EDITORIAL

Altered fibrin clot phenotype as predictor of the risk of recurrent venous thromboembolism: evidence is growing

Zsuzsa Bagoly

Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
MTA-DE Cerebrovascular and Neurodegenerative Research Group, University of Debrecen, Debrecen, Hungary

"Prediction is very difficult, especially about the future," goes an old Danish proverb, originally attributed to Niels Bohr. This common saying can be particularly applied to prediction of the risk of venous thromboembolism (VTE) recurrence. VTE, encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), has an annual incidence estimated at approximately 1 to 2 per 1000 individuals.[1] VTE is associated with high morbidity and mortality and imposes a significant financial burden on patients and health care providers. Although VTE is commonly considered an acute illness, it has substantial long-term consequences, including postthrombotic syndrome and chronic thromboembolic pulmonary hypertension. Additionally, there is a considerable risk of VTE recurrence; recurrent VTE rates are reported to be as high as 10% to 11% at 1 year, 21.5% to 30% at 5 years, and approximately 40% at 10 years.[2-4] This means that the risk of another VTE event after the first episode of VTE is significantly higher than in patients without previous VTE. It has been also observed that the risk of recurrence is highest during the first year after the event.[3]

VTE management can be divided into acute-phase treatment, which focuses on the elimination or reduction of the blood clot, and intermediate or long-term treatment, aimed at reducing the risk of VTE recurrence.[3] Based on meta-analyses, current guidelines recommend that the acute-phase treatment should last 3 months unless the risk of recurrence is sufficiently high, in which case treatment should be extended beyond this period.[5,6] Extended anticoagulation will reduce the risk of recurrence but must be carefully weighed against the risk of anticoagulation-related bleeding. In some cases, it is easy to predict the possibility of a very low or very high risk of recurrence in a patient and thus decide on an anticoagulation strategy. However, a large number of patients fall into a grey zone where the decision on 3 months versus extended therapy is more difficult.[3]

Provoked and unprovoked VTE events are associated with different rates of recurrence. Risk factors for VTE recurrence mostly include unprovoked events (eg, patient-specific risk factor such as male sex) or VTE location (proximal DVT, concomitant PE).[4] Surgically provoked VTE (VTE associated with a surgical procedure) has a very low rate of recurrence, less than 1% at 2 years.[3] Patients who develop VTE without a provoking factor have approximately a 7-fold higher rate of recurrence. Recurrence rates are even higher if VTE is associated with cancer or major thrombophilia.[3] Despite our current knowledge on risk factors for recurrence, prediction of recurrent VTE following anticoagulation cessation remains a challenge.

In order to facilitate decision making in the clinical setting, risk prediction models have been developed to estimate and summarize key risk factors for VTE recurrence. One of the first such tool was published by Rodger et al[7] ("Men Continue and HERDOO2" rule), followed by the Vienna risk model, the DASH score, and the Louzada score.[3] The HERDOO2 rule identifies women at low risk of recurrence (with 0 to 1 risk factors of the following: hyperpigmentation, edema, or erythema in either leg, increased D-dimer levels on anticoagulation, body mass index >30 kg/m^2, and age ≥65) in whom extended anticoagulant therapy is not recommended.[7] Although all the above risk prediction tools have their advantages, they are also limited in many ways, mostly by the absence of large prospective trials identifying the best model for risk stratification. The only parameter common to all the prediction models is sex, as it is known that male sex is associated with higher risk.[3,5] The only laboratory

