ORIGINAL ARTICLE

Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

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ABSTRACT

BACKGROUND

Ambulatory patients receiving systemic cancer therapy are at varying risk for venous thromboembolism. However, the benefit of thromboprophylaxis in these patients is uncertain.

METHODS

In this double-blind, randomized trial involving high-risk ambulatory patients with cancer (Khorana score of ≥2, on a scale from 0 to 6, with higher scores indicating a higher risk of venous thromboembolism), we randomly assigned patients without deep-vein thrombosis at screening to receive rivaroxaban (at a dose of 10 mg) or placebo daily for up to 180 days, with screening every 8 weeks. The primary efficacy end point was a composite of objectively confirmed proximal deep-vein thrombosis in a lower limb, pulmonary embolism, symptomatic deep-vein thrombosis in an upper limb or distal deep-vein thrombosis in a lower limb, and death from venous thromboembolism and was assessed up to day 180. In a prespecified supportive analysis involving the same population, the same end point was assessed during the intervention period (first receipt of trial agent to last dose plus 2 days). The primary safety end point was major bleeding.

RESULTS

Of 1080 enrolled patients, 49 (4.5%) had thrombosis at screening and did not undergo randomization. Of the 841 patients who underwent randomization, the primary end point occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and in 37 of 421 (8.8%) in the placebo group (hazard ratio, 0.66; 95% confidence interval [CI], 0.40 to 1.09; P=0.10) in the period up to day 180. In the prespecified intervention-period analysis, the primary end point occurred in 11 patients (2.6%) in the rivaroxaban group and in 27 (6.4%) in the placebo group (hazard ratio, 0.40; 95% CI, 0.20 to 0.80). Major bleeding occurred in 8 of 405 patients (2.0%) in the rivaroxaban group and in 4 of 404 (1.0%) in the placebo group (hazard ratio, 1.96; 95% CI, 0.59 to 6.49).

CONCLUSIONS

In high-risk ambulatory patients with cancer, treatment with rivaroxaban did not result in a significantly lower incidence of venous thromboembolism or death due to venous thromboembolism in the 180-day trial period. During the intervention period, rivaroxaban led to a substantially lower incidence of such events, with a low incidence of major bleeding. (Funded by Janssen and others; CASSINI ClinicalTrials.gov number, NCT02555878.)

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Venous thromboembolism is a frequent complication of cancer and cancer treatment, with serious consequences for patients.[1] Public health efforts have focused on thromboprophylaxis in short-term settings such as hospitalization and major surgery.[2] However, cancer therapy is predominantly delivered in the outpatient setting, leaving many patients with cancer at extended risk.

Two large, randomized trials in mixed cancer populations have evaluated extended prophylaxis with heparins.[3,4] Event rates and absolute benefit were low, and guidelines recommend against routine thromboprophylaxis in such patients.[1,5,6] However, there is substantial variation in risk, and patients who are at increased risk can be identified by a validated risk tool (Khorana score, which is assessed on a scale from 0 to 6, with higher scores indicating a higher risk of venous thromboembolism; the scoring system uses cancer type, body-mass index, and hematologic variables to gauge risk) (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[7] Studies suggest benefit from prophylaxis in patients with a score of 3 or higher.[8,9] Although other data suggest that there is a substantial risk even among patients with a score of 2, the benefit of thromboprophylaxis is unclear.[10,11]

Rivaroxaban is a potent, oral, highly selective direct inhibitor of factor Xa and is effective for primary and secondary thromboprophylaxis.[12,13] Therefore, we conducted the CASSINI trial to assess the efficacy and safety of rivaroxaban thromboprophylaxis in patients with a solid tumor or lymphoma who had a Khorana score of 2 or higher and were initiating a new systemic cancer regimen.

METHODS

PATIENTS

Patients were included if they were 18 years of age or older, were ambulatory outpatients with a solid tumor or lymphoma, had a Khorana score of 2 or higher at baseline, and had an expected survival of more than 6 months with a plan to start a new systemic regimen within 1 week before or after initiating the trial regimen. Patients were excluded if they had a primary brain tumor or known brain metastases, an Eastern Cooperative Oncology Group performance-status score of 3 or more (on a 5-point scale, with higher numbers indicating greater disability), or active bleeding or were at risk for bleeding. The original trial design has been described previously.[14] The trial protocol, including the statistical analysis plan, is available at NEJM.org.

