Soluble Vascular Endothelial Growth Factor (sVEGF) and the Risk of Venous Thromboembolism in Patients with Cancer: Results from the Vienna Cancer and Thrombosis Study (CATS)

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Abstract

Purpose: Cancer patients are at an increased risk of venous thromboembolism (VTE). VEGF promotes the growth of highly thrombogenic tumor vessels. Here, we explored the utility of soluble plasma VEGF-A (sVEGF) as a biomarker for the prediction of VTE in patients with cancer.

Experimental Design: Eight hundred four patients with newly diagnosed cancer or progression after remission were prospectively followed for 2 years until the occurrence of VTE or death (tumor sites: brain (n = 87), breast (n = 137), lung (n = 120), gastrointestinal (n = 143), pancreas (n = 53), prostate (n = 95), kidney (n = 22), myeloma and lymphoma (n = 99), and others (n = 46)). Primary endpoint was symptomatic or fatal VTE. sVEGF was measured by immunoassay in baseline plasma.

Results: Fifty-five patients developed VTE (6.8%) and 364 patients (45.3%) died. Five-hundred and forty-two (68.3%) participants had sVEGF levels above the detection limit of 0.5 pg/mL. The median sVEGF level (25th-75th percentile) was 8.1 pg/mL (0–17.7). The cumulative 2-year incidence of VTE was 10.2% [95% confidence interval (CI), 6.4–14.9] in patients with sVEGF greater than the 75th percentile of the sVEGF distribution (Q3, cutoff: 17.7 pg/mL), and 5.9% (95% CI, 4.2–7.9) in patients with lower levels (P = 0.03). The corresponding 2-year risk of death was 52.8% (95% CI, 46.0–60.0) and 43.9% (95% CI, 40.0–48.0), respectively (P = 0.02). In univariable time-to-VTE regression, elevated sVEGF was associated with VTE [subhazard ratio (SHR) per 10 pg/mL increase, 1.04; 95% CI, 1.00–1.09; P = 0.04]. The association between sVEGF and risk of VTE prevailed after multivariable adjustment for high-risk tumor sites, age, gender, factor VIII, thrombin generation potential, and soluble P-Selectin (adjusted SHR, 1.04; 95% CI, 1.00–1.09, P = 0.05).

Conclusions: Elevated sVEGF is associated with an increased risk of VTE in patients with cancer. Clin Cancer Res; 22(1); 200–6.

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Introduction

Venous thromboembolism (VTE) is a frequent complication and leading cause of death in cancer patients (1). Several individual risk factors related to patient-, tumor- and treatment characteristics determine the substantially increased overall risk of VTE in the cancer population (2). While primary thromboprophylaxis conceptually appears as a meaningful strategy to reduce the burden of cancer-associated VTE, its implementation is hampered by the great variation of VTE risk between patients (3). In this respect, recent progress has been made via the development of risk-scoring models that facilitate the identification of patients at a high risk of VTE (4, 5). Importantly, it has been demonstrated that the addition of selected biomarkers to preexisting risk-scoring models can increase the prognostic performance of these models (6). Further improvement of such scores by the identification of new prognostic biomarkers for VTE is believed to facilitate targeting thromboprophylaxis to the patients with the greatest net clinical benefit while sparing low-risk patients from potential bleeding complications (7).

VEGF-A is a key regulator and stimulating agent of angiogenesis (8), which promotes the formation of highly thrombogenic and leaky tumor vessels that are necessary for maintaining oxygen and energy supply at the site of the tumor lesion (9). VEGF further induces the expression of tissue factor (TF), the main initiator of the coagulation cascade in vivo, on endothelial cells (10). TF activity has been shown to be increased more than 100-fold after the exposition to VEGF and TNFα (11). Elevated levels of VEGF are present in the bloodstream of patients with highly prothrombotic malignancies, such as ovarian and renal carcinomas (12).
VEGF and VTE Risk in Cancer Patients

