

ORIGINAL ARTICLE

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., Danny Hill, M.D., Silvana Spadafora, M.D., Katherine Marquis, M.D., Mateya Trinkaus, M.D., Anna Tomiak, M.D., Agnes Y.Y. Lee, M.D., Peter L. Gross, M.D., Alejandro Lazo-Langner, M.D., Robert El-Maraghi, M.D., Glenwood Goss, M.D., Gregoire Le Gal, M.D., David Stewart, M.D., Timothy Ramsay, Ph.D., Marc Rodger, M.D., Debra Witham, B.Sc.N., and Philip S. Wells, M.D., for the AVERT Investigators*

ABSTRACT

BACKGROUND

Patients with active cancer have an increased risk of venous thromboembolism, which results in substantial morbidity, mortality, and health care expenditures. The Khorana score (range, 0 to 6, with higher scores indicating a higher risk of venous thromboembolism) has been validated to identify patients with cancer at elevated risk for this complication and may help select those who could benefit from thromboprophylaxis.

METHODS

We conducted a randomized, placebo-controlled, double-blind clinical trial assessing the efficacy and safety of apixaban (2.5 mg twice daily) for thromboprophylaxis in ambulatory patients with cancer who were at intermediate-to-high risk for venous thromboembolism (Khorana score, ≥ 2) and were initiating chemotherapy. The primary efficacy outcome was objectively documented venous thromboembolism over a follow-up period of 180 days. The main safety outcome was a major bleeding episode.

RESULTS

Of the 574 patients who underwent randomization, 563 were included in the modified intention-to-treat analysis. Venous thromboembolism occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (hazard ratio, 0.41; 95% confidence interval [CI], 0.26 to 0.65; $P < 0.001$). In the modified intention-to-treat analysis, major bleeding occurred in 10 patients (3.5%) in the apixaban group and in 5 patients (1.8%) in the placebo group (hazard ratio, 2.00; 95% CI, 1.01 to 3.95; $P = 0.046$). During the treatment period, major bleeding occurred in 6 patients (2.1%) in the apixaban group and in 3 patients (1.1%) in the placebo group (hazard ratio, 1.89; 95% CI, 0.39 to 9.24).

CONCLUSIONS

Apixaban therapy resulted in a significantly lower rate of venous thromboembolism than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of major bleeding episodes was higher with apixaban than with placebo. (Funded by the Canadian Institutes of Health Research and Bristol-Myers Squibb–Pfizer Alliance; AVERT ClinicalTrials.gov number, NCT02048865.)

From the Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa (M.C., R.M., G.G., G.L.G., D.S., T.R., M.R., D.W., P.S.W.), Centre Intégré de Santé et des Services Sociaux de l'Outaouais, Gatineau, QC (K.A.-N.), Jewish General Hospital, Lady Davis Institute for Medical Research, McGill University, Montreal (V.T.), Nova Scotia Health Authority, Halifax (S. Shivakumar), Lake-ridge Health, Oshawa, ON (A.S.), William Osler Health Centre, Brampton, ON (P.K.), Sault Area Hospital, Sault Ste. Marie, ON (D.H., S. Spadafora), Hôpital Régional de Rimouski, Rimouski, QC (K.M.), Markham Stouffville Hospital, Markham, ON (M.T.), Kingston General Hospital, Kingston, ON (A.T.), University of British Columbia, British Columbia Cancer Agency, Vancouver (A.Y.Y.L.), Hamilton Health Sciences, Hamilton, ON (P.L.G.), London Health Sciences Centre, London, ON (A.L.-L.), and Royal Victoria Regional Health Centre, Barrie, ON (R.E.-M.) — all in Canada. Address reprint requests to Dr. Wells at the Ottawa Hospital, General Campus, 501 Smyth Rd., Box 206, Ottawa, ON K1H 8L6, Canada, or at pwells@toh.ca.

