Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

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ABSTRACT  

BACKGROUND  
Patients receiving chemotherapy for cancer are at increased risk for venous thromboembolism. Limited data support the clinical benefit of antithrombotic prophylaxis.  

METHODS  
In this double-blind, multicenter trial, we evaluated the efficacy and safety of the ultra-low-molecular-weight heparin semuloparin for prevention of venous thromboembolism in patients receiving chemotherapy for cancer. Patients with metastatic or locally advanced solid tumors who were beginning to receive a course of chemotherapy were randomly assigned to receive subcutaneous semuloparin, 20 mg once daily, or placebo until there was a change of chemotherapy regimen. The primary efficacy outcome was the composite of any symptomatic deep-vein thrombosis, any nonfatal pulmonary embolism, and death related to venous thromboembolism. Clinically relevant bleeding (major and nonmajor) was the main safety outcome.  

RESULTS  
The median treatment duration was 3.5 months. Venous thromboembolism occurred in 20 of 1608 patients (1.2%) receiving semuloparin, as compared with 55 of 1604 (3.4%) receiving placebo (hazard ratio, 0.36; 95% confidence interval [CI], 0.21 to 0.60; P<0.001), with consistent efficacy among subgroups defined according to the origin and stage of cancer and the baseline risk of venous thromboembolism. The incidence of clinically relevant bleeding was 2.8% and 2.0% in the semuloparin and placebo groups, respectively (hazard ratio, 1.40; 95% CI, 0.89 to 2.21). Major bleeding occurred in 19 of 1589 patients (1.2%) receiving semuloparin and 18 of 1583 (1.1%) receiving placebo (hazard ratio, 1.05; 95% CI, 0.55 to 1.99). Incidences of all other adverse events were similar in the two study groups.  

CONCLUSIONS  
Semuloparin reduces the incidence of thromboembolic events in patients receiving chemotherapy for cancer, with no apparent increase in major bleeding. (Funded by Sanofi; ClinicalTrials.gov number, NCT00694382.)
VENOUS THROMBOEMBOLISM, A COMMON complication in patients with cancer,1-2 results in increased morbidity, mortality, medical care, and cost.3-4 In addition to surgery5 and prolonged hospital stays,6 chemotherapy is increasingly recognized as a risk factor for venous thromboembolism in patients with cancer.7-9 The risk of venous thromboembolism in patients receiving chemotherapy for cancer is dependent on many contributing factors, including the site and stage of the primary cancer, type and intensity of the chemotherapeutic regimen, age, coexisting conditions, and Eastern Cooperative Oncology Group (ECOG) performance status.10

Evidence from randomized, controlled trials concerning the clinical benefit of antithrombotic prophylaxis in ambulatory patients receiving chemotherapy for cancer is limited.11-14 The most recent guidelines15-17 state that further clinical trials are required before any recommendations can be made about the use of antithrombotic prophylaxis in ambulatory patients receiving chemotherapy for cancer.

Semuloparin is a hemisynthetic, ultra-low-molecular-weight heparin with high anti-Xa activity (approximately 160 U per milligram) and minimal anti-IIa activity (approximately 2 U per milligram).18 The average molecular weight is 2000 to 3000 daltons, and the half-life is 16 to 20 hours. After subcutaneous injection, semuloparin is 98% bioavailable and reaches the maximum plasma anti-Xa activity at 2 to 3 hours; its excretion is mainly renal. We conducted the SAVE-ONCO study to assess the efficacy and safety of semuloparin for prophylaxis against venous thromboembolism in patients receiving chemotherapy for cancer.

The administration of other anticoagulant agents and fibrinolytic agents was not allowed during the study period. The use of antiplatelet agents status of 3 or higher (see the definition in the study protocol, available with the full text of this article at NEJM.org), calculated creatinine clearance of less than 30 ml per minute, major surgery within 4 weeks before randomization, and any contraindication to anticoagulation or requirement for thromboprophylaxis.

A baseline risk assessment for venous thromboembolism was performed according to the following factors: history of venous thromboembolism, central venous catheter, obesity, age of 75 years or older, chronic respiratory failure, chronic heart failure, venous insufficiency or varicose veins, and use of hormonal therapy.

