ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

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ABSTRACT

BACKGROUND

Recent guidelines recommend consideration of the use of oral edoxaban or rivaroxaban for the treatment of venous thromboembolism in patients with cancer. However, the benefit of these oral agents is limited by the increased risk of bleeding associated with their use.

METHODS

This was a multinational, randomized, investigator-initiated, open-label, noninferiority trial with blinded central outcome adjudication. We randomly assigned consecutive patients with cancer who had symptomatic or incidental acute proximal deep-vein thrombosis or pulmonary embolism to receive oral apixaban (at a dose of 10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or subcutaneous dalteparin (at a dose of 200 IU per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily). The treatments were administered for 6 months. The primary outcome was objectively confirmed recurrent venous thromboembolism during the trial period. The principal safety outcome was major bleeding.

RESULTS

Recurrent venous thromboembolism occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; P<0.001 for noninferiority). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P=0.60).

CONCLUSIONS

Oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding. (Funded by the Bristol-Myers Squibb–Pfizer Alliance; Caravaggio ClinicalTrials.gov number, NCT03045406.)

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*A complete list of the investigators in the Caravaggio trial is provided in the Supplementary Appendix, available at NEJM.org.

VENOUS THROMBOEMBOLISM IS A COMmon cause of death and complications in patients with cancer.[1] The high risk of recurrent thromboembolism and bleeding in patients with cancer[2] makes anticoagulant treatment challenging, so specific studies involving these patients are necessary.

Major guidelines recommend the use of low-molecular-weight heparin for the treatment of cancer-associated venous thromboembolism and have recently added the use of edoxaban or rivaroxaban.[3-7] However, the clinical benefit of these oral agents is limited by a higher risk of bleeding than with low-molecular-weight heparin, mainly occurring at gastrointestinal sites.[8,9] The oral factor Xa inhibitor apixaban has shown favorable efficacy and safety in the general population with venous thromboembolism.[10]

In the Caravaggio trial, we wanted to assess whether oral apixaban would be noninferior to subcutaneous dalteparin, a low-molecular-weight heparin, for the prevention of recurrent venous thromboembolism in patients with cancer without increasing the risk of major bleeding.

METHODS

TRIAL DESIGN AND OVERSIGHT

This trial was a multinational, randomized, controlled, investigator-initiated, open-label, noninferiority trial with blinded adjudication of the outcomes. The rationale and design of this trial have been published previously[11] and are discussed in the protocol, which is available with the full text of this article at NEJM.org.

The trial was sponsored by FADOI (Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti) and was funded by an unrestricted grant from the Bristol-Myers Squibb–Pfizer Alliance. The trial was coordinated by the Clinical Research Unit of the University of Perugia, the Research Center of the FADOI Foundation, and the steering committee. The members of the steering committee were responsible for the design and oversight of the trial, development of the protocol, analysis of the data, writing of the manuscript, and the decision to submit the manuscript for publication.

The data were collected and maintained by the Exom Group and analyzed by SPARC Consulting under the supervision of the steering committee. A central adjudication committee whose members were unaware of the treatment assignments reviewed all suspected outcome events and causes of deaths. An independent data and safety monitoring board periodically reviewed trial outcomes. The composition of the trial committees is reported in the Supplementary Appendix, available at NEJM.org.

The Bristol-Myers Squibb–Pfizer Alliance played no role in the design or conduct of the trial, the collection or analysis of the data, or the review 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. No one who is not an author contributed to the writing of the manuscript.

The trial was performed in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol and its amendments were approved by the institutional review board or ethics committee at each trial center. All the patients provided written informed consent.

PATIENTS

Consecutive adults with cancer who had a newly diagnosed symptomatic or incidental proximal lower-limb deep-vein thrombosis or pulmonary embolism were eligible to participate in the trial.[11] Deep-vein thrombosis was defined as proximal if it was located in the popliteal or a more proximal vein. Incidental deep-vein thrombosis or pulmonary embolism were events detected on imaging tests performed for reasons other than clinical suspicion of venous thromboembolism. Incidental pulmonary embolism was defined as involving a segmental or more proximal pulmonary artery. The criteria for the diagnosis of deep-vein thrombosis and pulmonary embolism are listed in the Supplementary Appendix.