*A complete list of the AVERT Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on December 4, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1814468

Copyright © 2018 Massachusetts Medical Society.

PATIENTS WITH ACTIVE CANCER HAVE AN increased risk of venous thromboembolism, which results in substantial morbidity and mortality.¹⁻³ Although parenteral thromboprophylaxis can reduce the risk of venous thromboembolism among ambulatory patients undergoing chemotherapy, it is not routinely recommended in practice guidelines because the absolute risk reduction is modest and parenteral thromboprophylaxis is associated with an increased risk of major bleeding, high cost, and the inconvenience of daily injections.^{4,5} The Khorana score (range, 0 to 6, with higher scores indicating a higher risk of venous thromboembolism) has been validated to identify patients with an elevated risk of venous thromboembolism and may help select those who could benefit from prophylaxis.⁶⁻⁹ (For details on the Khorana score, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Patients who have a solid tumor and a Khorana score of 2 or higher have an estimated risk of symptomatic thrombosis of 9.6% during the first 6 months of chemotherapy.⁷

The use of direct oral anticoagulants as thromboprophylactic agents in patients with cancer can offer important advantages over parenteral agents, including route of administration, convenience, and cost. A previous small, phase 2 trial involving 125 patients suggested that the oral factor Xa inhibitor apixaban may be safe and effective.¹⁰ We conducted the Apixaban for the Prevention of Venous Thromboembolism in High-Risk Ambulatory Cancer Patients (AVERT) trial to assess the efficacy of apixaban thromboprophylaxis in ambulatory patients with cancer at intermediate-to-high risk for venous thromboembolism (Khorana score, ≥ 2).

METHODS

TRIAL DESIGN AND OVERSIGHT

The AVERT trial was a randomized, placebo-controlled, double-blind clinical trial comparing apixaban (2.5 mg twice daily) with placebo. The members of the steering committee (see the Supplementary Appendix) had final responsibility for the trial design, clinical protocol, and trial oversight. The institutional review board at each of the 13 participating sites approved the protocol, which has been published previously¹¹ and is available at NEJM.org.

Data were collected at the sites and entered in an online database managed by the Methods Centre of the Ottawa Hospital Research Institute. A central adjudication committee whose members were unaware of the treatment assignments reviewed all suspected outcome events. An independent data and safety monitoring board periodically reviewed trial outcomes. The investigators performed the statistical analyses and wrote the manuscript independent of the funders (Canadian Institutes of Health Research and Bristol-Myers Squibb–Pfizer Alliance), which played no role in the design or conduct of the trial, the collection or analysis of the data, or the reviewing or editing of the manuscript. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

TRIAL POPULATION

Patients who had a newly diagnosed cancer or progression of known cancer after complete or partial remission and who were initiating a new course of chemotherapy with a minimum treatment intent of 3 months were potentially eligible. Inclusion required a Khorana score of 2 or higher, an age of 18 years or older, and the capacity to provide written informed consent. Patients were excluded if they had conditions putting them at increased risk for clinically significant bleeding; hepatic disease associated with coagulopathy; a cancer diagnosis consisting solely of basal-cell or squamous-cell skin carcinoma, acute leukemia, or myeloproliferative neoplasm; a planned stem-cell transplantation; a life expectancy of less than 6 months; renal insufficiency with a glomerular filtration rate of less than 30 ml per minute per 1.73 m² of body-surface area; or a platelet count of less than 50,000 per cubic millimeter. Other exclusion criteria included the use of medications contraindicated with apixaban, pregnancy or potential pregnancy, breast-feeding, the use of continuous anticoagulation, and a weight of less than 40 kg.

RANDOMIZATION AND TRIAL INTERVENTION

Eligible patients underwent randomization by means of a centralized, Web-based randomization system to receive apixaban or placebo in a 1:1 ratio. Randomization was stratified according to age, sex, and participating center and occurred up to 5 days before the administration of the first chemotherapy. The experimental group received

apixaban at a dose of 2.5 mg twice daily, and the control group received identical placebo tablets twice daily; the treatment period was 180 days. The first dose of apixaban or placebo was administered within 24 hours after the initiation of chemotherapy. Patients were followed for up to 210 days or death, regardless of the duration of the treatment period.