STUDY DESIGN AND INTERVENTIONS
SAVE-ONCO was a randomized, double-blind, multicenter trial. It was placebo-controlled because prophylaxis of venous thromboembolism is not recommended or routinely used in patients receiving chemotherapy for cancer and because no anticoagulant drug is currently approved for this indication. The study was conducted in accordance with the protocol.

Eligible patients were randomly assigned to receive subcutaneous injections of semuloparin (20 mg once daily) or placebo. The dose of semuloparin was chosen on the basis of a phase 2 study of the drug as prophylaxis against venous thromboembolism after elective total knee replacement.19 Randomization was performed centrally by means of an interactive voice-response system. To balance the study groups, a minimization algorithm was used20,21 that took into account the following three factors: site of primary cancer, cancer stage (metastatic or locally advanced), and geographic region. The first dose of the study drug was to be administered on the first day of a course of chemotherapy (first regimen or a new regimen) and for the duration of chemotherapy (intended to be a minimum of 3 months). If chemotherapy was stopped within the first 3 months, the study medication was to be discontinued unless a new regimen was started. After the initial 3 months of administration, the study medication was to be discontinued when chemotherapy was stopped or when there was a change in the chemotherapy regimen.

The administration of other anticoagulant agents and fibrinolytic agents was not allowed during the study period. The use of antiplatelet agents

METHODS

PATIENTS
The patients included in this study were 18 years of age or older and planned to receive a course of chemotherapy for metastatic or locally advanced cancer of the lung, pancreas, stomach, colon or rectum, bladder, or ovary. Cancer types were selected on the basis of their broad representation among solid cancers and the high incidence of venous thromboembolism in patients receiving chemotherapy for these cancers.2

The main exclusion criteria were a life expectancy of less than 3 months, ECOG performance
or nonsteroidal antiinflammatory drugs was allowed if such treatment was considered to be necessary. All concomitant therapies were reported. The patients were seen monthly at their scheduled chemotherapy visits.

OUTCOME MEASURES
The primary efficacy outcome was the composite of any symptomatic deep-vein thrombosis in lower or upper limbs, any nonfatal pulmonary embolism, or death related to venous thromboembolism (fatal pulmonary embolism or unexplained death) occurring between randomization and 3 days after the last injection of the study drug, including periods when the study drug was temporarily discontinued. The secondary efficacy outcome of overall survival was to be assessed either 1 year after randomization or at the study end date (planned 7 months after randomization of the last patient to be enrolled), whichever came first.

The main safety outcome was any clinically relevant bleeding occurring between the first administration of the study drug and 3 days after the last administration of the study drug. An overt bleeding event was defined as major if it was fatal, occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome), was associated with a decrease in the hemoglobin level of 2.0 g per deciliter or more, or led to transfusion of 2 or more units of whole blood or red cells. Clinically relevant nonmajor bleeding was defined as any overt bleeding that required a medical intervention and did not meet any of the criteria for major bleeding. Efficacy and bleeding outcomes were assessed by a central independent adjudication committee, whose members were unaware of the study treatment.

STUDY OVERSIGHT
The study was designed by the steering committee members and sponsored by Sanofi. Data were collected through a clinical research organization and analyzed by Sanofi. No Sanofi employees were members of the steering committee or the data and safety monitoring board. All authors had access to all study data and contributed to the interpretation of the results. The first author wrote the first draft of the manuscript, and all the authors contributed to the revisions, with no conceptual contribution from anyone who was not an author and with no writing assistance, other than copy editing, from Excerpta Medica (which was supported by Sanofi). All authors vouch for the accuracy and completeness of the data reported.

The study was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board or ethics committee at each study center. Written informed consent was obtained from all patients before randomization. The data and safety monitoring board was responsible for monitoring the safety of the patients included in the trial.

STATISTICAL ANALYSIS
Assuming an event rate in the placebo group of about 4%, we calculated that 1600 patients per group would be required to detect a 50% reduction in relative risk in favor of semuloparin with a power of 90%, using a two-sided Fisher’s exact test at an alpha level of 0.05.

