To the editor:

P-selectin ready for prime time?

In a recent issue of *Blood*, Ay and colleagues reported that elevated serum P-selectin levels predict venous thromboembolism (VTE) in cancer patients. They postulated that this marker could identify patients at risk who could benefit from prophylactic anticoagulation.[1] Current guidelines do not recommend anticoagulant prophylaxis for ambulatory cancer patients, in part because a patient group at high enough risk for VTE to justify the risk of prophylaxis cannot be identified.[2] Ay et al's study results have the potential for major clinical impact. However, we raise the question, "Is P-selectin ready for prime time?"

There are several issues we want to raise with respect to this cohort study. The first relates to the potential for ascertainment bias. Initially there were 812 patients; subsequently, 135 (15%) were excluded. The specific reasons for exclusion are not clear. Baseline serum-soluble P-selectin (sP-selectin) values were obtained for each patient at the start of the observation period. It is unclear whether the clinicians who conducted initial interviews, regular follow-up, and the diagnosis of VTE were blinded to test results.

Our second issue relates to selection of the time point of patient follow-up for relating the sP-selectin value to VTE incidence. Figure 1 of Ay et al illustrates the cumulative incidence of VTE over 2 years.[1] We wonder if the authors chose to analyze the values at the 6-month point based on their observation that this is when the 2 curves were maximally separated (11.9% vs 3.7%) and all of the events in the high sP-selectin group, but only about one-half of the events in the other group, had occurred. A better time to estimate the effect is when all events have occurred. Thus, if the 12-month time point is selected, the cumulative incidences of VTE for the 2 groups are 11.9% versus 5.8%, resulting in a 2-fold rather than 3-fold risk.

Finally, it is unclear whether the choice of the 75th percentile to dichotomize the sP-selectin scale was predetermined or data-driven. We suggest that use of a receiver operating characteristic (ROC) curve would have been more appropriate in illustrating the performance of the sP-selectin value using multiple cutoffs. It is of interest that the authors used this method in an earlier paper on sP-selectin.[3]

sP-selectin clearly has limitations as a predictor of risk. Of the 173 patients in the upper quartile of sP-selectin, we calculated that 19 had VTE compared with 25 of 514 in the lower quartiles. With this cut-point, the sensitivity of sP-selectin is 43%, the specificity is 76%, and the negative predictive value is 95%, but the positive predictive value is only 11%. Hence, the test would be associated with a large number of false positives, limiting its potential for identifying candidates for prophylaxis. The results of Ay et al are encouraging but require validation in a larger prospective cohort.

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References

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Response

P-selectin ready for the "News at Six"

We thank Rana et al for their comments on our study.[1] In this prospective observational cohort study, we demonstrated that high levels of soluble P-selectin (sP-selectin) are predictive of venous thromboembolism (VTE) in cancer patients. In previous studies our group reported that high plasma levels of sP-selectin, which are modulated by variations of the P-selectin gene, are strongly associated with VTE in non–cancer patients.[2,3]

Initially we enrolled 812 patients in the Vienna Cancer and Thrombosis Study (CATS) for investigation of sP-selectin. From this group, 135 were excluded because, after reevaluation. they did not exactly fulfill the inclusion and exclusion criteria of the study. Reasons for exclusion are clearly outlined in the "Methods" section of our paper[1] (eg, long-term prophylaxis with low molecular weight heparin [LMWH] or tumor not confirmed by histology [n = 52], no complete information on follow-up [n = 61], or no adequate material for sP-selectin measurement was available [n = 12]). None of the clinicians conducting initial interviews, regular follow-up, and the diagnosis of VTE was aware of test results at any time. The technicians who performed testing of sP-selectin levels were also unaware at all times of our patients' characteristics. Moreover, the samples for serial measurements were blinded.

The cumulative probability of developing VTE after 6 months was analyzed not only because of the high risk for occurrence of VTE in cancer patients in the first 3 to 6 months after diagnosis, but also because we believe that this time period seems to be feasible for a prophylactic anticoagulation of cancer patients.

Use of the 75th percentile to dichotomize sP-selectin levels in our current study (53.1 ng/mL) was chosen because the cutoff level matched closely to the 95th percentile of sP-selectin in the control