OUTCOMES

The primary efficacy outcome was the first episode of objectively documented major venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) within the first 180 days (with a window of ± 3 days) after randomization. Venous thromboembolism was defined as any symptomatic or incidentally detected proximal deep-vein thrombosis of the lower or upper limbs, any nonfatal symptomatic or incidental pulmonary embolism, and pulmonary embolism–related death. Patients who presented with symptoms of venous thromboembolism during the follow-up period underwent diagnostic imaging for confirmation of the primary outcome. Routine ultrasonographic testing was not performed.

The main safety outcome was major bleeding, defined by the International Society on Thrombosis and Hemostasis as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, led to transfusion of 2 or more units of packed red cells, occurred in a critical site, or contributed to death.¹² The severity of major bleeding episodes was defined as follows: category 1, the episode was not considered to be a clinical emergency; category 2, the episode led to some treatment but was not considered to be a clinical emergency; category 3, the episode was considered to be a clinical emergency (e.g., hemodynamic instability or intracranial bleeding with neurologic symptoms); and category 4, the episode led to death before or almost immediately after the patient presented to the hospital.¹³ Other safety outcomes included clinically relevant non-major bleeding (see the Supplementary Appendix) and overall survival during the trial period.

All trial outcomes were adjudicated by an independent adjudication committee whose members were unaware of the treatment assignments. Death was adjudicated to be caused by pulmonary embolism, bleeding, cancer, or other cause. Death was attributed to pulmonary embolism if there was no other explanation or there was autopsy

or radiologic confirmation of pulmonary embolism. Adherence to the trial regimen was estimated with the use of a pill count recorded by patients in a medication diary and was defined as high if 80% or more of the pills were taken.

STATISTICAL ANALYSIS

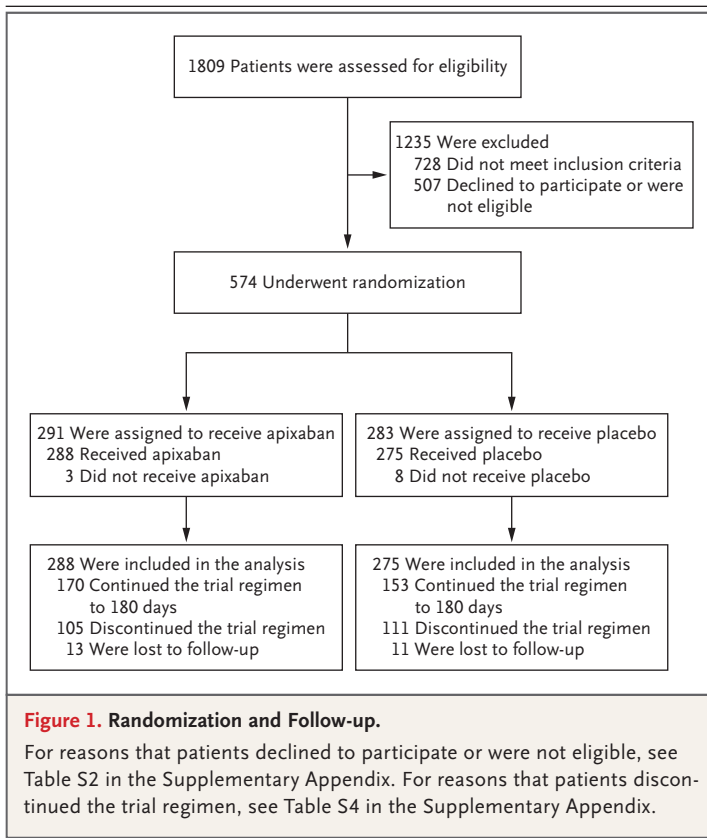
The trial hypothesis was that apixaban would be superior to placebo, resulting in a relative difference of at least 64% in the rate of the primary outcome (major venous thromboembolism), at a two-sided alpha level of 0.05 and with a power of 80%.^{7,14} We expected the event rate with placebo to be 10% over a period of 6 months. In considering a normal approximation to the binomial distribution, we estimated that the inclusion of 574 patients with a Khorana score of 2 or higher would be sufficient to show this difference.

