The association between malignancy and thrombosis has been known for at least a century [1], but in recent years, there has been a renewed interest in this major complication of malignancy. This new interest has been driven by two factors. First, there is an increased recognition of the clinical burden: rates of venous thromboembolism (VTE) have increased in frequency, driven by both an increase in symptomatic events related to newer antineoplastic regimens and agents and by an increase in incidentally discovered events related to improved computed tomography scan technology [2, 3]. Second, there is a greater appreciation of the consequences of VTE in cancer, particularly the impact on mortality. While it has been known for years that pulmonary embolism and arterial thromboembolic events such as stroke and myocardial infarction can lead directly to death, several recent studies suggest that the occurrence of VTE is associated with decreased long-term survival not directly attributable to a thromboembolic event. For instance, in an analysis of over 90,000 patients with primary lung cancer, VTE was a significant predictor of death within 2 years for both non-small-cell and small-cell lung cancers [stage-adjusted hazard ratio (HR) = 2.3, 95% confidence interval (CI) = 2.2–2.4, and HR = 1.5, 95% CI = 1.3–1.7, respectively] [4]. Hematologic malignancies are similarly affected. In patients with acute lymphoblastic leukemia, development of VTE was associated with a 40% increase in the risk of dying within 1 year [5]. In addition to long-term prognosis, early mortality is affected by VTE as well. In an analysis of causes of death in 4466 cancer patients receiving chemotherapy in a prospective registry, thrombosis (including both venous and arterial events) was the second leading cause of death (n = 13, 9.2%), after cancer progression [6]. The annualized death rate for VTE in this study was 448 per 100,000 patients, a 47-fold elevation (95% CI 6–89, P = 0.03) over the rate in the general population.

Given the burden and consequences of VTE in cancer, recent efforts have focused on identifying predictors of VTE in order to provide prophylaxis to high-risk subgroups. Multiple risk factors and biomarkers have been identified [7]. In 2008, my colleagues and I developed and validated a Clinical Risk Score that incorporates five simple clinical and laboratory variables (Table 1) [8]. The risk score was originally derived from a development cohort of 2701 patients and then validated in an independent cohort of 1365 patients from a prospective cohort study. Observed rates of VTE in the development and validation cohorts were 0.8% and 0.3% in the low-risk category, 1.8% and 2% in the intermediate-risk category and 7.1 and 6.7% in the high-risk category, respectively. This model was subsequently externally validated in a prospective population by the Vienna CATS study in 819 cancer patients [9]. However, it is unclear whether this Risk Score is applicable to newer agents (including antiangiogenic and targeted therapies) and whether it is predictive in other populations, such as those with advanced cancers post-multiple lines of chemotherapy.

What can we learn from this important study? Firstly, Mandala et al. demonstrate that the Risk Score, which was originally developed in USA cancer patients receiving primarily chemotherapy in the adjuvant or early-line setting, is also predictive of VTE in European patients, heavily pre-treated patients and patients receiving targeted therapy only (19% of the study population in this report). This is an important external validation of the Risk Score and is consistent with other recent reports [9, 11]. These findings support the use of the Risk Score in the clinic to identify high-risk cancer patients and in study design of thromboprophylaxis trials to identify high-risk subgroups. Support for thromboprophylaxis of high-risk patients comes from a subgroup analysis of Evaluation of AVE5026 in the Prevention of VTE in Cancer Patients Undergoing Chemotherpay (SAVE-ONCO), the largest trial of outpatient prophylaxis ever conducted, using semuloparin—a novel ultralow-molecular-weight heparin [12]. For the entire study population, VTE occurred in 20 of 1608 patients (1.2%) receiving semuloparin, as compared with 55 of 1604 (3.4%) receiving placebo (HR = 0.36; 95% CI 0.21–0.60; P < 0.001). When the Risk Score was applied to the SAVE-ONCO
population, rates in the placebo arm were higher and risk reduction was therefore greater in high-risk patients: 5.4% in the placebo arm versus 1.4% in the semuloparin arm, for score ≥ 3 [HR = 0.27] compared with 1.3% versus 1%, respectively, for score = 0 [HR = 0.71]. These findings suggest that the risk, cost and inconvenience of pharmacological thromboprophylaxis would not provide net benefit to patients in the low-risk group. The opposite is the case for high-risk patients. Note, however, that this was a post hoc subgroup analysis and current guidelines do not recommend outpatient prophylaxis except for high-risk myeloma patients receiving thalidomide- or lenalidomide-based combination regimens. High-risk patients, as defined by the Risk Score, are currently the subject of an National Institutes of Health-sponsored phase III randomized clinical trial of thromboprophylaxis.

A second lesson to be learnt from this report pertains to the selection of patients for phase I clinical trials. Phase I studies are crucially important to the development of new agents and the design of such studies is focused on identifying toxicity of new agents. If rates of complications are unexpectedly high, such drugs—even if effective anticancer agents—may not be developed further. Understanding basal rates of common complications, such as VTE, is therefore essential to successfully identify and develop safe and effective new agents. If high-risk patients (based on the Risk Score) are disproportionately included in a single phase I trial, high rates of VTE could occur and be falsely attributed to the investigational agent leading to delays or even abandonment of drug development. It is also worthwhile noting that 25% of patients who developed VTE stopped treatment, which would clearly impact the results of phase I studies that these patients were participating in.

One limitation of this report is that mortality outcomes by risk category were not provided. This is important because early mortality rates differed by risk category in a subsequent analysis of the registry population from which the Risk Score was derived [13]. Death from all causes within 4 months of treatment initiation occurred in 1.2%, 5.9% and 12.7% patients for the low-, intermediate- and high-risk score groups. HR estimates for mortality among the intermediate- and high-risk score groups were 3.56 [1.91–6.66] and 6.89 [3.50–13.57], respectively (P < 0.0001). Thus, in addition to predicting risk of VTE, the Risk Score may be effective in predicting early treatment-related mortality, and this has additional implications for enrollment of high-risk patients in phase I studies. Of note, in an earlier analysis of the consequences of VTE in 220 phase I cancer patients, the median survival of patients with and without VTE was 4.7 and 10.9 months, respectively (P = 0.0002) [14].

In summary, Mandala et al. provide valuable information on the incidence and implications of VTE in a large sample of phase I patients. This report confirms the validity of a previously developed risk assessment tool in this population and it provides food for thought to those involved in the design and enrollment of patients on phase I studies. Now that clinicians can identify a high-risk population, ongoing studies of thromboprophylaxis will hopefully provide tools to reduce the burden and consequences of VTE among patients with cancer.

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references

10. Mandala M, Clerici M, Corradino I et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the

Table 1. Predictive model for chemotherapy-associated VTE [8]

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥35 0000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level &lt;10 g/dl or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count &gt;11 0000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index ≥35 kg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

High-risk score ≥3; Intermediate-risk score = 1–2; Low-risk score = 0.


