VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

RAPID COMMUNICATION

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)

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Published at jco.org on May 10, 2018.

Processed as a Rapid Communication manuscript.

Written on behalf of the SELECT-D Collaborative Group.

The opinions, results, and conclusions reported here are those of the authors and are independent of the funding sources.

Clinical trial information: ISRCTN86712308; EudraCT 2012-005589-37.

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0732-183X/18/3620w-2017w/$20.00

ABSTRACT

Purpose
Venous thromboembolism (VTE) is common in patients with cancer. Long-term daily subcutaneous low molecular weight heparin has been standard treatment for such patients. The purpose of this study was to assess if an oral factor Xa inhibitor, rivaroxaban, would offer an alternative treatment for VTE in patients with cancer.

Patient and Methods
In this multicenter, randomized, open-label, pilot trial in the United Kingdom, patients with active cancer who had symptomatic pulmonary embolism (PE), incidental PE, or symptomatic lower-extremity proximal deep vein thrombosis (DVT) were recruited. Allocation was to dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2-6) or rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months). The primary outcome was VTE recurrence over 6 months. Safety was assessed by major bleeding and clinically relevant nonmajor bleeding (CRNMB). A sample size of 400 patients would provide estimates of VTE recurrence to within ± 4.5%, assuming a VTE recurrence rate at 6 months of 10%.

Results
A total of 203 patients were randomly assigned to each group, 58% of whom had metastases. Twenty-six patients experienced recurrent VTE (dalteparin, n = 18; rivaroxaban, n = 8). The 6-month cumulative VTE recurrence rate was 11% (95% CI, 7% to 16%) with dalteparin and 4% (95% CI, 2% to 9%) with rivaroxaban (hazard ratio [HR], 0.43; 95% CI, 0.19 to 0.99). The 6-month cumulative rate of major bleeding was 4% (95% CI, 2% to 8%) for dalteparin and 6% (95% CI, 3% to 11%) for rivaroxaban (HR, 1.83; 95% CI, 0.68 to 4.96). Corresponding rates of CRNMB were 4% (95% CI, 2% to 9%) and 13% (95% CI, 9% to 19%), respectively (HR, 3.76; 95% CI, 1.63 to 8.69).

Conclusion
Rivaroxaban was associated with relatively low VTE recurrence but higher CRNMB compared with dalteparin.

J Clin Oncol 36:2017-2023. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Venous thromboembolism (VTE) is a common occurrence in patients with malignant disease. Acute VTE is treated with anticoagulant therapy to prevent recurrent thrombosis, including potentially fatal pulmonary embolism (PE). The risk of recurrent thrombosis is increased at least two-fold in patients with cancer compared with patients without cancer.[1] Furthermore, there is an increased risk of anticoagulant-induced bleeding in patients with cancer compared with patients without.[2] For more than a decade, low molecular weight heparin (LMWH) for at least 6 months has been the standard treatment for acute VTE in patients with cancer.[3,4] In cancer-associated thrombosis, there is limited evidence on the duration of anticoagulant therapy beyond 6 months. Guidelines recommend that treatment continue as long as the cancer is active.[5]

Over the last decade, a new class of anticoagulant, which directly inhibits a clotting factor and is not a vitamin K antagonist (VKA), has

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2018.78.8034

Data Supplement
DOI: https://doi.org/10.1200/JCO.2018.78.8034

DOI: https://doi.org/10.1200/JCO.2018.78.8034

emerged for the prevention and treatment of acute VTE. The direct oral anticoagulants (DOACs) are dabigatran, inhibiting activated factor II (thrombin), and rivaroxaban, apixaban, and edoxaban, inhibiting activated factor X. These agents are noninferior to VKAs in patients with acute VTE.[6-10]

LMWH requires daily subcutaneous injection; DOACs are taken orally and do not require laboratory monitoring. In patients with anorexia and vomiting, oral administration can be problematic.[11]