The primary analysis was performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of apixaban or placebo on or before day 180 (± 3 days). We performed a time-to-event analysis on the primary efficacy outcome. The hazard ratio for venous thromboembolism was estimated with the use of a Cox proportional-hazards model that was controlled for age, sex, and center. The time to the first outcome event was estimated by the Kaplan–Meier method. We also performed a time-to-event analysis of the primary efficacy outcome and the safety outcome occurring while the patient took the active drug or placebo plus 2 days after their last dose. Secondary analyses included a competing-risk analysis to account for deaths from causes other than venous thromboembolism or bleeding.^{15,16} We used a multivariate logistic-regression model to estimate the odds ratio for having an episode of venous thromboembolism associated with the use of apixaban as compared with placebo, with controls for age, sex, and center. Finally, multiple-imputation analyses on both venous thromboembolism and major bleeding outcomes were conducted.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From February 2014 through April 2018, a total of 574 patients underwent randomization at 13 centers in Canada. A total of 563 patients were included in the primary efficacy and safety analy-



ses (Fig. 1). The baseline characteristics of the patients were well balanced (Table 1). The mean age of the patients was 61 years, and the majority of patients (58.2%) were women. The most common types of primary cancer were gynecologic (25.8%), lymphoma (25.3%), and pancreatic (13.6%). A total of 131 patients (22.8%) were using antiplatelet or nonsteroidal antiinflammatory therapy. The number of patients with solid tumors who had metastatic disease was 73 in the apixaban group and 67 in the placebo group. The breakdown of chemotherapy drugs according to category at trial enrollment is shown in Table S3 in the Supplementary Appendix.

The median duration of the treatment period was 157 days (interquartile range, 78 to 168) in the apixaban group and 155 days (interquartile range, 83 to 168) in the placebo group. The median duration of follow-up was 183 days in each group. Reasons for not continuing the trial regimen up to 180 days were balanced between the two groups (Table S4 in the Supplementary Ap-

pendix). The trial regimen was discontinued as per patients' wish by 34 patients in the apixaban group and 41 patients in the placebo group. The rate of adherence to the trial regimen was high in both groups, at 83.6% in the apixaban group and 84.1% in the placebo group.

EFFICACY AND SAFETY OUTCOMES

The primary efficacy outcome occurred in 12 of 288 patients (4.2%) in the apixaban group and in 28 of 275 patients (10.2%) in the placebo group (hazard ratio, 0.41; 95% confidence interval [CI], 0.26 to 0.65; $P < 0.001$) (Table 2 and Fig. 2). The competing-risk analysis that accounted for deaths from causes other than venous thromboembolism or bleeding was consistent with the primary analysis (hazard ratio, 0.42; 95% CI, 0.27 to 0.65). The adjusted odds ratio for venous thromboembolism associated with the use of apixaban as compared with placebo was 0.39 (95% CI, 0.20 to 0.76). During the treatment period, the primary outcome occurred in 3 of 288 patients (1.0%) in the apixaban group and in 20 of 275 patients (7.3%) in the placebo group (hazard ratio, 0.14; 95% CI, 0.05 to 0.42). During the additional 30 days of follow-up after day 180, 1 patient in the apixaban group had deep-vein thrombosis and 1 in the placebo group died from pulmonary embolism.