Correspondence to:
Zsuzsa Bagoly, MD, PhD,
Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen,
Nagyerdei krt. 98, 4032 Debrecen, Hungary, phone: +36 52 431 956,
email: bagoly@med.unideb.hu
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parameter included in the models is the D-dimer level (HERDOO2, Vienna, and DASH models).[3,7] D-dimer is indeed one of the most extensively studied laboratory tests associated with VTE recurrence. Numerous studies have demonstrated that elevated D-dimer levels are associated with an increased risk of VTE recurrence.[3,5] In most studies D-dimer was explored after cessation of anticoagulation. Beside a D-dimer level of 500 ng/ml or lower, a few other parameters (such as the peak thrombin level lower than 400 nM as measured by the thrombin generation test after anticoagulation cessation) have also been proposed to identify patients at low risk of VTE recurrence. However, thrombin generation has not been widely used for this purpose as yet.[8] It is interesting why it is so difficult to predict the risk of VTE recurrence by using currently available hemostasis tests. It is biologically plausible that the prothrombotic state of the patient must determine the risk of VTE recurrence; however, it remains a challenge to find an optimal hemostasis laboratory test to detect hypercoagulability.

Growing evidence, mostly derived from case-control studies, suggests that formation of more compact clots composed of thinner, highly branched fibers (the so-called prothrombotic clot phenotype) may predispose to arterial thromboembolism and VTE.[9] Fibrin clots of the prothrombotic phenotype are relatively resistant to lysis, as they are characterized by small pores, low fibrin clot permeability coefficient (K_s), and reduced clot lysis time (CLT). Such unfavorably altered fibrin clot properties have been described in patients after unprovoked VTE and in patients who experienced long-term complications of VTE, for example, chronic pulmonary hypertension or post-thrombotic syndrome.[9] In recent cohort studies, Cieslik et al[4] and Zabczyk et al[10] have shown that lower K_s and prolonged CLT are associated with the risk of recurrent DVT and recurrent PE, respectively. Importantly, in the paper by Cieslik et al,[4] recurrent DVT was predicted by the prothrombotic phenotype (defined as the combination of reduced K_s and prolonged CLT), and not by a single clot feature. In this cohort of 320 consecutive patients aged 18 to 70 years following a first DVT episode, the assessment of plasma clot properties after 3 months of anticoagulant treatment since the index event showed that individuals characterized by low K_s and prolonged CLT were at the highest risk of recurrent DVT (odds ratio, 15.8; CI, 7.5–33.5).[4] Notably, in both studies unfavorable clot characteristics were independent predictors of recurrent DVT or PE, regardless of several known risk factors.[4,10]

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Mrozińska et al[11] sought to assess the association between fibrin clot properties measured 3 months after the DVT event and the HERDOO2 rule in women after unprovoked VTE. Plasma fibrin clot properties and thrombin generation were assessed in 80 women younger than 70 years after a first unprovoked VTE episode. The results were assessed separately and also in combination with a group of 32 women after hormone-related VTE. The prothrombotic clot phenotype defined as $K_s \leq 6.55 \times 10^{-9}$ cm^2 and CLT >99.5 min was found to be associated with a higher risk of recurrent VTE (HERDOO2 score >1) separately in women after unprovoked VTE (OR, 5.33; 95% CI, 1.29–22.02) and after combining them with the group of patients with hormone-related VTE (OR, 6.04; 95% CI, 1.94–18.8). Thrombin generation was not associated with a higher risk of VTE recurrence as defined by the HERDOO2 rule in this cohort. Therefore, the key finding of the present study is a lower K_s and a markedly prolonged CLT (by 23.8%) in women with high risk of VTE recurrence, which supports the concept that the prothrombotic fibrin clot phenotype contributes to a prothrombotic state following VTE.

The study by Mrozińska et al[11] also provides important insights into factors that potentially modify clot structure. According to literature, treatment with statins has been associated with a reduction in VTE occurrence.[3,5,12] A causative relationship, however, has not been fully elucidated yet. In the cohort studied by Mrozińska et al,[11] women with high HERDOO2 scores were less commonly treated with statins. The authors observed faster fibrinolysis in women receiving statins, which, in line with a few previous reports, supports the role of statins as modifiers of clot properties.[9,13,14]