In the EINSTEIN trials (ClinicalTrials.gov identifiers: NCT00440193 and NCT00439725) , which compared rivaroxaban with LMWH followed by a VKA in patients with acute symptomatic deep vein thrombosis (DVT) or acute PE,[9,10] only 5.5% of patients had active cancer at baseline.[12] The comparator to the DOAC was a VKA, whereas the standard treatment in cancer is long-term LMWH.[3] Because the generalizability to patients with active cancer was unclear, we conducted a trial to assess VTE recurrence rates in patients with active cancer, treated with either rivaroxaban or dalteparin. The trial provided an opportunity to address the question of the duration of anticoagulant therapy beyond 6 months, based on the premise that the presence of residual DVT on compression ultrasound (CUS) after 5 months of anticoagulant therapy is a marker for increased risk of recurrent VTE.[13] The comparison of dalteparin and rivaroxaban over 6 months is reported.

PATIENTS AND METHODS

Design

Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) was a randomized, open-label, multicenter pilot trial.

Patient Population

The inclusion criteria were patients with active cancer (solid and hematologic malignancies) presenting with a primary objectively confirmed VTE, either symptomatic lower-extremity proximal DVT, symptomatic PE, or incidental PE. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell skin carcinoma) in the previous 6 months, any treatment for cancer within the previous 6 months, recurrent or metastatic cancer, or cancer not in complete remission (hematologic malignancy). In addition, patients had to be age $\geq$ 18 years of age; weigh $\geq$ 40 kg; have an Eastern Cooperative Oncology Group performance status of $\leq$ 2; and have adequate hematologic, hepatic, and renal function.

The exclusion criteria included taking any previous treatment dose of anticoagulant or $>$ 75 mg aspirin per day (planned start time of study therapy was $>$ 96 hours after starting anticoagulant for this VTE), having a history of VTE, clinically significant liver disease, bacterial endocarditis, active bleeding or high risk of bleeding, or uncontrolled hypertension, and inadequate contraceptive measures if of childbearing potential. Concomitant use of strong cytochrome P- 450 3A4 inhibitors or inducers or P-glycoprotein inhibitors or inducers was not permitted. After approval by ethics committees in the United Kingdom and by the Medicines and Healthcare Products Regulatory Agency, each center approved the study protocol. All patients provided written informed consent.

Random Assignment and Study Interventions

Patients were randomly assigned centrally by telephoning Warwick Clinical Trials Unit. Consenting patients were randomly assigned at a one-to-one ratio using a computer-based minimization algorithm with stratification by stage of disease (early or locally advanced disease *v* metastatic disease for solid tumors *v* hematologic malignancy), baseline platelet count ($\leq$ 350,000 *v* $>$ 350,000/μL), type of VTE (symptomatic VTE *v* incidental PE), and risk of clotting by tumor type (high *v* low risk). Trial staff, participants, and investigators were not blinded to treatment allocation.

For patients assigned to dalteparin, 200 IU/kg was administered subcutaneously once daily for the first 30 days of treatment, and then 150 IU/kg was administered subcutaneously once daily for an additional 5 months. The LMWH was supplied by the National Health Service. The total daily dose was not to exceed 18,000 IU. The dose was also adjusted or discontinued for low platelet count and significant renal failure until recovery.

For patients assigned to rivaroxaban, 15-mg tablets were administered orally with food twice daily for the first 3 weeks, followed by 20-mg tablets once daily for a total of 6 months. If platelet counts were $<$ 50,000/mm^3, rivaroxaban was to be discontinued until the platelet count recovered to $>$ 50,000/mm^3. A dose reduction or discontinuation was specified for different levels of renal impairment.

After approximately 5 months of receiving study medication, patients with an index DVT underwent CUS of the lower limbs. If the CUS showed residual DVT or patients had presented with a PE, they were eligible to be randomly assigned to 6 months of rivaroxaban or placebo. Patients had to still be receiving trial treatment, be without a VTE recurrence, and satisfy the baseline inclusion criteria to be approached for the second random assignment.