Patients with confirmed cancer other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, known intracerebral metastases, or acute leukemia were eligible to participate in the trial. Active cancer was defined as cancer that had been diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrollment or during 6 months before randomization, or recurrent locally advanced or metastatic cancer. Patients with a history of cancer (as compared with active cancer) included those in whom a diagnosis had been made within 2 years before enrollment. Exclusion criteria — which included

patients' clinical characteristics, issues related to anticoagulant treatment, bleeding risk, and standard issues from clinical trials of anticoagulant agents — are listed in the Supplementary Appendix.

RANDOMIZATION AND TRIAL INTERVENTION

Eligible patients were randomly assigned in a 1:1 ratio to receive monotherapy with either apixaban or dalteparin for 6 months. Randomization was centrally performed through an interactive online system and stratified according to the type of venous thromboembolism (symptomatic or incidental) and timing of the cancer diagnosis (active or historical). The maximum proportion of patients with incidental venous thromboembolism or a history of cancer was set at 20% of the overall trial population for each of the strata. Therapeutic doses of low-molecular-weight heparin, fondaparinux, or unfractionated heparin were allowed for a maximum of 72 hours before randomization.

Apixaban was given orally at a dose of 10 mg twice daily for the first 7 days and 5 mg twice daily thereafter. Dalteparin was given subcutaneously at a dose of 200 IU per kilogram of body weight once daily for the first month, after which the dose was reduced to 150 IU per kilogram daily. The maximum daily dose allowed for dalteparin was 18,000 IU. Apixaban was supplied by Bristol-Myers Squibb and dalteparin by Pfizer. Trial drugs could be temporarily withheld in case of a platelet count lower than 50,000 per cubic millimeter or any condition associated with an increased risk of bleeding, including surgery, invasive procedures, or deterioration of renal function. During the trial, the protocol was amended to allow adjustments of the dose of dalteparin on the basis of the platelet count according to the country-specific labeling of the drug.

OUTCOME MEASURES

The primary outcome was objectively confirmed recurrent venous thromboembolism, which included proximal deep-vein thrombosis of the lower limbs (symptomatic or incidental), symptomatic deep-vein thrombosis of the upper limbs, and pulmonary embolism (symptomatic, incidental, or fatal) occurring during the 6-month trial period. The criteria for the diagnosis of recurrent venous thromboembolism and a list of the secondary efficacy outcomes are provided in the Supplementary Appendix.

The principal safety outcome was major bleeding, which was defined as acute clinically overt bleeding associated with one or more of the following: a decrease in the hemoglobin level of at least 2 g per deciliter, a transfusion of 2 or more units of red cells, bleeding occurring at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), bleeding resulting in surgical intervention, or fatal bleeding, all occurring during the trial-drug period through 72 hours after the last dose was administered. A list of the secondary safety outcomes is provided in the Supplementary Appendix.

The central adjudication committee determined whether death was from cancer, pulmonary embolism, bleeding, cardiovascular events, or other causes. Pulmonary embolism was adjudicated as the cause of death on the basis of objective diagnostic testing performed before death, during autopsy, or when pulmonary embolism was the most probable cause of death.

SURVEILLANCE AND FOLLOW-UP

Trial visits were scheduled at enrollment and at 4 weeks, 3 months, 6 months, and 7 months after randomization. Additional visits were scheduled if new symptoms or signs of venous thromboembolism or bleeding occurred or if the investigator determined that such an evaluation was needed. Clinical examination, laboratory testing, and diagnostic imaging were performed if the patient had symptoms or signs suggestive of recurrent venous thromboembolism or bleeding.