All patients who underwent randomization were included in the primary efficacy population (intention-to-treat population), and those who underwent randomization and received at least one dose of the study treatment were included in the safety population. To correct for competing risks (deaths from causes other than venous thromboembolism for efficacy, or fatal bleeding for safety) in the primary efficacy and safety analyses, a cumulative incidence approach was followed with the use of Gray’s two-sample test (two-sided alpha 0.05). Hazard ratios and 95% confidence intervals were calculated with the use of the Fine and Gray regression model. Cumulative incidence functions were estimated separately for the two study groups with the use of the Prentice nonparametric estimator and a model of cause-specific hazards, together with 95% confidence intervals. (Confidence intervals were calculated by means of the Keiding and Anderson formula, and variance by means of the delta method.)

Efficacy was assessed in subgroups defined by factors known to affect the risk of venous thromboembolism. For each factor, the heterogeneity of the treatment effect across subgroups was assessed by means of a treatment interaction test with the use of the Fine and Gray regression model. The Simes procedure was applied to adjust the interaction P values for multiple testing. For overall survival, comparison between the two treatment
groups was performed by means of a two-sided log-rank test, at a significance level of 0.05. The hazard ratio with 95% confidence interval was estimated with the use of the Cox regression model. Fine and Gray regression models were generated with the use of R software, version 2.10 or higher (R Development Core Team). All other statistical analyses were generated with the use of SAS software, version 9 or higher (SAS Institute).

**RESULTS**

**PATIENTS**

A total of 3212 patients underwent randomization at 395 centers in 47 countries and were included in the intention-to-treat population for the efficacy analysis. A total of 3172 patients received at least one dose of the study drug and were included in the safety analysis (Fig. 1 in the Supplementary Appendix, available at NEJM.org). The baseline characteristics of the patients, main thromboembolic risk factors for venous thromboembolism, ECOG performance status (Table 1 in the Supplementary Appendix), and most common chemotherapy regimens were well balanced between the groups. The most common primary cancers (i.e., final diagnoses) were lung cancer (in 36.6% of patients) and cancer of the colon or rectum (in 28.9%); approximately two thirds of the patients had metastatic cancer.

The duration of treatment was similar in the two study groups, with a median of approximately 3.5 months. Reasons for not completing the treatment were well balanced between the groups. The most common reasons were adverse events (15.9% and 17.5%) and the patient's request (18.1% and 17.4%); most requests to stop treatment were unrelated to an adverse event.

**EFFICACY OUTCOMES**

The primary efficacy outcome occurred in 20 of 1608 patients (1.2%) in the semuloparin group, as compared with 55 of 1604 (3.4%) in the placebo group (hazard ratio, 0.36; 95% confidence interval [CI], 0.21 to 0.60; P<0.001) (Fig. 1). Semuloparin was associated with a reduction in the risk of both deep-vein thrombosis (odds ratio, 0.32; 95% CI, 0.15 to 0.62) and fatal and nonfatal pulmonary embolism (odds ratio, 0.41; 95% CI, 0.19 to 0.85) (Table 1). No heterogeneity of the treatment effect was detected for any subgroups defined according to stratification factors: stage of cancer (P=0.32 for interaction), site of cancer (P=0.80 for interaction), and geographic region (P=0.53 for interaction). The treatment effect was consistent across the number of baseline risk factors for venous thromboembolism (P=0.84 for interaction) (Table 1).

Semuloparin did not influence overall survival: the rate of death was 43.4% in the semuloparin group, as compared with 44.5% in the placebo group (hazard ratio, 0.96; 95% CI, 0.86 to 1.06; P=0.40). The hazard ratio for overall survival was 0.86 (95% CI, 0.70 to 1.05) among patients who had locally advanced cancer and 1.00 (95% CI, 0.89 to 1.13) among those with metastatic cancer (P=0.20 for interaction).