Follow-Up

All patients were assessed at 3-month intervals until month 12 and then at 6-month intervals until month 24. Physical examination (as clinically indicated) and routine hematology and biochemistry were performed at each visit. Computed tomography scans and venous ultrasonography of upper and lower limbs were performed if clinically indicated.

Outcomes

The primary outcome of the trial was VTE recurrence. Recurrent proximal DVT (definition listed in Appendix Table A1, online only) was confirmed using CUS. Recurrent PE, either symptomatic or incidental PE, and fatal PE were defined as listed in Appendix Table A1. In addition, other sites of venous thrombosis (eg, subclavian vein, hepatic vein, and inferior vena cava) were counted as primary outcome events. Although the study protocol did not specify central adjudication of suspected VTE events, reported VTE events were subsequently adjudicated by a central committee unaware of treatment allocation after the study was completed.

Secondary outcomes were major bleeding and clinically relevant nonmajor bleeding (CRNMB[9]; Appendix Table A2, online only).[14] Bleeding events were adjudicated by an independent committee of experienced clinicians unaware of treatment allocation. Adverse events experienced from trial entry until 30 days after the end of trial treatment were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[15]

Statistics

We conducted a pilot trial to obtain estimates of recurrent VTE rates to gauge the feasibility of recruiting to a phase III trial and assess the assumptions for the second random assignment. A target sample size of 530 patients would provide estimates of VTE recurrence rates at 6 months to within an 8% width of the 95% CI, assuming a VTE recurrence rate at 6 months of 10%.[3] In addition, it would ensure that the sample size would be large enough to allow sufficient numbers for the second random assignment—a total of 300 patients randomly assigned (150 to each arm) to provide estimates for a future definitive duration study.