STATISTICAL ANALYSIS

The hypothesis of the trial was that apixaban would be noninferior to dalteparin for the primary outcome (recurrent venous thromboembolism) with a prespecified noninferiority margin of 2.00 for the upper limit of the two-sided 95% confidence interval of the hazard ratio. We determined that the enrollment of 934 patients would provide a power of 80% to show the noninferiority of apixaban at a one-sided alpha level of 0.025, assuming an estimated 6-month incidence of the primary efficacy outcome of 7% with dalteparin. The sample size was increased to 1168 patients to account for up to 20% loss in

total patient-years.[11] No formal interim analysis was planned.

The primary efficacy data set (modified intention-to-treat population) and safety data set consisted of all the patients who had undergone randomization and received at least one dose of a trial drug. The secondary efficacy data set consisted of all the patients who had undergone randomization (intention-to-treat population) along with the per-protocol population; the latter consisted of all the patients in the intention-to-treat population who completed the trial in full compliance with the protocol and without any major deviation. No adjustment for multiple comparisons was performed for analyses of secondary efficacy outcomes and subgroup comparisons.

We used a Cox proportional-hazards model that included treatment group and stratification factors as covariates to analyze the time until the first event of the primary outcome during the 6-month trial period. Proportional-hazards assumptions were tested with the use of a generalized Wald test for a joint hypothesis on all interaction terms specified in the statistical models. The evaluation of the primary outcome was done by considering the time from randomization until the first recurrent event of venous thromboembolism (primary trial outcome) or until the occurrence of death unrelated to venous thromboembolism (competing event); the time until the last follow-up visit was used if neither a recurrent venous thromboembolism or a competing event occurred within the 6-month follow-up (censored time). We used the Fine and Gray regression model to compute the hazard ratio and two-sided 95% confidence intervals for the comparison between apixaban and dalteparin after adjustment for the competing risk of death unrelated to venous thromboembolism.[12] We tested the superiority of apixaban over dalteparin as a secondary analysis of the primary outcome only if noninferiority was shown. Reported 95% confidence intervals were not adjusted for multiple comparisons and therefore cannot be used to infer effects.

We compared the incidence of major bleeding (the principal safety outcome) and clinically relevant nonmajor bleeding in patients treated with apixaban or dalteparin in the safety data set. All data were analyzed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND TREATMENTS

From April 2017 through June 2019, a total of 1170 patients underwent randomization at 119 centers in nine European countries, Israel, and the United States; 1155 patients were included in the modified intention-to-treat analysis (Fig. 1). The demographic and clinical characteristics of the patients were similar in the two treatment groups (Table 1). The types of cancer and the categories of anticancer drugs that were either continued or started after randomization are reported in Tables S1, S2, and S3 in the Supplementary Appendix. The median duration of the assigned treatment was 178 days (interquartile range, 106 to 183) in the apixaban group and 175 days (interquartile range, 79 to 183) in the dalteparin group (P=0.15); reasons for the discontinuation of a trial drug are provided in Table S4. Before permanent discontinuation of a trial drug, 41 patients in the apixaban group and 51 patients in the dalteparin group had received less than 80% of the prescribed treatment.

PRIMARY EFFICACY AND SAFETY OUTCOMES

The primary outcome of recurrent venous thromboembolism occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; P<0.001 for noninferiority; P=0.09 for superiority) (Table 2). Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P=0.60) (Table 2). Major gastrointestinal bleeding occurred in 11 patients (1.9%) in the apixaban group and in 10 patients (1.7%) in the dalteparin group; major non-gastrointestinal bleeding occurred in 11 patients (1.9%) and 13 patients (2.2%), respectively. There were no fatal bleeding episodes in the apixaban group and 2 in the dalteparin group. The types of major bleeding in the two groups are reported in Table S5. The times until recurrent venous thromboembolism and major bleeding according to treatment group during the overall trial period are provided in Figure 2.