In the modified intention-to-treat analysis, major bleeding occurred in 10 patients (3.5%) in the apixaban group and in 5 patients (1.8%) in the placebo group (hazard ratio, 2.00; 95% CI, 1.01 to 3.95; $P = 0.046$) (Table 2 and Fig. 3). A total of 3 of the 15 major bleeding episodes were considered to be a clinical emergency, and no bleeding into critical organs was noted. During the treatment period, major bleeding occurred in 6 of 288 patients (2.1%) in the apixaban group and in 3 of 275 patients (1.1%) in the placebo group (hazard ratio, 1.89; 95% CI, 0.39 to 9.24). Adverse events were reported in 131 patients in the apixaban group and 127 patients in the placebo group; only 1 event in the apixaban group and 2 events in the placebo group were classified as being related to the trial regimen. The multiple-imputation analyses for venous thromboembolism and major bleeding that accounted for patients lost to follow-up were consistent with the primary analyses.

Death occurred in 35 patients (12.2%) in the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N = 291)	Placebo (N = 283)
Age — yr	61.2±12.4	61.7±11.3
Male sex — no. (%)	121 (41.6)	119 (42.0)
Weight — kg	80.0±22.3	82.6±21.4
Creatinine clearance >50 ml/min — no. (%)	275 (94.5)	265 (93.6)
Tumor type — no. (%)		
Brain	14 (4.8)	10 (3.5)
Bladder	1 (0.3)	4 (1.4)
Lung	31 (10.7)	28 (9.9)
Testicular	2 (0.7)	1 (0.4)
Stomach	25 (8.6)	19 (6.7)
Pancreatic	37 (12.7)	41 (14.5)
Lymphoma	76 (26.1)	69 (24.4)
Myeloma	7 (2.4)	8 (2.8)
Gynecologic	74 (25.4)	74 (26.1)
Colon	3 (1.0)	8 (2.8)
Prostate	0	1 (0.4)
Other	21 (7.2)	20 (7.1)
Khorana score — no. (%)†		
2	186 (63.9)	190 (67.1)
3	78 (26.8)	68 (24.0)
4	26 (8.9)	24 (8.5)
5	1 (0.3)	1 (0.4)
6	0	0
Components of the Khorana score besides tumor type — no. (%)		
Prechemotherapy leukocyte count >11,000/mm ³	83 (28.5)	102 (36.0)
Hemoglobin <10 g/dl or use of red-cell growth factors	66 (22.7)	50 (17.7)
Prechemotherapy platelet count ≥350,000/mm ³	119 (40.9)	126 (44.5)
Body-mass index ≥35‡	72 (24.7)	67 (23.7)
Concomitant antiplatelet medication — no. (%)§	67 (23.0)	64 (22.6)
ECOG performance-status score — no./total no. (%)¶		
0 or 1	186/218 (85.3)	188/217 (86.6)
≥2	32/218 (14.7)	29/217 (13.4)
Previous venous thromboembolism — no. (%)	9 (3.1)	8 (2.8)

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. None of the differences between the two groups were considered to be statistically significant at an alpha level of 0.05.

† Khorana scores range from 0 to 6, with higher scores indicating a higher risk of venous thromboembolism among patients with cancer. For details, see Table S1 in the Supplementary Appendix. Inclusion in the trial required a Khorana score of 2 or higher.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Antiplatelet medications could include nonsteroidal antiinflammatory drugs.

¶ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 4, with higher scores indicating greater disability.

Table 2. Efficacy and Safety Clinical Outcomes.