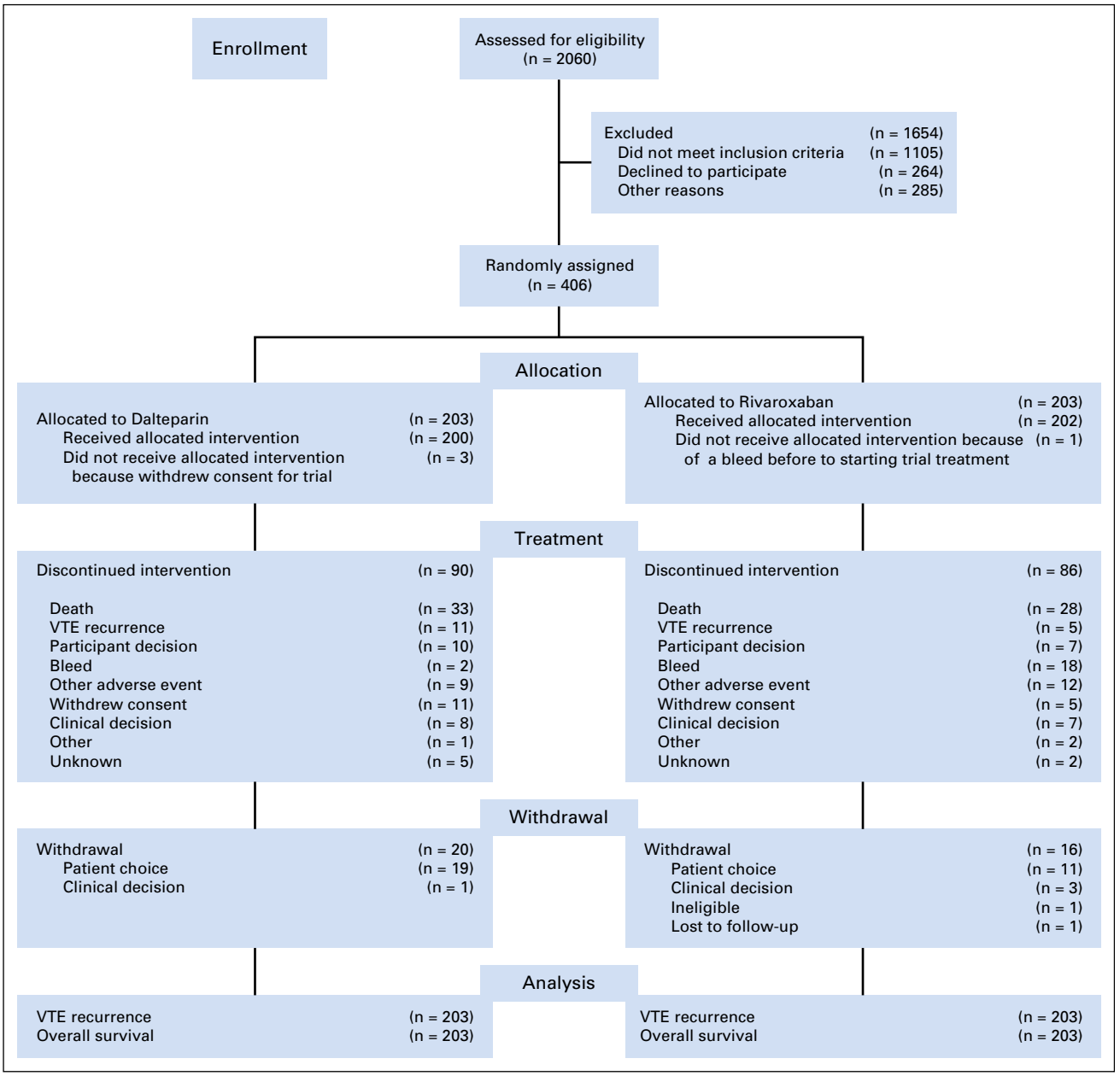

Fig 1. CONSORT diagram, including enrollment and outcomes. VTE, venous thromboembolism.

On September 1, 2016, based on a recommendation from the data and safety monitoring committee (DSMC), the second random assignment was closed, with only 92 patients recruited, because it was considered futile to continue. At the same time, the sample size for the trial was reduced to a total of 400 patients (200 patients in each arm), because recruitment was slower than anticipated. This would still allow estimates of the primary outcome to be within a 95% CI of 9%, instead of 8% as originally planned.

A safety analysis was planned for the first 220 patients (110 in each arm). This would be sufficient to detect an excess of 10% in major bleeding and CRNMB rates (80% power; 5% one- sided significance level, assuming a 5% rate in the control arm).

Because of censoring, VTE recurrence was analyzed using the time to a VTE recurrence, which was calculated from the date of random assignment to the date of first VTE recurrence event or censored at the analysis date of 6 months or date last known to be VTE recurrence free, if earlier. Cumulative incidence curves for the time to VTE recurrence were estimated using the complement of the Kaplan-Meier estimates, and the VTE recurrence rate at 6 months and 95% CIs were obtained. Kaplan-Meier estimates were also obtained for bleeding and survival. A Cox model was used to obtain hazard ratios (HRs) and associated 95% CIs and to evaluate independent prognostic factors for VTE recurrence. A competing risk analysis was performed using the cumulative incidence competing risk method to account for death as a competing risk.[16]

RESULTS

Patient Population

Between September 6, 2013, and December 22, 2016, a total of 2,060 patients were screened, and 670 eligible patients were