SECONDARY OUTCOMES

The combined cumulative incidence of recurrent venous thromboembolism or major bleeding

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┌─────────────────────────────────────────────────────────────┐
│              1170 Patients underwent randomization            │
└─────────────────────────────────────────────────────────────┘
         │                                         │
         ▼                                         ▼
┌──────────────────────────┐         ┌──────────────────────────┐
│ 585 Were assigned to      │         │ 585 Were assigned to      │
│ receive apixaban          │         │ receive dalteparin        │
└──────────────────────────┘         └──────────────────────────┘
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9 Did not receive the assigned treatment	6 Did not receive the assigned treatment

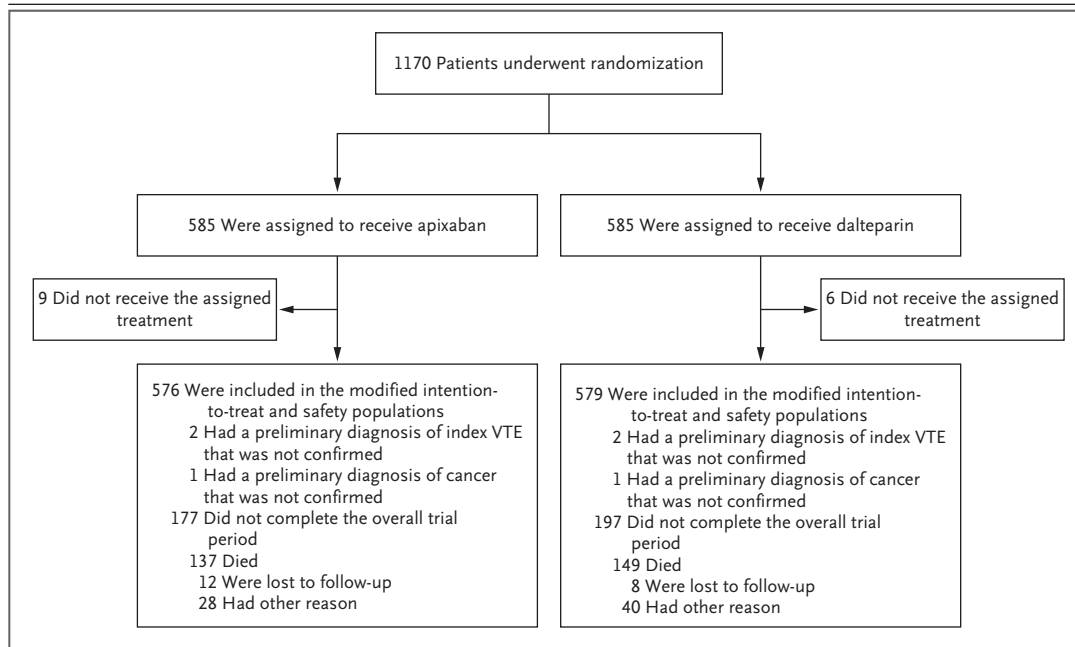|	
576 Were included in the modified intention-to-treat and safety populations 2 Had a preliminary diagnosis of index VTE that was not confirmed 1 Had a preliminary diagnosis of cancer that was not confirmed 177 Did not complete the overall trial period 137 Died 12 Were lost to follow-up 28 Had other reason	579 Were included in the modified intention-to-treat and safety populations 2 Had a preliminary diagnosis of index VTE that was not confirmed 1 Had a preliminary diagnosis of cancer that was not confirmed 197 Did not complete the overall trial period 149 Died 8 Were lost to follow-up 40 Had other reason

Figure 1. Enrollment and Outcomes.

The modified intention-to-treat population and the safety population both included all the patients who had undergone randomization and received at least one dose of apixaban or dalteparin. VTE denotes venous thromboembolism. Of the 137 deaths in the apixaban group, 2 occurred after the data cutoff for the secondary outcome analysis at 210 days.

was 8.9% in the apixaban group and 11.4% in the dalteparin group (hazard ratio, 0.70; 95% CI, 0.45 to 1.07) (Table 2). Clinically relevant nonmajor bleeding occurred in 52 patients (9.0%) with apixaban and in 35 patients (6.0%) with dalteparin (hazard ratio, 1.42; 95% CI, 0.88 to 2.30); major or clinically relevant nonmajor bleeding occurred in 70 patients (12.2%) and in 56 patients (9.7%), respectively (hazard ratio, 1.16; 95% CI, 0.77 to 1.75). The sites of clinically relevant nonmajor bleeding in the two groups are provided in Table S5.2. Sensitivity analyses for the per-protocol population are shown in Tables S6 and S7.