Outcome	Apixaban (N=288)	Placebo (N=275)	Hazard Ratio (95% CI)*	P Value
Venous thromboembolism — no. (%)	12 (4.2)	28 (10.2)	0.41 (0.26–0.65)	<0.001
Deep-vein thrombosis — no. (%)	7 (2.4)	12 (4.4)		
Pulmonary embolism — no. (%)†	5 (1.7)	16 (5.8)‡		
Incidental pulmonary embolism — no./total no.	3/5	6/16		
Major bleeding episode				
Any episode — no. (%)	10 (3.5)	5 (1.8)	2.00 (1.01–3.95)	0.046
Severity of episode — no./total no. (%)§				
Category 1	1/10 (10)	0		
Category 2	8/10 (80)	3/5 (60)		
Category 3	1/10 (10)	2/5 (40)		
Category 4	0	0		
Clinically relevant nonmajor bleeding — no. (%)¶	21 (7.3)	15 (5.5)	1.28 (0.89–1.84)	
Outcome occurred during the treatment period — no. (%)				
Venous thromboembolism	3 (1.0)	20 (7.3)	0.14 (0.05–0.42)	
Major bleeding episode	6 (2.1)	3 (1.1)	1.89 (0.39–9.24)	
Death from any cause — no. (%)	35 (12.2)	27 (9.8)	1.29 (0.98–1.71)	

* Confidence intervals were not adjusted for multiple comparisons.

† This includes patients who also had deep-vein thrombosis.

‡ One patient died 6 days after receiving a diagnosis of pulmonary embolism.

§ The severity of major bleeding episodes was defined as follows: category 1, the episode was not considered to be a clinical emergency; category 2, the episode led to some treatment but was not considered to be a clinical emergency; category 3, the episode was considered to be a clinical emergency (e.g., hemodynamic instability or intracranial bleeding with neurologic symptoms); and category 4, the episode led to death before or almost immediately after the patient presented to the hospital.¹³

¶ Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the use of medical intervention, contact with a physician, interruption of the assigned trial regimen, discomfort, or impairment of activities of daily living.

apixaban group and 27 patients (9.8%) in the placebo group (Table 2). Of the 62 deaths, 54 (87%) were related to cancer or cancer progression. All causes of death according to trial group are reported in Table S5 in the Supplementary Appendix.

DISCUSSION

The AVERT trial showed that thromboprophylaxis with apixaban resulted in a significantly lower rate of venous thromboembolic complications than placebo among ambulatory patients with cancer who were starting chemotherapy and had a Khorana score of 2 or higher. Venous thromboembolism in patients with cancer who are receiving chemotherapy has a substantial effect on care, including an increase in health care expenditure and a negative effect on quality of life.^{17,18} Furthermore, the treatment of venous thromboembolism with therapeutic anticoagulation is chal-

lenging in patients with cancer because it often involves daily injections of low-molecular-weight heparin and is associated with a high risk of thrombosis recurrence and serious bleeding complications. Coexisting conditions that are common in this context, such as thrombocytopenia and renal impairment, as well as the use of concomitant antiplatelet therapy (in 22.8% of our patients), further increase the risk of bleeding among patients with cancer.¹⁹ Therefore, prevention of venous thromboembolic complications is important and clinically relevant.

In our trial, the absolute between-group difference in the rate of venous thromboembolism was 6.0 percentage points (number needed to treat, 17) and was driven predominantly by a lower rate of pulmonary embolism in the apixaban group than in the placebo group (Table 2). The 10.2% rate of symptomatic or incidentally detected venous thromboembolism at 6 months in the placebo

group is consistent with rates reported in previous studies involving patients with cancer with a Khorana score of 2 or higher.⁷ Our analysis of outcomes during the treatment period showed a more favorable benefit (hazard ratio, 0.14; 95% CI, 0.05 to 0.42) than previous studies that assessed parenteral thromboprophylaxis.^{20,21} The reasons for this discrepancy are unclear, but the use of a different agent and a twice-daily dosing regimen may account for some of the difference.