Table 1. Patient Baseline Characteristics by Trial Arm

Characteristic	No. (%) Dalteparin (n = 203)	No. (%) Rivaroxaban (n = 203)
Male sex	98 (48)	116 (57)
Age, years		
Median	67	67
Range	34-87	22-87
BMI, kg/m^2		
Median	26.6	26.7
Range	15.1-50.4	14.9-46.2
ECOG PS		
0	61 (30)	58 (29)
1	95 (47)	90 (44)
2	43 (21)	52 (26)
White ethnicity	197 (96)	192 (94)
Stage of disease		
Early/locally advanced	79 (39)	81 (40)
Metastatic	118 (58)	118 (58)
Hematologic malignancy	6 (3)	4 (2)
Platelet count ≤ 350,000/μL	168 (83)	168 (83)
Qualifying VTE		
Symptomatic VTE	98 (48)	95 (47)
PE	38 (18)	40 (19)
DVT*	57 (28)	53 (25)
PE and DVT	2 (1)	2 (1)
Unknown	1 (1)	0 (0)
Incidental PE†	105 (52)	108 (53)
VTE high-risk tumor type	170 (84)	169 (83)
Anticoagulation for qualifying VTE before random assignment	162 (80)	158 (78)
Time on anticoagulant before starting study treatment, hours		
Median	48	48
Range	17-96	16-97‡
Time since diagnosis of primary tumor to random assignment, months		
Median	6.0	6.4
IQR	3.3-19.8	3.3-21.9
Currently receiving cancer treatment§	142 (70)	140 (69)
Chemotherapy	120 (85)	113 (81)
Radiotherapy	10 (7)	6 (4)
Targeted therapy	22 (15)	21 (15)
Endocrine therapy	15 (11)	15 (11)
Primary tumor type		
Bladder	4 (2)	10 (5)
Brain	2 (1)	1 (1)
Breast	20 (10)	20 (10)
Cancer unknown primary	3 (2)	3 (1)
Chronic lymphoid leukemia	2 (1)	1 (1)
Colorectal	47 (23)	55 (27)
Gallbladder	2 (1)	2 (1)
Gastric	7 (3)	4 (2)
Gynecologic	7 (3)	6 (3)
Kidney	5 (3)	2 (1)
Lung	25 (12)	22 (11)
Lymphoma	12 (6)	11 (5)
Multiple myeloma	3 (2)	2 (1)
Esophageal/gastroesophageal	19 (9)	11 (5)
Ovarian	18 (9)	12 (6)
Pancreatic	11 (5)	19 (9)
Prostate	8 (4)	13 (7)
Sarcoma	0	2 (1)
Other	5 (3)	6 (3)
Unknown	3 (2)	1 (1)

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.
*One patient with incidental DVT.
†Six patients had an incidental PE but were also found to have a DVT (dalteparin, n = 2; rivaroxaban, n = 4).
‡One patient was on anticoagulation for 97 hours.
§Patients could receive more than one treatment.

approached for participation; 264 patients declined random assignment (Fig 1). A total of 406 patients were recruited from 58 sites across the United Kingdom; 203 patients were allocated to each trial arm.

The baseline characteristics were reasonably comparable between treatment arms (Table 1). The qualifying event was a symptomatic DVT or PE in 193 patients (48%) and an incidental PE in 213 patients (52%). Fifty-eight percent of patients presented with metastatic disease (Table 1). Colorectal cancer was the primary in approximately 25% of patients (Table 1), and 282 patients (69%) were receiving anticancer treatment at the time of their VTE, a majority of whom (83%) were receiving chemotherapy (n = 233; Table 1).

Of the 406 patients randomly assigned, 11 were subsequently found to be ineligible as a result of lower-extremity distal DVT (n = 5), jugular vein DVT (n = 2), unconfirmed PE (n = 1), previous DVT (n = 1), incidental DVT (n = 1), or started trial treatment late because of pharmacy issues (n = 1). These 11 patients who were allocated dalteparin (n = 7) or rivaroxaban (n = 4) were included in the analysis on the basis of an intention to treat. A total of 216 patients (54%) completed 6 months of trial treatment. The main reason for not completing the study treatment in both arms was death (Fig 1).

The median duration of treatment was 5.8 months (interquartile range, 3.0-6.0 months) for dalteparin and 5.9 months (interquartile range, 2.5-6.0 months) for rivaroxaban. A total of 99 patients (24%) reported missing doses, 44 (22%) of whom were receiving dalteparin and 55 (27%) of whom were receiving rivaroxaban. The main reasons were requiring surgery or a procedure or patient decision.

