 (6.1–8.5)	0.02
			0.001[b]			0.002[b]
Lag phase, s	36 (35–49)	45 (38–47)	0.15	41 (40–45)	43 (42–47)	0.41
			0.03[b]			0.30[b]
ΔAbs_{max} at 405 nm	0.89 (0.84–0.92)	0.80 (0.73–0.85)	0.001	0.82 (0.70–0.85)	0.80 (0.74–0.87)	0.84
			0.01[b]			0.89[b]
CLT, min	104.5 (75–115)	84 (71–104)	0.25	103 (100–117)	85 (68–95)	0.008
			0.055[b]			0.003[b]
$D\text{-}D_{rate}$, mg/l/min	0.067 (0.065–0.069)	0.070 (0.065–0.075)	0.15	0.083 (0.066–0.084)	0.071 (0.066–0.076)	0.28
			0.54[b]			0.19[b]
$D\text{-}D_{max}$, mg/l	4.04 (3.85–4.33)	3.70 (3.38–3.89)	0.004	3.62 (3.24–3.74)	3.69 (3.38–4.21)	0.39
			0.07[b]			0.39[b]

Data are presented as median (interquartile range) unless indicated otherwise. Categorical data were compared using the 2-sided Fisher exact test, while continuous variables were compared using the 2-sided Mann–Whitney test.

a Data for women only

b *P* value after adjustment for fibrinogen level

Abbreviations: ΔAbs_{max}, maximum absorbance at 405 nm; CLT, clot lysis time; COPD, chronic obstructive pulmonary disease; $D\text{-}D_{max}$, maximum D-dimer concentrations; $D\text{-}D_{rate}$, rate of increase of D-dimer levels; HRT, hormone replacement therapy; hsCRP, high-sensitivity C-reactive protein; K_s, hydrostatic pressure-based fibrin clot permeation; VTE, venous thromboembolism

polymerization curves showed less favorable characteristics in the patients with VTE recurrence from the failed thromboprophylaxis group but not in the non-thromboprophylaxis group, which supports the concept of more prothrombotic clot features in the former group. In terms of fibrinolysis capacity, our findings provide evidence that the 2 lysis assays cannot discriminate patients at risk of recurrent VTE during follow-up, which could be at least partly related to the specific protocols used,[12] and we cannot exclude that another approach might show intergroup differences, given the well-known association between clot permeability and lysability.

Study limitations should be acknowledged. The group size was relatively small but the occurrence of VTE despite thromboprophylaxis is infrequent.[4] Additionally, our results cannot be applied to other groups of patients, such as the elderly and those with cancer or recent cardiovascular events, that is, with factors known to affect fibrin clot features.[13-15] No laboratory investigations were performed during the follow-up and some variables including fibrinogen may have changed over time. Nonetheless, the data at baseline have a prognostic value in this clinical setting.

In conclusion, our study shows that unfavorably changed fibrin clot characteristics are associated with recurrent post-discharge VTE despite appropriate thromboprophylaxis during hospitalization. A larger study with a longer follow-up is needed to validate our findings and assess the actual prognostic value of plasma fibrin clot variables, particularly K_s, in populations of patients with VTE.

ARTICLE INFORMATION

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