**SAFETY**

The overall incidence of major and clinically relevant nonmajor bleeding was 2.8% in the semuloparin group (45 of 1589 patients), as compared with 2.0% in the placebo group (32 of 1583) (hazard ratio, 1.40; 95% CI, 0.89 to 2.21). Major bleeding occurred in 19 patients (1.2%) who received semuloparin and in 18 (1.1%) who received placebo (hazard ratio, 1.05; 95% CI, 0.55 to 1.99). Two fatal bleeding events occurred in the semuloparin group, as compared with four in the placebo group; five episodes of nonfatal bleeding in a critical area or organ were noted, all in the semuloparin group (Table 2).

Serious adverse events were reported in 418 patients (26.3%) in the semuloparin group and 403 (25.5%) in the placebo group (Table 3). The incidence of thrombocytopenia was similar in the semuloparin and placebo groups: 7.1% (113 patients) and 7.6% (121), respectively. There were no cases of heparin-induced thrombocytopenia.

During the treatment period, the proportion of patients with an alanine aminotransferase level that was more than 3 times the upper limit of the normal range was 5.3% in the semuloparin group and 4.3% in the placebo group; this abnormality combined with a total bilirubin level that was more than 2 times the upper limit of the normal range was noted in 1.0% and 1.5% of patients, respectively. The combination of hepatocellular damage and impaired bilirubin excretion can be a harbinger of serious or fatal liver toxicity (Hyp's law). None of these cases were
considered to meet the criteria for Hy’s law, as adjudicated by an independent expert who was unaware of the study-group assignments.

DISCUSSION

The results of this study show that thromboprophylaxis with the ultra-low-molecular-weight heparin semuloparin, as compared with placebo, reduces the risk of venous thromboembolism among patients receiving chemotherapy for cancer, with no apparent increase in the incidence of major bleeding. The treatment effect on the primary end point was consistent in subgroups defined by the primary site and stage of cancer and the baseline risk of venous thromboembolism.

Venous thromboembolism occurring in patients receiving chemotherapy for cancer has a substantial impact on care. This complication may lead to otherwise unnecessary hospitalization, interruption of chemotherapy, and anticoagulant treatment or insertion of a vena cava filter. Venous thromboembolism is associated with an increase in health care expenditures and has a significant effect on the quality of life of patients with cancer. Furthermore, the treatment of venous thromboembolism is problematic in patients with cancer, owing to coexisting conditions, chemotherapy-related thrombocytopenia, the high risk of recurrence, and bleeding.

Current guidelines recommend antithrombotic prophylaxis for patients with cancer who are admitted to the hospital for medical illness (administered for the duration of the hospital stay) and for patients who have undergone surgery for cancer (extended for up to 5 weeks) but not for routine use in ambulatory patients receiving chemotherapy. This study suggests a benefit from antithrombotic prophylaxis with semuloparin in patients receiving chemotherapy for cancer.
The mechanism underlying the prothrombotic effect of cancer chemotherapy has been only partially elucidated and is likely to be multifactorial.29 Cancer cells can promote the activation of blood coagulation directly by generating thrombin or indirectly by stimulating endothelial cells and circulating mononuclear cells to synthesize and express several procoagulant factors. Cancer chemotherapy has been shown to both amplify the prothrombotic effect of cancer cells5 and cause direct damage to the vascular endothelium.30 Regardless of the mechanism, the benefit of anti-thrombotic drugs could be due to counteraction of the prothrombotic effect of chemotherapy.31

In our study, the incidence of symptomatic deep-vein thrombosis, pulmonary embolism, or death related to venous thromboembolism in the placebo group was 3.4%, which was consistent with the hypothesized incidence (approximately 4%). The rate of these events in the placebo group ranged from 2.5% among patients with no baseline risk factors for venous thromboembolism to 12.5% among patients with three or more risk factors. This rate is likely to be higher in clinical