TRIAL DESIGN AND INTERVENTIONS

CASSINI was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3b trial. It was placebo controlled because routine thromboprophylaxis is not recommended in current guidelines, and no anticoagulant is approved for this indication. All the patients provided written informed consent.

Enrolled patients underwent venous duplex compression ultrasonography of both legs to rule out preexisting proximal deep-vein thrombosis. Prophylactic anticoagulation is inadequate therapy for existing thrombosis.[9,15,16] Patients without thrombosis were randomly assigned in a 1:1 ratio to receive rivaroxaban at a dose of 10 mg or placebo orally once daily for 180 days (with a window of ±3 days) according to a computer-generated randomization schedule. Randomization was stratified according to whether the pancreas was the primary tumor site. The trial visits occurred at week 8 (with a window of ±7 days), week 16 (with a window of ±7 days), and at day 180 or the end of the trial intervention (with a window of ±3 days) and included screening compression ultrasonography of both legs at each visit.

END-POINT MEASURES

The primary efficacy end point was the composite of objectively confirmed symptomatic or asymptomatic proximal deep-vein thrombosis in a lower limb, symptomatic deep-vein thrombosis in an upper limb or distal deep-vein thrombosis in a lower limb, symptomatic or incidental pulmonary embolism, and death from venous thromboembolism, as adjudicated by an independent clinical end-point committee whose members were unaware of the trial-group assignments. Secondary efficacy end points included components of the primary end point, including symptomatic venous thromboembolism as well as clinically relevant events that were not included in the primary composite end point, such as death from any cause, confirmed arterial thromboembolism, and confirmed visceral thromboembolism.

The primary safety end point was the occur-

rence of major bleeding as defined by the International Society on Thrombosis and Hemostasis (ISTH; bleeding leading to transfusion or to a decrease in the hemoglobin level of >2 g per deciliter) during the intervention period (defined as the period from the first dose of rivaroxaban or placebo through the last dose plus 2 days).[17] Secondary safety end points were the percentages of patients with ISTH-defined[17] clinically relevant nonmajor bleeding, minor bleeding, and any bleeding during the intervention period (see the Supplementary Appendix). Major and clinically relevant nonmajor bleeding events were adjudicated by an independent clinical-events committee whose members were unaware of the trial-group assignments. Prespecified subgroup analyses were planned for subgroups according to the stratification factor (pancreas as primary tumor site [yes vs. no]), age, sex, race or ethnic group, body-mass index, primary tumor type, stage, Khorana score, performance-status score, geographic region, and creatinine clearance (Table S3 in the Supplementary Appendix).

TRIAL OVERSIGHT

The trial was designed by members of the steering committee, with input regarding end-point selection and statistical analysis from regulatory authorities, and was cosponsored by Janssen and Bayer. The steering committee provided oversight of trial conduct and data reporting. Data were collected by Janssen and analyzed in collaboration with steering committee members. No Janssen employees were members of the steering committee or the data and safety monitoring board. All the authors had access to all the data and contributed to the interpretation of results. The first author wrote the initial draft of the manuscript, and all the authors contributed to revisions, with no conceptual contributions from anyone who was not an author and with no other writing assistance. Assistance in formatting the manuscript and preparing the files for submission was provided by two medical writers and funded by Janssen. All the authors vouch for the accuracy and completeness of the data reported and for the adherence of the trial to the protocol.

The trial was performed in accordance with the principles of the Declaration of Helsinki and with local regulations. The protocol was approved by an institutional review board at each trial site.

STATISTICAL ANALYSIS

Assuming an absolute difference in event rates of 8.5 percentage points between the two trial groups and assuming that 20% of the patients would withdraw or be withdrawn from the trial, we estimated that approximately 700 patients would need to undergo randomization in order for the trial to detect a relative risk that was 58.6% lower in favor of rivaroxaban, at a power of more than 90% with an overall two-sided alpha level of 0.05. The planned sample size was revised during the trial to approximately 800 because the withdrawal rate was higher than expected.