In the last 30 years, experimental data have proved that fibrin networks composed of thinner, highly branched fibers are less permeable and less susceptible to lysis.[9] Using this knowledge to study the prognostic values of fibrin clot properties in patients is an evolving field; nevertheless, the clinical importance of such investigations is increasingly becoming apparent. The structure and function of the clot is a fundamental base for thrombosis in a wide range of vascular diseases, including arterial and venous disorders. There is growing evidence that the prothrombotic clot phenotype contributes to arterial vascular diseases, for example, in patients with acute coronary syndrome or stroke.[12,15] The majority of previous studies in this area used a cross-sectional retrospective design, but large-scale longitudinal studies are also becoming available.[15] Recently, the prothrombotic clot phenotype has been recognized as a factor contributing to the heightened risk for thrombosis in patients with liver cirrhosis. As a result of the growing number of studies, some inherited or acquired modifiers of clot structure have been identified. This also provides a chance to develop therapies that could "normalize" fibrin structure and select patients that would benefit from such treatment.[12,14] Beside statins, also aspirin, fibrates, and indirect and direct factor Xa and thrombin inhibitors have been suggested to have a favorable effect on fibrin clot structure.[14]

Specific therapeutic agents aimed at altering fibrin clot structure are still needed, and their development remains an exciting area of research. Although it will always be a difficult task to predict future thrombotic events, research focusing on novel markers of prothrombotic states might provide new insights into determinants and predictors of altered clot structure, thus bringing about potential breakthroughs in the treatment and prevention of VTE.

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REFERENCES

1 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016; 41: 3-14.

2 Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism: a prospective cohort study in 1,626 patients. Haematologica. 2007; 92: 199-205.

3 Barnes GD, Kanthi Y, Froehlich JB. Venous thromboembolism: predicting recurrence and the need for extended anticoagulation. Vasc Med. 2015; 20: 143-152.

4 Cieslik J, Mrozinska S, Broniatowska E, Undas A. Altered plasma clot properties increase the risk of recurrent deep vein thrombosis: a cohort study. Blood. 2018; 131: 797-807.

5 Fahrni J, Husmann M, Gretener SB, Keo HH. Assessing the risk of recurrent venous thromboembolism: a practical approach. Vasc Health Risk Manag. 2015; 11: 451-459.

6 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016; 149: 315-352.

7 Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ. 2008; 179: 417-426.

8 Hron G, Kollars M, Binder BR, et al. Identification of patients at low risk for recurrent venous thromboembolism by measuring thrombin generation. JAMA. 2006; 296: 397-402.

9 Undas A. Prothrombotic fibrin clot phenotype in patients with deep vein thrombosis and pulmonary embolism: a new risk factor for recurrence. Biomed Res Int. 2017; 2017: 8196256.

10 Zabczyk M, Plens K, Wojtowicz W, Undas A. Prothrombotic fibrin clot phenotype is associated with recurrent pulmonary embolism after discontinuation of anticoagulant therapy. Arterioscler Thromb Vasc Biol. 2017; 37: 365-373.

11 Mrozińska S, Cieślik J, Broniatowska E, Undas A. Unfavorably altered plasma clot properties in women with a HERDOO2 score greater than 1 and prediction of recurrent venous thromboembolism. Pol Arch Intern Med. 2018; 128: 572-579.

12 Ariëns RAS. Novel mechanisms that regulate clot structure/function. Thromb Res. 2016; 141 (suppl 2): S25-S27.

13 Undas A, Celinska-Löwenhoff M, Löwenhoff T, Szczeklik A. Statins, fenofibrate, and quinapril increase clot permeability and enhance fibrinolysis in patients with coronary artery disease. J Thromb Haemost. 2006; 4: 1029-1036.

14 Bridge KI, Philippou H, Ariëns RAS. Clot properties and cardiovascular disease. Thromb Haemost. 2014; 112: 901-908.

15 Sumaya W, Wallentin L, James SK, et al. Fibrin clot properties independently predict adverse clinical outcome following acute coronary syndrome: a PLATO substudy. Eur Heart J. 2018; 39: 1078-1085.