Translational Relevance
Venous thromboembolism (VTE) is a frequent complication and leading cause of death in patients with cancer. Prophylactic anticoagulation (PA) has been shown to reduce the risk of cancer-associated VTE by half, but comes at the cost of an increased risk of bleeding. Biomarkers hold great promise to identify cancer patients with the highest VTE risk and net clinical benefit of PA, while sparing low-VTE-risk cancer patients from PA-associated bleeding complications. In this study, we report the identification of a novel biomarker for cancer-associated VTE, soluble VEGF-A (sVEGF). We observed a significant association between elevated sVEGF and an excessively increased risk of VTE during a 2-year prospective follow-up of 804 cancer patients. This prognostic relationship was independent of major other prognostic factors for VTE, such as tumor type and stage. We propose sVEGF as a candidate biomarker for the personalization of VTE prophylaxis in patients with malignant diseases.

Materials and Methods
Study population and design
In this study, we analyzed 804 patients from the Vienna Cancer and Thrombosis Study (CATS), an ongoing cohort study to investigate prognostic factors and biomarkers for VTE in cancer patients. The 804 patients in this analysis were enrolled between October 2003 and March 2008. The exact inclusion and exclusion criteria of CATS were described extensively in previous reports (18, 19). Briefly, patients 18 years or older with newly diagnosed malignancy or disease progression after complete or partial remission were recruited after written informed consent and followed-up for 2 years until the occurrence of VTE, death, or censoring alive. The following tumor sites were included: blood (myeloma and lymphoma), brain, breast, bronchus, colorectal, kidney, pancreas, prostate, and "selected others" (mainly sarcomas and gynecologic tumors). Exclusion criteria were clinically overt infection, thromboembolic events (both arterial and venous) within the last 3 months, and continuous anticoagulation. Patients that underwent surgery or radiotherapy within the past 2 weeks before recruitment, and/or chemotherapy within the past 3 months were ineligible. At baseline, study patients underwent a detailed interview and chart review to ascertain clinicopathological variables, and venous blood samples were taken for storage in our biobank. The study protocol was approved by the local Institutional Review Board before any patient-related activities took place (EC number: 126/2003, ethic-kom@meduniwien.ac.at).

Outcome Measures
The primary endpoint of this study was symptomatic nonfatal and fatal VTE. Diagnosis of VTE had to be confirmed by objective methods [(duplex ultrasound or venography for deep vein thrombosis (DVT), ventilation/perfusion scan or computed tomography (CT) of the chest for non-fatal pulmonary embolism (PE), and autopsy records for fatal PE)]. VTE events were independently adjudicated by an external committee consisting of experts in diagnostic radiology and vascular medicine. No routine screening for VTE was performed. Incidentally discovered VTE (e.g., PE on restaging CT scans) was counted as an event given the independent adjudication committee deemed the VTE event to be of clinical significance. Secondary endpoint was death from any cause.

Laboratory analysis
Baseline venous blood samples were obtained by atraumatic antecubital venipuncture for laboratory analysis. Biomarker measurements (sVEGF and others) were performed in platelet-poor citrated plasma, which was obtained by drawing baseline blood into citrate vacuum tubes [Vacutette; Greiner-Bio-One; 9 parts blood and 1 part sodium citrate (concentration: 0.129 mmol/L)] and centrifuged at 3,000 g for 10 minutes to obtain platelet-poor plasma. Plasma aliquots were stored at −80°C until testing was performed in series. sVEGF was measured by a multiplex immunoassay [(xMAP technology from Luminex (sVEGF detection limit = 0.5 pg/ml)]. Specific anti-VEGF antibodies as well as recombinant growth factors were obtained from R&D Systems. The biomarkers D-Dimer, soluble P-Selectin (sP-Selectin), peak of thrombin generation, prothrombin fragment 1.2, and coagulation factor VIII activity (FVIII) were measured as described in previous reports (18–22).