Death from any cause by day 210 occurred in 135 patients (23.4%) in the apixaban group and in 153 patients (26.4%) in the dalteparin group (Table S8). Most deaths were related to cancer (85.2% in the apixaban group and 88.2% in the dalteparin group); 4 deaths related to venous thromboembolism and 2 deaths related to bleeding occurred in each treatment group. The 2 deaths from bleeding in the apixaban group occurred more than 3 days after the discontinuation of the trial drug. Data on event-free survival are shown in Figure S1.

SUBGROUP ANALYSES

Subgroup analyses for recurrent venous thromboembolism and major bleeding are shown in Figures S2 and S3. A significant interaction was noted between age subgroups and treatment for recurrent venous thromboembolism. Adverse events reported in the trial are shown in Tables S9, S10, and S11. The most common adverse event was progression of cancer.

DISCUSSION

In the Caravaggio trial, we found that oral apixaban was noninferior to subcutaneous dalteparin for the treatment of recurrent venous thromboembolism in patients with cancer. The efficacy of apixaban was consistent with and contributes to evidence of the efficacy of direct oral anticoagulants in the treatment of venous thromboembolism in such patients.[8,9] The frequencies of major bleeding were similar with apixaban and dalteparin, including major gastrointestinal bleeding. These findings with respect to bleeding are in contrast to the results of previous studies, which showed a higher incidence of bleeding with other direct oral antico-

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

Characteristic	Apixaban (N = 576)	Dalteparin (N = 579)
Age — yr	67.2±11.3	67.2±10.9
Male sex — no. (%)	292 (50.7)	276 (47.7)
Weight — kg	75.7±16.1	76.1±16.7
Platelet count <100,000 per mm^3 — no. (%)	21 (3.6)	22 (3.8)
Creatinine clearance ≤50 ml per min — no. (%)	51 (8.9)	61 (10.5)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	304 (52.8)	334 (57.7)
Deep-vein thrombosis only	272 (47.2)	245 (42.3)
Symptomatic deep-vein thrombosis or pulmonary embolism	460 (79.9)	465 (80.3)
Incidental deep-vein thrombosis or pulmonary embolism†	116 (20.1)	114 (19.7)
History of venous thromboembolism before index event — no. (%)	45 (7.8)	61 (10.5)
Type of cancer — no. (%)		
Active	559 (97.0)	565 (97.6)
Recurrent locally advanced or metastatic	389 (67.5)	396 (68.4)
Cancer treatment — no. (%)‡		
At enrollment	350 (60.8)	367 (63.4)
Within previous 6 mo	143 (24.8)	129 (22.3)
During trial period	344 (59.7)	346 (59.8)
ECOG performance-status score — no. (%)§		
0	186 (32.3)	170 (29.4)
1	281 (48.8)	277 (47.8)
2	109 (18.9)	132 (22.8)

* Plus–minus values are means ±SD.
† Incidental venous thromboembolism (deep-vein thrombosis or pulmonary embolism) was defined as thromboembolism that was detected by means of imaging tests performed for reasons other than clinical suspicion of venous thrombo-embolism.
‡ Cancer treatments include anticancer drug therapy (cytotoxic, hormonal, targeted, or immunomodulatory), radiotherapy, surgery, or a combination of these therapies.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 4, with higher values indicating greater disability.

agulants than with dalteparin in a similar population.[8,9,13] Episodes of nonmajor bleeding were numerically higher in the apixaban group, a finding that has been observed in previous studies of other direct oral anticoagulants.[8,9] Bleeding episodes in the genitourinary system and upper airways were the primary reasons for the increased incidence of nonmajor clinically relevant bleeding in the apixaban group.

