Received: 13 March 2020 | Accepted: 17 March 2020

DOI: 10.1111/jth.14803

COMMENTARY

Dynamic prediction modeling for cancer-associated venous thromboembolism

Nick van Es

Department of Vascular Medicine, Amsterdam University Medical Center, Amsterdam, the Netherlands

Correspondence: Nick van Es, Department of Vascular Medicine, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
Email: n.vanes@amsterdamumc.nl

Venous thromboembolism (VTE) is a frequent complication in cancer patients, affecting about 1% to 20% of patients annually dependent on tumor type.[1] Universal thromboprophylaxis is not recommended,[2,3] mainly due to the substantial number needed to treat and concerns about bleeding. Selection of high-risk patients for thromboprophylaxis has therefore been an area of active research over the past decade. Most risk assessment tools for cancer-associated VTE rely on readily available clinical and laboratory risk factors,[4,5] although coagulation biomarkers such as D-dimer,[6] soluble P-selection,[7] and markers for neutrophil extracellular traps[8] appear to have independent additional predictive value.

A major limitation of traditional risk models is their static nature; in the setting of cancer, clinical and laboratory items are evaluated only once shortly after diagnosis or prior to initiating chemotherapy. Cancer patients at high risk can then be offered thromboprophylaxis for a limited duration or even indefinitely, while thromboprophylaxis is not considered justified in low-risk patients. However, there are two main issues with such an approach. First, many variables included in risk scores may vary substantially over time. For example, blood counts and body mass index (as used in the Khorana score[4]) can change during follow-up because of cancer treatment, comorbidities, and cachexia. Second, static models do not capture the different circumstances and clinical events that may increase the short-term risk of VTE in cancer patients during the course of their disease, such as changes in chemotherapy regimen following disease progression, hospitalization because of infectious disease, or diagnostic or therapeutic procedures. Indeed, recent observations suggest that performance of risk scores for cancer-associated VTE decreases after the first weeks of follow-up.[9] Risk models that are "dynamic" and constantly update risk estimates during follow-up hold promise to overcome this limitation.[10]

In this issue of the *Journal of Thrombosis and Haemostasis*, Posch and colleagues present an elegant study showing the potential benefit of a dynamic assessment of D-dimer levels to predict cancer-associated VTE.[11] In this prospective substudy of the landmark CATS cohort study, 167 patients with gastrointestinal, lung, or brain cancer were included and followed for 250 days for the occurrence of VTE. D-dimer levels were measured at baseline and for a maximum of six times during follow-up. By using a complex, state-of-the-art, and sometimes experimental competing-risk survival model, Posch and colleagues succeeded in analyzing the longitudinal D-dimer measurements and risk of VTE in a joint fashion. Their main finding was that D-dimer levels increased by 0.47 µg/mL (34%) per month in patients who developed VTE during follow-up, while levels remained relatively stable in other patients (−0.06 µg/mL [−2.6%] per month). A doubling of D-dimer levels appeared to be associated with a 2.8-fold increased risk of VTE, independent of established clinical VTE risk factors.

It has to be noted that this unique study should foremost be considered a proof-of-concept study; replication is much welcomed and needed. The number of patients and events in the current exploratory study was low, which precluded detailed analyses in subgroups of cancer types. The impact of dynamic factors that are likely to influence both D-dimer levels and the risk of VTE, such as chemotherapy, hospitalization, and invasive procedures, could not be studied. The high cumulative VTE incidence (12% at 250 days) indicates that a high-risk group was studied that is not representative of the overall cancer population, in which the risk is generally lower. Whether the increase in D-dimer levels during follow-up reflected occult, undetected VTE or actually predicted new VTE is unknown; in the former situation, prophylactic therapy might not be effective

Manuscript handled by: David Lillicrap

Final decision: David Lillicrap, 17 March 2020

enough. From a practical perspective, more research is needed on the timing of serial D-dimer measurements and on the cut-offs that should lead to management decisions. The frontloading of VTE events raises the question whether D-dimer testing should be repeated more frequently shortly after diagnosis to identify high-risk patients. Conversely, one could speculate that decreases in D-dimer during follow-up may lead to stopping thromboprophylaxis that was started soon after cancer diagnosis.

Although the results of this study cannot yet be readily translated to clinical practice, the authors should be commended on their innovative and creative approach to model cancer-associated VTE, as they have done before.[12] It would be interesting to explore whether a dynamic version of clinical risk scores with readily available items, such as the Khorana score, could improve prediction without the need for D-dimer testing. Yet, a major benefit of an actual *prediction model* as presented by Posch and colleagues compared to a *risk score* is the possibility to estimate accurate risks rather than roughly grouping patients as "low" or "high risk." Such risk personalization could help clinicians to counsel their patients for thromboprophylaxis while further individualizing preventative approaches. Studies like the one presented by Posch and colleagues are a small step in the right direction on the long and winding road towar precision medicine.

CONFLICT OF INTEREST

Nick van Es has received advisory board honoraria from Daiichi Sankyo, Bayer, and LEO Pharma that were transferred to his institute.

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