Statistical analysis
All statistical analyses were performed using Stata (Windows version 13, Stata Corp.) and R (Version 3.1.1, The R core development team, Vienna, Austria). Continuous variables were summarized with medians (25th–75th percentile), whereas categorical data were described by absolute frequencies and percentages. The correlation between two continuous variables was evaluated with Spearman rank correlation coefficient. Univariable between-group comparisons were performed with χ² tests for categorical data, and t tests or ANOVA for continuous data, respectively. R², the coefficient of explained variation in sVEGF, was calculated using linear regression with log(x + 1)–transformed sVEGF as the dependent variable. For estimation of VTE risk, competing risk cumulative incidence estimators according to Marubini and Valsecchi (Stata module stcompet) were implemented (23). In all analyses, death from any cause except fatal VTE (which is counted as a VTE event) was defined as the competing event of interest. To study the association between VEGF and the rate of VTE, we performed a cause-specific analysis of VTE hazards using log-rank tests and Cox regression (24). In contrast, the association between VEGF and the absolute risk of VTE was studied with a subdistribution approach using Gray test (R library cmpsk) and Fine and Gray regression (Stata program streg; ref. 24). For multivariable adjustment, six covariates were selected a priori, namely age and sex (as demographic variables of general interest), tumor
Table 1. Distribution of baseline variables overall and by sVEGF levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (% missing)</th>
<th>Overall (n = 804)</th>
<th>VEGF &lt; Q3 (n = 607)</th>
<th>VEGF ≥ Q3 (n = 197)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rho (ρ)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at entry, y</td>
<td>804 (0.0%)</td>
<td>631 (54.2–69.2)</td>
<td>63.0 (54.3–68.7)</td>
<td>63.3 (53.5–71.8)</td>
<td>0.77</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>802 (0.3%)</td>
<td>25.0 (22.3–28.1)</td>
<td>24.9 (22.4–28.1)</td>
<td>25.1 (21.8–28.1)</td>
<td>0.72</td>
<td>0.00 (0.95)</td>
</tr>
<tr>
<td>Female gender</td>
<td>804 (0.0%)</td>
<td>433 (53.9%)</td>
<td>338 (55.7%)</td>
<td>95 (48.2%)</td>
<td>0.77</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td>Tumor site</td>
<td>804 (0.0%)</td>
<td>—</td>
<td>—</td>
<td>95 (48.2%)</td>
<td>0.77</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td>Brain</td>
<td>—</td>
<td>87 (10.8%)</td>
<td>66 (10.9%)</td>
<td>21 (10.7%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Breast</td>
<td>—</td>
<td>137 (17.0%)</td>
<td>101 (16.6%)</td>
<td>36 (18.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bronchus</td>
<td>—</td>
<td>120 (14.9%)</td>
<td>84 (13.8%)</td>
<td>36 (18.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Colorectal</td>
<td>—</td>
<td>105 (13.1%)</td>
<td>82 (13.5%)</td>
<td>23 (11.7%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kidney</td>
<td>—</td>
<td>22 (2.7%)</td>
<td>16 (2.6%)</td>
<td>6 (3.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>—</td>
<td>84 (10.5%)</td>
<td>68 (11.2%)</td>
<td>16 (8.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Myeloma</td>
<td>—</td>
<td>15 (1.9%)</td>
<td>13 (2.1%)</td>
<td>2 (1.0%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other site</td>
<td>—</td>
<td>48 (6.0%)</td>
<td>36 (5.9%)</td>
<td>12 (6.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prostate</td>
<td>—</td>
<td>53 (6.6%)</td>
<td>36 (5.9%)</td>
<td>17 (8.6%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Prostate</td>
<td>—</td>
<td>95 (11.8%)</td>
<td>77 (12.2%)</td>
<td>18 (9.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stomach</td>
<td>—</td>
<td>38 (4.7%)</td>
<td>28 (4.6%)</td>
<td>10 (5.1%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>High-risk or very-high-risk tumor site&lt;sup&gt;c&lt;/sup&gt;</td>
<td>804 (0.0%)</td>
<td>546 (67.2%)</td>
<td>411 (68.2%)</td>
<td>135 (31.5%)</td>
<td>0.68</td>
<td>—</td>
</tr>
<tr>
<td>Localized disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td>804 (0.0%)</td>
<td>467 (58.1%)</td>
<td>363 (59.8%)</td>
<td>104 (52.8%)</td>
<td>0.08</td>
<td>—</td>
</tr>
<tr>
<td>Newly diagnosed cancer</td>
<td>804 (0.0%)</td>
<td>596 (74.1%)</td>
<td>452 (74.6%)</td>
<td>143 (72.6%)</td>
<td>0.57</td>
<td>—</td>
</tr>
<tr>
<td>Stage&lt;sup&gt;e&lt;/sup&gt;</td>
<td>684 (15.0%)</td>
<td>—</td>
<td>—</td>
<td>0.315</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stage I</td>
<td>—</td>
<td>79 (11.6%)</td>
<td>65 (12.7%)</td>
<td>14 (8.2%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stage II</td>
<td>—</td>
<td>158 (23.1%)</td>
<td>120 (23.4%)</td>
<td>38 (22.2%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stage III</td>
<td>—</td>
<td>89 (13.0%)</td>
<td>68 (12.3%)</td>
<td>21 (12.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stage IV</td>
<td>—</td>
<td>357 (52.3%)</td>
<td>250 (50.6%)</td>
<td>98 (57.3%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tumor grade&lt;sup&gt;f&lt;/sup&gt;</td>
<td>690 (14.2%)</td>
<td>—</td>
<td>—</td>
<td>0.757</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G1</td>
<td>—</td>
<td>51 (7.4%)</td>
<td>41 (7.9%)</td>
<td>10 (5.8%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G2</td>
<td>—</td>
<td>312 (45.2%)</td>
<td>233 (45.1%)</td>
<td>79 (45.7%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G3</td>
<td>—</td>
<td>262 (38.0%)</td>
<td>193 (37.3%)</td>
<td>69 (39.9%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>G4</td>
<td>—</td>
<td>65 (9.4%)</td>
<td>50 (9.7%)</td>
<td>15 (8.7%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of erythropoietin-stimulating agents (ESA) within 3 months before or after study inclusion</td>
<td>804 (0.0%)</td>
<td>37 (4.6%)</td>
<td>25 (4.1%)</td>
<td>12 (6.1%)</td>
<td>0.251</td>
<td>—</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; ref, reference category; PAI-1, plasminogen activator inhibitor 1.