Cumulative event rates for the primary efficacy composite end point were estimated with the use of the Kaplan–Meier method, and the P value was calculated by the two-sided log-rank test, stratified according to tumor type. The primary efficacy analysis was based on the intention-to-treat analysis population, which comprised all the patients who had undergone randomization, with data from randomization through day 180. The analysis plan specified that if superiority of rivaroxaban over placebo was established for the primary efficacy composite end point, a sequential approach that used a closed-testing hierarchical procedure would be used to test two secondary end points: symptomatic venous thromboembolism or venous thromboembolism–related death and death from any cause for the data from randomization through day 180. There were no adjustments for multiple comparisons for other secondary and additional end points, and the results of these end points are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive effects regarding rivaroxaban treatment for these end points.

A prespecified supportive analysis of the primary efficacy composite end point was based on the same population (all the patients who underwent randomization) but only during the intervention period (first receipt of trial agent to last dose plus 2 days). The primary efficacy and safety end points were also analyzed with the use of a stratified Cox proportional-hazards model, with trial group as a covariate and tumor type (pancreatic vs. not pancreatic) as a stratification factor, to provide a point estimate (hazard ratio)

and two-sided 95% confidence interval. All the statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

A total of 1080 patients were enrolled and provided written informed consent at 143 centers in 11 countries. A total of 49 patients (4.5%) did not undergo randomization because of the presence of deep-vein thrombosis at baseline screening, and 190 patients had other reasons for not undergoing randomization (Fig. S1 in the Supplementary Appendix). Overall, 841 patients who underwent randomization were included in the intention-to-treat efficacy analyses, and 809 patients who had received at least one dose of rivaroxaban or placebo were included in the safety analysis. The characteristics of the patients were well balanced at baseline, except that more patients with a history of venous thromboembolism were randomly assigned to the rivaroxaban group than to the placebo group (Table 1). The most common primary cancer was pancreatic cancer (in 32.6% of the patients), and 54.5% of the patients with a solid tumor had metastatic disease.

The mean intervention period was 4.3 months. A total of 43.7% of the patients in the rivaroxaban group and 50.2% of those in the placebo group prematurely discontinued the respective trial agent; the reasons were similar in the two groups (Table S2 in the Supplementary Appendix). The rate of adherence, which was based on the duration of exposure to rivaroxaban or placebo (and took interruptions to the regimen into account), was high. In the safety population, the mean (±SD) percentage of patients who adhered to the trial regimen was 98.4±4.0% in the rivaroxaban group and 98.4±5.0% in the placebo group.

EFFICACY END POINTS

The primary efficacy composite end point occurred in 25 of 420 patients (6.0%) in the rivaroxaban group and in 37 of 421 (8.8%) in the placebo group (hazard ratio, 0.66; 95% confidence interval [CI], 0.40 to 1.09; P=0.10) in the observation period up to day 180, which was the primary analysis (Fig. 1A). (After adjustment for the competing risk of death, the hazard ratio was 0.64 [95% CI, 0.39 to 1.07].) Of the 62 patients who had a primary end-point event, 24 (39%) did so after the discontinuation of the trial regimen. In the prespecified analysis involving the same population (all the patients who had undergone randomization) with assessment during the intervention period, the primary efficacy end point occurred in 11 of 420 patients (2.6%) in the rivaroxaban group and 27 of 421 (6.4%) in the placebo group (hazard ratio, 0.40; 95% CI, 0.20 to 0.80) (Fig. 1B). No heterogeneity of effect of rivaroxaban treatment was detected for any prespecified subgroup (P>0.10 for all comparisons) (Figs. S3 and S4 in the Supplementary Appendix). A breakdown of the components of the primary end points for the two observation periods (up to day 180 and during the intervention) is provided (Table 2). All the prespecified supportive analyses are reported in Table S4 in the Supplementary Appendix.

In addition to primary end-point events, arterial thromboembolism occurred in 4 of 420 patients (1.0%) in the rivaroxaban group and in 7 of 421 (1.7%) in the placebo group. A prespecified analysis of the composite of the primary end point with the addition of arterial and visceral thromboembolic events in the period up to day 180 showed that the incidence of events was lower in the rivaroxaban group than in the placebo group (6.9% vs. 10.7%; hazard ratio, 0.62; 95% CI, 0.39 to 0.99).