The rate of major bleeding was significantly higher with apixaban than with placebo in the modified intention-to-treat analysis (3.5% and 1.8%, respectively; hazard ratio, 2.00; 95% CI, 1.01 to 3.95; number needed to harm, 59), but the rate was not significantly higher with apixaban than with placebo in the analysis of outcomes during the treatment period (2.1% and 1.1%, respectively; hazard ratio, 1.89; 95% CI, 0.39 to 9.24; number needed to harm, 100). The between-group difference in the rate of major bleeding complications was mainly due to higher rates of gastrointestinal bleeding, hematuria, and gynecologic bleeding with apixaban than with placebo. This finding is consistent with the results of previous studies of direct oral anticoagulants involving patients with active cancer.^{22,23} We found that major bleeding occurred mainly in patients who had entered the trial with gastrointestinal or gynecologic cancer. However, severe (category 3 or 4) major bleeding episodes (Table 2) were only 20% of all major bleeding episodes, and the rate of these severe episodes was similar in the apixaban group and the placebo group. There were no cases of fatal bleeding or bleeding into critical organs.¹² Similarly, the 7.3% rate of clinically relevant nonmajor bleeding at 6 months in the apixaban group is lower than previously reported rates among patients with cancer with a Khorana score of 3 or higher who received thromboprophylaxis over a 3-month period.⁹

Our trial also showed no significant between-group difference in overall survival. This probably reflects the fact that many of our patients had advanced cancer, which was the most common cause of death. Although prevention of venous thromboembolism would ideally reduce overall mortality, a different trial design and a much larger sample would be required to address this question.

As with all trials of thromboprophylaxis involving patients with cancer, between-trial com-

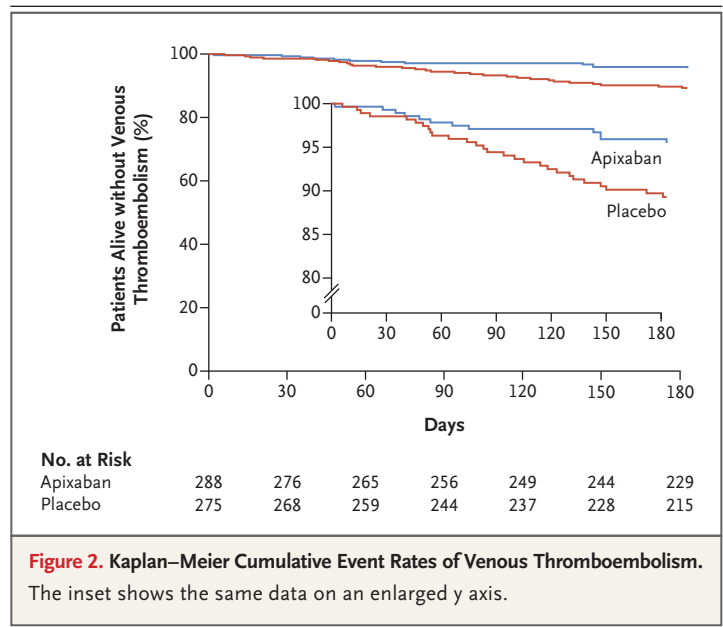


Figure 2. Kaplan–Meier Cumulative Event Rates of Venous Thromboembolism. The inset shows the same data on an enlarged y axis.