<sup>a</sup>The cutoff for Q3 is set at 17.65 pg/mL.

<sup>b</sup>P values are from χ<sup>2</sup> tests for categorical variables, and t tests (when appropriate with correction for heteroscedasticity) for continuous variables.

<sup>c</sup>Rho (ρ) indicates the Spearman rank correlation coefficient with P value (no adjustment for multiplicity done).

<sup>d</sup>High-risk or very-high-risk tumor sites are defined according to Khan et al. with extensions according to Ay et al. (high-risk sites: lung, colon, kidney, myeloma, lymphoma, gynecologic; very-high-risk: brain, stomach, pancreas).

<sup>e</sup>Localized disease is defined as the absence of clinically overt metastatic disease at baseline (with brain tumors being per se defined as localized).

<sup>f</sup>Stage cannot be provided for the remaining 15% of patients because no UICC-conforming staging system (i.e., stages I, II, III, and IV) is defined for some tumor entities (glioblastoma (n = 87), multiple myeloma (n = 15), selected types of lymphoma (such as chronic lymphocytic leukemia (1.9%))).

<sup>g</sup>Grading cannot be provided for the remaining patients because a specific grading system (i.e., G1–G4) is not defined for some tumor entities (multiple myeloma and lymphoma).

[snip of text from the main body of the paper, discussing the clinical significance of these findings]
we Z-standardized these biomarkers and compared their univariate subhazard ratios (SHR). Mortality data were analyzed with Kaplan–Meier product-limit-estimators, the log-rank test, and uni- and multivariable Cox-Models. No evidence for nonproportional hazards according to sVEGF emerged in any of the models for both the VTE and mortality endpoint.

**Results**

**Baseline analysis**

At baseline, the median age (Q1-Q3) of the study population was 63.1 (54.2–69.2), and 433 (53.9%) of the 804 patients were female (Table 1). The majority of patients suffered from newly diagnosed malignancy (n = 596, 74.1%), and had no clinical evidence for metastatic disease (n = 467, 58.1%).