For the secondary efficacy end point of death from any cause in the period up to day 180, there were 84 deaths (20.0% of the patients) in the rivaroxaban group and 100 deaths (23.8%) in the placebo group (hazard ratio, 0.83; 95% CI, 0.62 to 1.11). A prespecified composite of the primary end point plus death from any cause occurred in 23.1% of the patients in the rivaroxaban group and in 29.5% of those in the placebo group (hazard ratio, 0.75; 95% CI, 0.57 to 0.97) (Fig. S2 in the Supplementary Appendix). Prespecified secondary efficacy end-point analyses are reported in Table S5 in the Supplementary Appendix.

SAFETY END POINTS

Major bleeding occurred in 8 of 405 patients (2.0%) receiving rivaroxaban and in 4 of 404 (1.0%) receiving placebo (hazard ratio, 1.96; 95% CI, 0.59 to 6.49) (Table 3). Sites of major bleeding included gastrointestinal sites in 8 patients, intraocular sites in 2 patients, and intracranial

Table 1. Characteristics of the Trial Population at Baseline.*

Characteristic	Placebo (N=421)	Rivaroxaban (N=420)	Total (N=841)
Age — yr			
Median	62	63	63
Range	28–88	23–87	23–88
Male sex — no. (%)	206 (48.9)	222 (52.9)	428 (50.9)
Race — no. (%)†			
White	346 (82.2)	352 (83.8)	698 (83.0)
Black	18 (4.3)	13 (3.1)	31 (3.7)
Asian	5 (1.2)	6 (1.4)	11 (1.3)
Other	21 (5.0)	10 (2.4)	31 (3.7)
Not reported	31 (7.4)	39 (9.3)	70 (8.3)
Khorana score — no. (%)‡			
<2	3 (0.7)	5 (1.2)	8 (1.0)
2	295 (70.1)	281 (66.9)	576 (68.5)
3	96 (22.8)	106 (25.2)	202 (24.0)
4	25 (5.9)	26 (6.2)	51 (6.1)
≥5	2 (0.5)	2 (0.5)	4 (0.5)
Previous venous thromboembolism — no. (%)			
Deep-vein thrombosis	2 (0.5)	11 (2.6)	13 (1.5)
Pulmonary embolism	0	2 (0.5)	2 (0.2)
Primary tumor type — no. (%)§			
Pancreatic	138 (32.8)	136 (32.4)	274 (32.6)
Breast	9 (2.1)	9 (2.1)	18 (2.1)
Gastric or gastroesophageal junctional	87 (20.7)	89 (21.2)	176 (20.9)
Genitourinary¶	17 (4.0)	15 (3.6)	32 (3.8)
Lung	72 (17.1)	62 (14.8)	134 (15.9)
Lymphoma	26 (6.2)	33 (7.9)	59 (7.0)
Ovarian	30 (7.1)	24 (5.7)	54 (6.4)
Other	42 (10.0)	52 (12.4)	94 (11.2)

* A total of 1080 patients were enrolled in the trial, of whom 49 (4.5%) had deep-vein thrombosis at baseline. A total of 841 patients underwent randomization. Additional characteristics of the patients at baseline are provided in Table S8 in the Supplementary Appendix. The baseline characteristics of the patients were well balanced between the two groups, except that more patients with a history of venous thromboembolism were randomly assigned to the rivaroxaban group (P=0.01 by the chi-square test for comparing proportions). Percentages may not add up to 100 because of rounding.

† Race was reported by the patients. "Other" race included patients who reported being Native American, Hawaiian or Pacific Islander, other race, or mixed race. A total of 70 patients did not report race; these patients were primarily from France, where this information could not be collected because of local regulations.

‡ Khorana scores range from 0 to 6, with higher scores indicating a higher risk of venous thromboembolism. Eight patients had a Khorana score of less than 2, which was a protocol violation.

§ A complete listing of the primary tumor types and sites is provided in Table S8 in the Supplementary Appendix.

¶ Genitourinary cancers included renal, bladder, ureteral, and testicular cancers but not prostate cancer.

sites in 2 patients. Clinically relevant nonmajor bleeding occurred in 2.7% of the patients in the rivaroxaban group and in 2.0% of those in the placebo group (hazard ratio, 1.34; 95% CI, 0.54 to 3.32). There was one fatal bleeding event, which occurred in the rivaroxaban group. The incidence of adverse events and serious adverse events was similar in the two groups (Table 4).