Safety Analysis

The DSMC reviewed the results of the safety analysis of the first 220 patients. The data did not cross the safety boundary of 10% excess in major bleeding or CRNMB. The DSMC also noted a nonsignificant difference in major bleeding between arms in the 19 patients with cancer of the esophagus or gastroesophageal junction. These cancers were subsequently excluded from enrollment as a precautionary measure.

Recurrent VTE

Twenty-six patients treated with dalteparin (n = 18) or rivaroxaban (n = 8) experienced a recurrent VTE within the first 6 months after random assignment, including two patients with symptomatic PE and six with incidental PE receiving dalteparin,

Table 2. Recurrent VTE

Thrombosis	No. (%)* Dalteparin (n = 203)	Rivaroxaban (n = 203)
VTE recurrence	18	8
Location of recurrence		
Lower extremity	7 (39)	3 (38)†
Femoral vein	5	2
Popliteal vein	3	1
Iliac vein	2	2
IVC	0	1
PE	9 (50)	4 (50)
Other	2 (11)	2 (25)
Brachial, subclavian, or jugular	1	1
Renal plus IVC	1	0
Extrahepatic portal vein	0	1
Type of PE		
Symptomatic	2 (11)	2 (25)
Incidental	6 (33)	1 (13)
Fatal PE	1 (6)	1 (13)

Abbreviations: IVC, inferior vena cava; PE, pulmonary embolism; VTE, venous thromboembolism.
*Percentages are out of the total with VTE recurrence.
†One patient had deep vein thrombosis and PE.

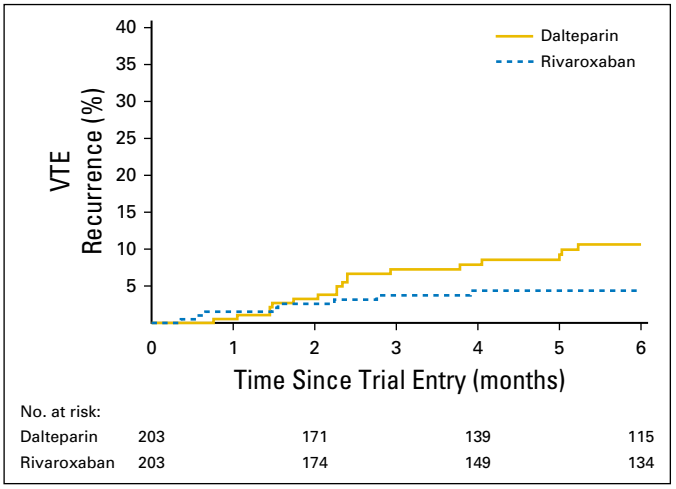

Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

compared with two symptomatic and one incidental PE in those receiving rivaroxaban. There was one fatal PE in each arm (Table 2). The cumulative VTE recurrence rate at 6 months was 11% (95% CI, 7% to 16%) for patients receiving dalteparin and 4% (95% CI, 2% to 9%) for patients receiving rivaroxaban (HR, 0.43; 95% CI, 0.19 to 0.99; Fig 2). A competing risk analysis showed similar results (Appendix Fig A1, online only). Site of primary tumor (stomach or pancreas *v* other; HR, 5.55; 95% CI, 1.97 to 15.66; lung, lymphoma, gynecologic, or bladder *v* other; HR, 2.69; 95% CI, 1.11-6.53) and VTE type (symptomatic VTE *v* incidental PE; HR, 2.78; 95% CI, 1.20 to 6.41) predicted for VTE recurrence.

Bleeding

Six patients receiving dalteparin had major bleeds, compared with 11 patients in the rivaroxaban arm (Table 3). The cumulative major bleed rate at 6 months was 4% (95% CI, 2% to 8%) for dalteparin and 6% (95% CI, 3% to 11%) for rivaroxaban (HR, 1.83; 95% CI, 0.68 to 4.96; Fig 3). Most major bleeding events were GI, and there were no CNS bleeds (Table 3). Patients with esophageal or gastroesophageal cancer tended to experience more major bleeds with rivaroxaban than with dalteparin—four (36%) of 11 versus one (11%) of 19 (Appendix Table A3, online only).