Our trial included patients with predominantly advanced active cancer and acute symptomatic venous thromboembolism. Patients with a large variety of cancer types, including approximately one third that occurred at gastrointestinal sites, were included in the trial, which was consistent with the cancer distribution in the general population. Cancers associated with high thromboembolic risk, such as lung and colorectal cancers, were well represented.[14] No anticancer therapy was excluded, which led to the inclusion of patients receiving a broad array of cytotoxic and biologic therapies. The frequencies of recurrent venous thromboembolism and major bleeding at 6 months in patients receiving dalteparin were consistent with the results of previous studies.[8,9] In our trial, the prevalence of

Table 2. Clinical Outcomes during the Trial Period.*

Outcome	Apixaban (N = 576)	Dalteparin (N = 579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal pulmonary embolism§	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	
Primary safety outcome — no. (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
Secondary outcomes — no. (%)				
Recurrent venous thromboembolism or major bleeding	51 (8.9)	66 (11.4)	0.70 (0.45–1.07)	
Clinically relevant nonmajor bleeding	52 (9.0)	35 (6.0)	1.42 (0.88–2.30)	
Major or clinically relevant nonmajor bleeding‖	70 (12.2)	56 (9.7)	1.16 (0.77–1.75)	
Death from any cause**	135 (23.4)	153 (26.4)	0.82 (0.62–1.09)	
Event-free survival††	422 (73.3)	397 (68.6)	1.36 (1.05–1.76)	

* The overall trial period for the primary efficacy outcome was the time from randomization through 6 months.
† The primary efficacy outcome (objectively confirmed recurrent venous thromboembolism) during the 6-month trial period was also the primary outcome.
‡ Two of the recurrences of venous thromboembolism in the apixaban group were upper-extremity deep-vein thrombosis.
§ A total of 3 patients in the apixaban group and 3 patients in the dalteparin group died from unexplained causes for which pulmonary embolism could not be ruled out.
¶ One patient in the apixaban group had an event that was categorized as major bleeding since it resulted in a surgical intervention.
‖ In patients who had more than one event, only the first event was counted.
** Death was assessed up to 210 days after randomization.
†† Event-free survival was defined as the absence of recurrent venous thromboembolism, major bleeding, or death.

active cancer, the extent of disease, and the use of anticancer treatments were similar to those among the patients enrolled in most trials.[8,9,15,16]

Episodes of recurrent venous thromboembolism were numerically lower in patients in the apixaban group than in the dalteparin group because of the lower incidence of recurrent pulmonary embolism. As has been observed in other studies,[8,9] the time-to-event curves appeared to diverge in our trial at about 30 days,

when the dose of dalteparin was reduced. It is uncertain whether this divergence suggests that continuing with the initial dose of dalteparin might have improved the efficacy of this agent, a possible benefit that must be balanced with the potential increase in bleeding.