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**Table 1.** Primary Efficacy Outcome, According to Treatment Group.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Semuloparin (N = 1608)</th>
<th>Placebo (N = 1604)</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any VTE or VTE-related death — no. (%)</td>
<td>20 (1.2)</td>
<td>55 (3.4)</td>
<td>0.36 (0.21–0.60)</td>
</tr>
<tr>
<td>Symptomatic deep-vein thrombosis</td>
<td>11 (0.7)</td>
<td>34 (2.1)</td>
<td>0.32 (0.15–0.62)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>3 (0.2)</td>
<td>9 (0.6)</td>
<td>0.33 (0.07–1.18)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>8 (0.5)</td>
<td>25 (1.6)</td>
<td>0.32 (0.13–0.69)</td>
</tr>
<tr>
<td>Proximal</td>
<td>4 (0.2)</td>
<td>19 (1.2)</td>
<td>0.21 (0.06–0.58)</td>
</tr>
<tr>
<td>Distal</td>
<td>4 (0.2)</td>
<td>12 (0.7)</td>
<td>0.33 (0.09–0.99)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>10 (0.6)</td>
<td>24 (1.5)</td>
<td>0.41 (0.19–0.85)</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>3 (0.2)</td>
<td>15 (0.9)</td>
<td>0.20 (0.05–0.63)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3 (0.2)</td>
<td>12 (0.7)</td>
<td>0.25 (0.06–0.83)</td>
</tr>
<tr>
<td>Detected during tumor evaluation</td>
<td>0</td>
<td>3 (0.2)</td>
<td>NE</td>
</tr>
<tr>
<td>Any VTE-related death</td>
<td>7 (0.4)</td>
<td>9 (0.6)</td>
<td>0.77 (0.27–2.13)</td>
</tr>
<tr>
<td>Outcome according to primary cancer site — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>9/591 (1.5)</td>
<td>25/589 (4.2)</td>
<td>0.36 (0.17–0.77)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3/126 (2.4)</td>
<td>14/128 (10.9)</td>
<td>0.22 (0.06–0.76)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1/204 (0.5)</td>
<td>4/207 (1.9)</td>
<td>0.25 (0.03–2.20)</td>
</tr>
<tr>
<td>Colon or rectum</td>
<td>5/464 (1.1)</td>
<td>9/461 (2.0)</td>
<td>0.54 (0.18–1.60)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1/32 (3.1)</td>
<td>3/31 (9.7)</td>
<td>0.30 (0.03–2.95)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1/191 (0.5)</td>
<td>0/188</td>
<td>NE</td>
</tr>
<tr>
<td>Outcome according to stage of cancer — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>16/1097 (1.5)</td>
<td>38/1095 (3.5)</td>
<td>0.42 (0.23–0.75)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>4/511 (0.8)</td>
<td>17/509 (3.3)</td>
<td>0.23 (0.08–0.68)</td>
</tr>
<tr>
<td>Outcome according to no. of risk factors for VTE — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9/923 (1.0)</td>
<td>23/932 (2.5)</td>
<td>0.39 (0.18–0.84)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>9/652 (1.4)</td>
<td>27/632 (4.3)</td>
<td>0.32 (0.15–0.68)</td>
</tr>
<tr>
<td>≥3</td>
<td>2/33 (6.1)</td>
<td>5/40 (12.5)</td>
<td>0.56 (0.11–2.93)</td>
</tr>
</tbody>
</table>

* Data are for the 3212 patients in the intention-to-treat population. Multiple outcomes occurred in individual patients. CI denotes confidence interval, NE not estimable, and VTE venous thromboembolism.
† Odds ratios are reported for the individual components of the composite primary outcome. Hazard ratios were not calculated for these values, owing to the low number of events.
practice because of the steady increase in the risk of venous thromboembolism during the past few decades, possibly linked to the aging population, the prolonged survival of patients with cancer, and the increased use of prothrombotic cancer treatment such as antiangiogenic drugs. In addition, since this study included a placebo group, patients who required thromboprophylaxis were not eligible.

This study showed the clinical benefit of thromboprophylaxis with semuloparin in a large group of patients, across a broad representation of cancers, both locally advanced and metastatic disease, and a wide range of chemotherapy regimens. However, stratification for the risk of venous thromboembolism among patients with cancer may be clinically useful. Several criteria have been proposed to identify patients with cancer who are at high risk for venous thromboembolism, including specific cancer type, chemotherapy regimen, level of serum tissue-factor microparticles or P-selectin, and predictive scores for chemotherapy-related thrombosis. The most recent guidelines of the National Comprehensive Cancer Network emphasize the need for assessment of the risk of venous thromboembolism in ambulatory patients with cancer and the need for randomized studies of patients with a favorable risk–benefit ratio.