Five hundred forty-nine (68.3%) out of 804 patients had sVEGF levels above the detection limit of 0.5 pg/mL (Table 2). A group of patients with elevated baseline sVEGF (n = 197) was defined by dichotomizing sVEGF into a binary variable at the 75th percentile of its distribution (Q3, cutoff: 17.65 pg/mL; Q3 defines the "elevated sVEGF" group). On average, patients with elevated sVEGF had higher platelet counts, lower hemoglobin, as well as higher levels of D-Dimer and peak thrombin generation (Table 1). Weak evidence was found for an association between localized disease and lower VEGF (P = 0.08). The distribution of other baseline variables appeared to be comparable between the two sVEGF groups.

Weak positive correlations were observed between sVEGF and leukocyte count, platelet count, D-Dimer, thrombin generation, fibrinogen, von Willebrand factor (vWF), lactate dehydrogenase (LDH), and C-reactive protein (CRP; all rho ≥ 0.16 and all P < 0.01, Table 1). A negative correlation was found between sVEGF and hemoglobin (rho = -0.17, P < 0.001). A multiple linear regression model with sVEGF as the dependent variable and high- and very-high-risk tumor sites, sex, age, BMI, and thrombocyte and leukocyte count as independent variables was performed to study the amount of variation in sVEGF that may be explained by these markers ("Multiple Model 1," Supplementary File S1). R², the coefficient of determination of this model, was 0.03, suggesting that these variables explain only around 3% of the variation in sVEGF. A corresponding model with CRP, platelet count, D-Dimer, fibrinogen, peak of thrombin generation, LDH, and vWF as the independent variables explained 7% of the variation in sVEGF ("Multiple Model 2," Supplementary File S1).

**sVEGF and the risk of VTE**

In the overall study population, the cumulative incidence of VTE at 6, 12, and 24 months of follow-up was 5.0%, 6.2%, and 6.9%, respectively. Patients with elevated sVEGF (i.e., >Q3) had a higher rate of VTE than patients with sVEGF ≤ Q3 (log-rank test P = 0.02). The cumulative 6-, 12-, and 24-month incidences of VTE (95% CI) were 8.6% (5.2–13.1), 10.2% (6.4–14.9), and 10.2% (6.4–14.9) in the VEGF > Q3 group, and 3.8% (2.5–5.6), 5.0% (2.9–7.6), and 5.0% (2.9–7.6) in the VEGF ≤ Q3 group.

Strong evidence for an association between elevated sVEGF and the risk of VTE was found (Gray test P = 0.03).

**Table 2.** Distribution of sVEGF overall and by VTE event status

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Mean ± SD</th>
<th>Median (Q1–Q3)</th>
<th>Min-max</th>
<th>sVEGF &gt; 0.5 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 804)</td>
<td>17.7 ± 38.6</td>
<td>8.1 (0–17.7)</td>
<td>0–512.3</td>
<td>549 (68.3%)</td>
</tr>
<tr>
<td>No VTE during F/U (n = 749)</td>
<td>17.0 ± 34.6</td>
<td>8.1 (0–17.5)</td>
<td>0–397.2</td>
<td>505 (67.4%)</td>
</tr>
<tr>
<td>VTE during F/U (n = 55)</td>
<td>27.5 ± 74.5</td>
<td>9.4 (1.8–25.0)</td>
<td>0–512.3</td>
<td>44 (80.0%)</td>
</tr>
</tbody>
</table>

Abbreviations: F/U, follow-up; Q1 and Q3, first and third quartiles of the sVEGF distribution.
sVEGF was associated with a 4% increase in the risk of VTE (SHR, 1.05; 95% CI, 1.00–1.09, P = 0.04). The 12-month risk of death was 27.9% (95% CI, 24.5–31.6) in the VEGF≤Q3 group, and 35.6% (95% CI, 29.4–42.8) in the VEGF>Q3 group (HR, 1.34; 95% CI, 1.06–1.68, P = 0.01; Fig. 2). This association prevailed after multivariable adjustment for high- and very-high-risk tumor types, localized versus distant disease, D-Dimer, and leukocyte and platelet count (HR, 1.33; 95% CI, 1.05–1.68, P = 0.02; full model shown in Supplementary File S1). We did not observe any evidence for interactions between sVEGF and tumor type, D-Dimer, and C-reactive protein.