DISCUSSION

We compared the use of rivaroxaban with placebo for primary thromboprophylaxis in ambulatory patients with cancer who were at high risk for venous thromboembolism and were initiating a new systemic cancer therapy. The design specified a primary intention-to-treat analysis of the period up to day 180, regardless of whether events occurred after discontinuation of the trial regimen. Although the primary end point occurred in a lower percentage of patients who had been randomly assigned to the rivaroxaban group in this analysis, the difference was not significant. In a prespecified supportive analysis involving the same population but assessing the more conventional period of during the intervention, we found a difference of 4 percentage points in favor of rivaroxaban over placebo with regard to the primary composite end point of venous thromboembolism and venous thromboembolism–related death.

Our findings are consistent with the results of two previous large trials of thromboprophylaxis in mixed cancer populations, PROTECHT (Prophylaxis of Thromboembolism during Chemotherapy) and SAVE-ONCO, which both used a similarly defined intervention period for the primary analysis.[3,4] Although the lower risk with the active drug than with placebo in the intervention-period analysis that was observed in the CASSINI trial was similar to the results in these previous trials, the absolute difference in risk was nearly doubled (4 percentage points, vs. 2.2 percentage points in the SAVE-ONCO trial and 1.9 percentage points in the PROTECHT trial), which probably reflects our inclusion of a high-risk population. It is noteworthy that this absolute difference in risk occurred despite the exclusion of the 4.5% of the enrolled patients who had deep-vein thrombosis at screening. This intervention probably reduced the incidence of subsequent symptomatic events. The lower risk with rivaroxaban than with placebo in the intervention-period analysis that we observed in the CASSINI trial is greater than that observed in other medical settings.[18-20] Arterial and isolated distal thromboembolism are both prevalent and consequential in patients with cancer.[21,22] The lower rates of both arterial and distal asymptomatic events with rivaroxaban than with placebo that we observed in our trial, although not included in the primary end point, could further increase the net benefit of prophylaxis for patients.

One limitation of our trial was that nearly

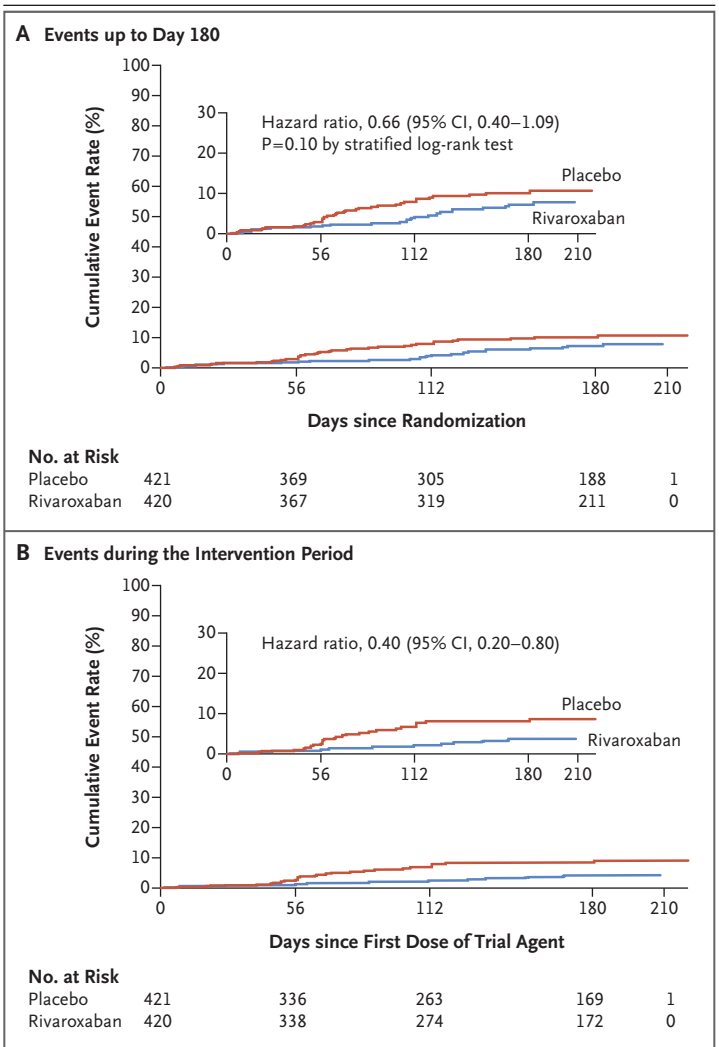

Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point in the Intention-to-Treat Population, According to Trial Group.