In our study, death related to venous thromboembolism contributed only marginally to the composite efficacy outcome. It should be noted that, per the predefined rules of the central independent adjudication committee, death was considered to be related to venous thromboembolism if pulmonary embolism was confirmed at autopsy or if the clinical course was compatible with pulmonary embolism and there was not a more compelling alternative cause of death. However, in our study, the large majority of patients died at home and an autopsy was almost never performed. Therefore, it is likely that the lower treatment effect of semuloparin on death related to venous thromboembolism reflects the conservative adjudication of this end point.

This was a double-blind, placebo-controlled study with confirmed symptomatic, clinically relevant events as study outcomes. The sample size was large enough to evaluate the benefits and risks of semuloparin in the target population. Furthermore, all the study outcomes were assessed by a central independent adjudication committee, whose members were unaware of the study-group assignments. Almost 99% of the patients who underwent randomization were included in the efficacy and safety analyses.

In conclusion, this study shows that semuloparin, as compared with placebo, reduces the incidence of venous thromboembolism in patients with metastatic or locally advanced cancer, with no apparent increase in major bleeding.

### Table 2. Clinically Relevant Bleeding Events during Treatment.*

<table>
<thead>
<tr>
<th>Bleeding Events</th>
<th>Semuloparin (N = 1589)</th>
<th>Placebo (N = 1583)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically relevant bleeding</td>
<td>45 (2.8)</td>
<td>32 (2.0)</td>
<td>1.41 (0.89–2.25)</td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>19 (1.2)</td>
<td>18 (1.1)</td>
<td>1.05 (0.55–2.04)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding‡</td>
<td>26 (1.6)</td>
<td>14 (0.9)</td>
<td>1.86 (0.98–3.68)</td>
</tr>
</tbody>
</table>

* Data are for the 3172 patients included in the safety analysis.
† Data include six instances of fatal bleeding: two in patients in the semuloparin group (one patient committed suicide and one had a convulsion that was suspected to be due to a bleeding brain metastasis) and four in patients in the placebo group (all of whom had gastrointestinal bleeding). There were also five instances of nonfatal bleeding in a critical area or organ in the semuloparin group (cerebral hematoma that was suspected to be due to cavernoma rupture in one patient, who recovered with sequelae; pericardial bleeding in two patients, who recovered; intraocular bleeding in one patient with a retinal detachment, who recovered; and intracranial bleeding in one patient with a brain metastasis, who recovered).
‡ Data include 13 serious events (9 in the semuloparin group and 4 in the placebo group), 16 events leading to the discontinuation of treatment (9 in the semuloparin group and 7 in the placebo group), and 38 events in patients who recovered (24 in the semuloparin group and 14 in the placebo group). Multiple events occurred in individual patients.

### Table 3. Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Semuloparin (N = 1589)</th>
<th>Placebo (N = 1583)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1350 (85.0)</td>
<td>1339 (84.6)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event related to study drug</td>
<td>242 (15.2)</td>
<td>187 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event†</td>
<td>418 (26.3)</td>
<td>403 (25.5)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event leading to death</td>
<td>193 (12.1)</td>
<td>185 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event leading to permanent</td>
<td>241 (15.2)</td>
<td>260 (16.4)</td>
<td></td>
</tr>
<tr>
<td>discontinuation of study drug</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percentages do not add up to 100 because some events were classified in multiple categories.
† Serious adverse events were classified as those that, at any dose, resulted in death or were life-threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in persistent or serious disability or incapacity, were a congenital anomaly, or were a medically important event.
REFERENCES


34. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor beva-

35. We thank Katherine Roberts of Excerpta Medica for editing an earlier draft of the manuscript, the nursing staff of the participating centers for their enthusiastic cooperation, and the patients included in the study for their trust and support.