### Discussion

In this prospective cohort study, we have provided evidence for an association between elevated levels of sVEGF and a higher risk of VTE in patients with cancer. Furthermore, we could confirm the association of elevated sVEGF and poor overall survival.

#### sVEGF and the pathogenesis of VTE in cancer

Using a sVEGF multiplex immunoassay, we found that sVEGF was present in the bloodstream of approximately 70% of the investigated patients. Interestingly, the other 30% of patients with undetectable sVEGF experienced only half the risk of developing VTE. It was well established in experimental studies that endothelial cells and several subsets of leukocytes can express sVEGF on their surface (10, 16), and that activated platelets release VEGF from their α-granules (17). Surprisingly, we found that leukocyte and platelet count explained less than 3% of the variation in sVEGF, which increased to 7% when we considered vWF and LDH, among others, as independent variables. Given that vWF and sP-Selectin are contained in α-granules (25), and LDH is secreted by degranulating platelets (26), the weak correlations between sVEGF, LDH, sP-Selectin, and vWF may indicate that at least some of the amount of sVEGF originates from the α-granules of activated platelets. Furthermore, vWF and sP-Selectin are also released from Weibel-Palade bodies of activated endothelial cells (25). The observed correlations between sVEGF, vWF, and sP-Selectin could thus also be indicative of endothelial activation, a process that is a well-established hallmark of cancer-associated hypercoagulability and inflammation (27).

Some of the sVEGF in the bloodstream may originate directly from tumor cells. The weak correlation between sVEGF and LDH, an intracellular enzyme that is released by decaying tumor cells,
Furthermore, correlations between sVEGF and in might re.

Parentheses the number of VTE events within a time interval.

Number at risk (deaths)

| sVEGF>Q3 | 197 (46) |
| sVEGF≤Q3 | 607 (84) |

Figure 2.
Cumulative incidence of death according to baseline sVEGF. Q3 is the third quartile of the sVEGF distribution (cutoff: 17.65 pg/mL); the risk table below the graph reports (i) numbers at risk of death at the beginning of each time interval, and (ii) in parentheses the number of VTE events within a time interval.

Published OnlineFirst August 24, 2015; DOI: 10.1158/1078-0432.CCR-14-3358

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Conclusion

We demonstrated a prospective association between elevated plasma sVEGF and an increased risk of VTE in patients with cancer. This association was independent of major known prognostic factors, such as tumor type and biomarkers indicative of a prothrombotic state. Furthermore, we confirmed the role of increased sVEGF as an adverse prognostic factor for mortality. In conclusion, we propose sVEGF as a novel biomarker for cancer-associated VTE.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: F. Posch, J. Thaler, C. Zielinski, I. Pabinger, C. Ay Development of methodology: F. Posch, I. Pabinger Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Thaler, G-J. Zlabinger, O. Konigsbrugg, C. Zielinski, C. Ay Writing, review, and/or revision of the manuscript: F. Posch, J. Thaler, G-J. Zlabinger, I. Pabinger, C. Ay Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Posch, J. Thaler, S. Koder, C. Zielinski, C. Ay Study supervision: J. Thaler, I. Pabinger, C. Ay

Acknowledgments

The authors thank Petra Waidhofer-Sollner, MSc, for technical assistance and Prof. Sylvia Metz-Schimmerl, MD, and Prof. Andrea Willfort-Ehringer, MD, for their efforts in independently adjudicating the VTE events of this study.

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Received December 28, 2014; revised April 30, 2015; accepted August 16, 2015; published OnlineFirst August 24, 2015.

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Soluble Vascular Endothelial Growth Factor (sVEGF) and the Risk of Venous Thromboembolism in Patients with Cancer: Results from the Vienna Cancer and Thrombosis Study (CATS)

Florian Posch, Johannes Thaler, Gerhard-Johann Zlabinger, et al.


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