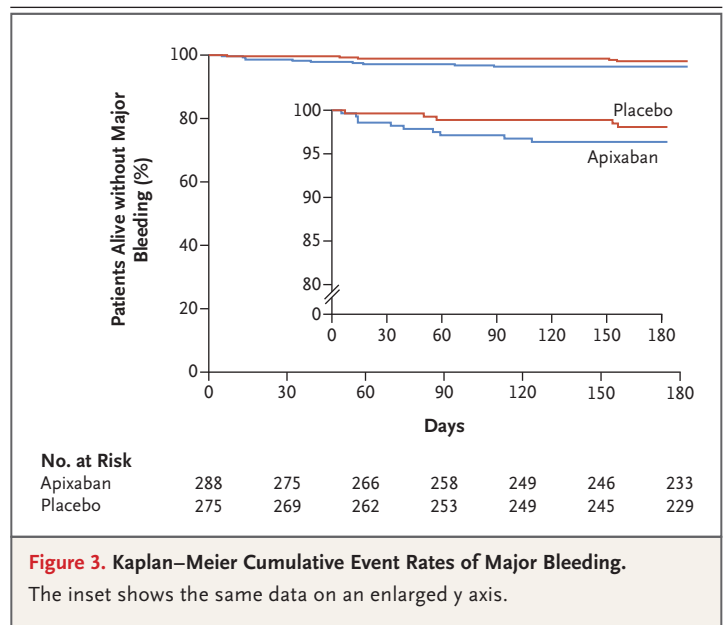


Figure 3. Kaplan–Meier Cumulative Event Rates of Major Bleeding. The inset shows the same data on an enlarged y axis.

parisons can be biased owing to differences in tumor types in patients enrolled in the trial. We had a high proportion of patients with gynecologic, lymphoma, or pancreatic tumors and very few patients with colorectal or prostate cancers. However, this is expected, because these latter tumors are not recognized as posing a high risk of venous thromboembolism according to the Khorana score. Each participating center in Canada provides comprehensive cancer care in

their respective region, and patients with all tumor types were assessed for eligibility and enrollment, so we believe that our results are generalizable to a broad spectrum of patients with cancer who received different types of cancer treatment. However, owing to the sample size, we have limited ability to make definitive conclusions about outcomes associated with individual tumor types or individual chemotherapy regimens. Finally, only 5.9% of patients had renal dysfunction as defined by a creatinine clearance of 50 ml or less per minute, so our results may less applicable to patients with renal dysfunction, who are

known to have a higher risk of bleeding than patients with normal renal function.

In conclusion, apixaban at a dose of 2.5 mg twice daily resulted in a significantly lower risk of venous thromboembolism than did placebo among ambulatory patients with cancer who were initiating chemotherapy and had an intermediate-to-high risk of venous thromboembolism.

Supported by the Canadian Institutes of Health Research and Bristol-Myers Squibb–Pfizer Alliance.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. Toft Sørensen H, Mellempkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000;343:1846-50.
2. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost* 2006;4:529-35.
3. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. *Arch Intern Med* 2004;164:190-4.
4. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev* 2016;12:CD008500.
5. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol* 2015;33:654-6.
6. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008;111:4902-7.
7. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood* 2010;116:5377-82.
8. van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica* 2017;102:1494-501.
9. Khorana AA, Francis CW, Kuderer NM, et al. Dalteparin thromboprophylaxis in cancer patients at high risk for venous thromboembolism: a randomized trial. *Thromb Res* 2017;151:89-95.
10. Levine MN, Gu C, Liebman HA, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *J Thromb Haemost* 2012;10:807-14.
11. Kimpton M, Wells PS, Carrier M. Apixaban for the prevention of venous thromboembolism in high-risk ambulatory cancer patients receiving chemotherapy: rational and design of the AVERT trial. *Thromb Res* 2018;164:Suppl 1:S124-S129.
12. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
13. Bleker SM, Brekelmans MPA, Eerenberg ES, et al. Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists: an individual patient data meta-analysis. *Thromb Haemost* 2017;117:1944-51.
14. Lustig DB, Rodriguez R, Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. *Thromb Res* 2015;136:1099-102.
15. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res* 2007;13:559-65.
16. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
17. Lyman GH, Culakova E, Poniewierski MS, Kuderer NM. Morbidity, mortality and costs associated with venous thromboembolism in hospitalized patients with cancer. *Thromb Res* 2018;164:Suppl 1:S112-S118.
18. Elting LS, Escalante CP, Cooksley C, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. *Arch Intern Med* 2004;164:1653-61.
19. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002;100:3484-8.
20. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012;366:601-9.
21. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009;10:943-9.
22. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018;378:615-24.
23. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018;36:2017-23.

Copyright © 2018 Massachusetts Medical Society.