The primary efficacy end point was a composite of objectively confirmed symptomatic proximal or distal deep-vein thrombosis in a lower limb, asymptomatic proximal deep-vein thrombosis in a lower limb, symptomatic deep-vein thrombosis in an upper limb, symptomatic or incidental nonfatal pulmonary embolism, or venous thromboembolism–related death during the period up to day 180 (Panel A). Every patient was accounted for in the analysis of the primary efficacy composite end point during the intervention period, which was defined as the time from receipt of the first dose of rivaroxaban or placebo to the last dose plus 2 days (Panel B). An imputation rule that used the time that a patient was in the double-blind period after randomization was implemented for patients who never received a dose of rivaroxaban or placebo in order to ensure that patients were not excluded from the intervention-period analysis for the intention-to-treat population. The insets show the same data on an enlarged y axis.

Table 2. Primary Efficacy End Points during the Period up to Day 180 and during the Intervention, According to Trial Group.*

End Point	Up to Day 180			During Intervention		
	Placebo (N=421)	Rivaroxaban (N=420)	Hazard Ratio (95% CI)	Placebo (N=421)	Rivaroxaban (N=420)	Hazard Ratio (95% CI)
Primary efficacy composite end point	37 (8.8)	25 (6.0)	0.66 (0.40–1.09)†	27 (6.4)	11 (2.6)	0.40 (0.20–0.80)
Symptomatic event‡	19 (4.5)	15 (3.6)	—	12 (2.9)	5 (1.2)	—
Symptomatic proximal DVT in lower limb	8 (1.9)	9 (2.1)	1.12 (0.43–2.91)	4 (1.0)	3 (0.7)	0.72 (0.16–3.22)
Symptomatic distal DVT in lower limb	5 (1.2)	2 (0.5)	0.40 (0.08–2.07)	2 (0.5)	0	NA
Symptomatic DVT in upper limb	6 (1.4)	4 (1.0)	0.67 (0.19–2.39)	6 (1.4)	2 (0.5)	0.33 (0.07–1.63)
Symptomatic nonfatal pulmonary embolism	5 (1.2)	5 (1.2)	1.02 (0.29–3.52)	0	1 (0.2)	NA
Asymptomatic event‡	18 (4.3)	9 (2.1)	—	15 (3.6)	5 (1.2)	—
Asymptomatic proximal DVT in lower limb	11 (2.6)	4 (1.0)	0.35 (0.11–1.11)	10 (2.4)	3 (0.7)	0.29 (0.08–1.07)
Incidental pulmonary embolism	10 (2.4)	6 (1.4)	0.59 (0.21–1.62)	5 (1.2)	2 (0.5)	0.38 (0.07–1.98)
Venous thromboembolism–related death	3 (0.7)	1 (0.2)	0.33 (0.03–3.18)	1 (0.2)	1 (0.2)	0.97 (0.06–15.55)

* Data for both periods are for all 841 patients who underwent randomization (intention-to-treat population). The period up to day 180 was used for the primary analysis and the period during the intervention for a supportive analysis. All the events were adjudicated by an independent committee whose members were unaware of the trial-group assignments. DVT denotes deep-vein thrombosis, and NA not applicable (i.e., could not be estimated).
† P=0.10 by the stratified log-rank test.
‡ Numbers in the symptomatic and asymptomatic rows correspond to the number of patients who had any one of the symptomatic or asymptomatic events, respectively. There were 10 patients with more than one type of symptomatic event and 4 with more than one type of asymptomatic event. A total of 3 patients had both symptomatic and asymptomatic events.