Our trial investigated the efficacy and safety of apixaban during the initial 6-month treatment of venous thromboembolism in patients with cancer. Additional studies are required to
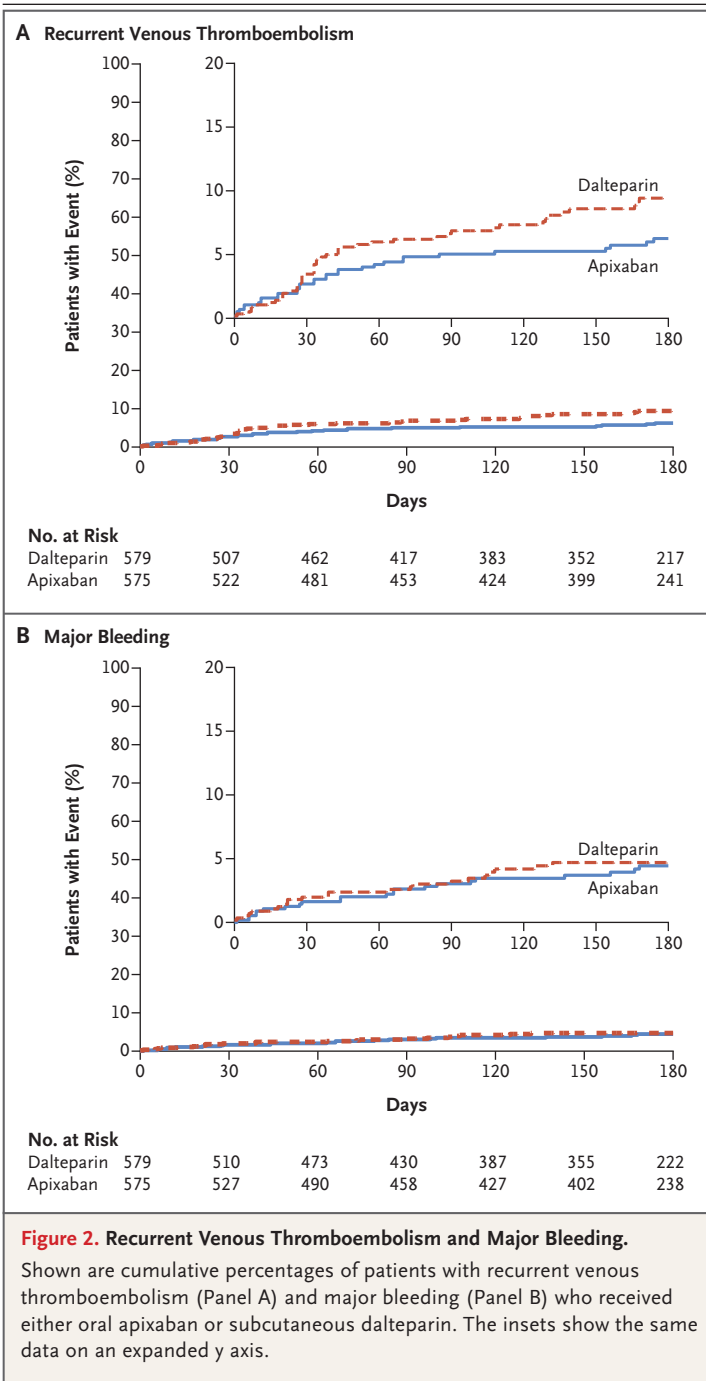
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A Recurrent Venous Thromboembolism

No. at Risk

Dalteparin	579	507	462	417	383	352	217
Apixaban	575	522	481	453	424	399	241

B Major Bleeding

No. at Risk

Dalteparin	579	510	473	430	387	355	222
Apixaban	575	527	490	458	427	402	238

Figure 2. Recurrent Venous Thromboembolism and Major Bleeding.
Shown are cumulative percentages of patients with recurrent venous thromboembolism (Panel A) and major bleeding (Panel B) who received either oral apixaban or subcutaneous dalteparin. The insets show the same data on an expanded y axis.

in efficacy with increasing age that was shown in the subgroup analysis should be considered as hypothesis generating and warrants attention in future studies.

Our trial has several limitations. First, it was an open-label trial to avoid the use of parenteral placebo for 6 months. However, the numbers of suspected recurrences of venous thromboembolism were similar in the two treatment groups, and all suspected trial outcome events were centrally adjudicated in a blinded manner. Second, gastrointestinal bleeding was not a prespecified trial outcome; however, after the publication of results of studies of other direct anticoagulants, such bleeding emerged as a relevant safety outcome. Third, patients with brain tumors, known cerebral metastases, or acute leukemia were not enrolled for safety reasons, so our results cannot be extrapolated to these patient groups. Finally, as in the large majority of studies regarding the treatment of venous thromboembolism, the sample size of our trial was powered for the primary outcome (recurrent venous thromboembolism) and was not powered to make definitive conclusions about bleeding.

The favorable safety profile that we found for apixaban is in agreement with the results of previous randomized trials of this drug with respect to the treatment of venous thromboembolism in the general population.[10,17] Taken together, these findings may expand the proportion of patients with both cancer and venous thromboembolism who would be eligible for treatment with apixaban, including patients with gastrointestinal cancer. On the basis of these findings, we concluded that oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding.

assess the clinical benefit of a more extended treatment duration for venous thromboembolism in these patients. In patients younger than 65 years of age, apixaban was seen to be more effective than dalteparin at preventing recurrent venous thromboembolism. The apparent decrease

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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.

APPENDIX

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