Table 3. Primary Safety End Points, According to Trial Group.*

End Point	Placebo (N=404)	Rivaroxaban (N=405)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary safety end point: major bleeding	4 (1.0)	8 (2.0)	1.96 (0.59–6.49)	0.26
Secondary safety end point: clinically relevant nonmajor bleeding	8 (2.0)	11 (2.7)	1.34 (0.54–3.32)	0.53
Major and clinically relevant nonmajor bleeding	12 (3.0)	19 (4.7)	1.54 (0.75–3.17)	0.24

* Data are for the 809 patients who took at least one dose of placebo or rivaroxaban (safety population) during the intervention period and as adjudicated by an independent committee whose members were unaware of the group assignments. Bleeding events were defined according to the International Society on Thrombosis and Hemostasis.[17]

47% of the enrolled patients prematurely discontinued the trial regimen. However, these discontinuation rates are not unexpected in a population of patients with cancer who have mostly advanced disease, and the rates were similar to those in the PROTECHT and SAVE-ONCO trials, taking into account the longer trial period in the CASSINI trial.[2,3] Rates of discontinuation that included discontinuations due to adverse events were lower in the rivaroxaban group than in the placebo group, which argues against bias in further planned analyses. Patients who discontinued the trial regimen were still followed up for efficacy, and 39% of all the primary endpoint events occurred in these patients. Another potential limitation of the intervention-period analysis is the possibility of dependent censoring. We evaluated the baseline characteristics

and outcomes of the patients who discontinued the trial regimen and of those who continued in the trial, and we did not find major differences (Tables S6 and S7 in the Supplementary Appendix). The consistency of the results in the intention-to-treat and intervention-period analyses provide further reassurance that dependent censoring does not explain the results observed in the intervention period.

An additional feature of our trial is the introduction of serial screening and the effect on symptomatic events. It has long been established that one tenth of untreated asymptomatic thrombi result in symptomatic pulmonary embolism, an observation that suggests that such thrombi are not surrogate end points but rather are clinically meaningful.[23] Thromboembolism has increasingly been identified incidentally during imaging studies for cancer.[24-26] Such incidental events are associated with recurrence rates and mortality that are similar to those associated with symptom-detected events, which again underscores their clinical significance.[27] Reflecting current consensus, guidelines recommend that incidental venous thromboembolism be treated similarly to symptom-detected events with the exception of visceral thrombi.[5,28] Although we report symptomatic venous thromboembolism separately as a subcategory in Table 2, it is difficult to estimate the "true" rate that would have occurred had the trial design not altered natural history with early detection and anticoagulation. Results from a trial of thromboprophylaxis in patients with the same Khorana score cutoff of 2 or higher but without screening at baseline or during the trial — reported in this issue of the *Journal*[29] — could provide clarification.

Death that was related to venous thromboembolism contributed only marginally to the primary end point. Given that no autopsies were performed and that most patients died at home with cancer, it is possible that the true rate of venous thromboembolism–related death was underestimated. This hypothesis is supported by findings that all-cause mortality was 3.8 percentage points lower in the rivaroxaban group than in the placebo group and that the percentage of patients who had a composite end-point event of venous thromboembolism and death from any cause was 6.4 percentage points lower.

In any primary prevention approach, the preservation of patients' safety is essential. We found that the incidence of major bleeding was 1 percentage point higher in the rivaroxaban group than in the placebo group, with an overall incidence of major bleeding of 2% in the rivaroxaban group. In a previous randomized trial of dalteparin thromboprophylaxis in high-risk patients, the incidence of clinically relevant nonmajor bleeding was 7 times as high among patients who received dalteparin as among those in the observation group.[9] In contrast, we observed that such incidence in the rivaroxaban group was higher by a factor of 2.

In conclusion, the results of the CASSINI trial provide important information regarding the baseline prevalence and incidence of thromboembolism among high-risk ambulatory patients with cancer. However, in this placebo-controlled trial, we did not establish the benefit of treatment with rivaroxaban, because the between-group difference in the prespecified primary efficacy end point up to day 180 was not significant.

Table 4. Adverse Events.*

Event	Placebo (N=404)	Rivaroxaban (N=405)
	no. of patients with event (%)	
Any adverse event	317 (78.5)	306 (75.6)
Serious adverse event†	175 (43.3)	168 (41.5)
Any adverse event related to trial agent‡	19 (4.7)	30 (7.4)
Any adverse event leading to permanent discontinuation of trial agent	82 (20.3)	66 (16.3)
Any adverse event leading to death	106 (26.2)	85 (21.0)

* Some adverse events were included in multiple categories in this table.
† Serious adverse events were classified as those that, at any dose, resulted in death or were life-threatening, led to inpatient hospitalization or prolonged existing hospitalization, resulted in persistent serious disability or incapacity, were a congenital anomaly, or were a medically important event.
‡ The relatedness of the adverse event to the trial agent was determined by the treating investigator.

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

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APPENDIX

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