An additional seven patients receiving dalteparin had CRNMB compared with 25 patients in the rivaroxaban arm (Table 3). The cumulative rate of CRNMB at 6 months was 4% (95% CI, 2% to 9%) for dalteparin and 13% (95% CI, 9% to 19%) for rivaroxaban (HR, 3.76; 95% CI, 1.63 to 8.69). Most CRNMBs were GI or urologic (Table 3).

Survival

A total of 104 patients died within 6 months (dalteparin, n = 56; rivaroxaban, n = 48). Overall survival at 6 months was 70% (95% CI, 63% to 76%) with dalteparin and 75% (95% CI, 69% to 81%) with rivaroxaban (Appendix Fig A2, online only).

DISCUSSION

The primary goal of our trial was to obtain estimates of the VTE recurrence rates in patients with cancer treated with rivaroxaban or dalteparin. The 6-month cumulative risk of recurrent VTE in the patients receiving dalteparin was consistent with what had been postulated based on the trial, Low-Molecular–Weight Heparin Versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) .[3] Given that rivaroxaban was noninferior to initial LMWH followed by a VKA in the EINSTEIN trials,[9,10] and that in CLOT, dalteparin reduced recurrent VTE by 50% compared with LMWH followed by a VKA,[3] we estimated that the 6-month cumulative risk of recurrent VTE in patients receiving rivaroxaban would be 10% at best. In fact, the observed 6-month recurrent VTE risk with rivaroxaban was only 4%. It is unlikely that this reduction in recurrent VTE risk in favor of rivaroxaban was by chance, because the 95% CI of the HR did not include 1.0.

Most of the cases of recurrent PE in the dalteparin arm were incidental, related to computed tomography imaging for tumor status. This did not seem to be the case for the rivaroxaban arm. It is conceivable that the increased detection of incidental PE was a chance occurrence.

An important secondary objective of our trial was to assess rates of major bleeding and CRNMB. The rates of major bleeding in both trial arms were relatively low and consistent with previously observed rates.[3,4] Most major bleeding events were GI. Upper GI bleeding is a challenge in patients with atrial fibrillation receiving rivaroxaban.[17] There was a signal that cancer of the esophagus and gastroesophagus was associated with rivaroxaban-associated major bleeding. CNS bleeding is a concern in patients with cancer receiving anticoagulant therapy, and there were no such bleeds in the trial.

There was a three-fold relative increase in CRNMB with rivaroxaban compared with dalteparin. Such bleeds were not trivial, because they had to satisfy at least one of the following criteria: requiring medical intervention, unscheduled contact with a physician, interruption or discontinuation of study drug, or discomfort or impairment of activities of daily life.

Table 3. Bleeding Events

Type of Bleed	Dalteparin (n = 203)	Rivaroxaban (n = 203)
Major bleeding	6	11
Criteria to define major bleeding*		
Clinically overt and decrease in hemoglobin level of ≥ 2 g/dL over 24 hours	5	6
Clinically overt and transfusion of ≥ 2 units of packed red cells	3	10
Clinically overt and critical site (eg, intracranial, retroperitoneal)	0	0
Clinically overt and contributes to death	1	1
Sites of major bleed*		
GI		
Esophageal	1	3
Stomach	3	2
Lower GI	0	1
Site unknown	0	2
Genitourinary		
Hematuria	0	1
Other		
Epistaxis	0	1
Intraoperative hemorrhage	0	1
Hematoma	1	0
Abdominal hematoma related to surgical clip	1	0
CRNMB	7	25
Criteria to define CRNMB*		
Overt bleeding with medical intervention	0	8
Unscheduled contact with a physician	2	15
Interruption or discontinuation of a study drug	4	22
Discomfort or impairment of activities of daily life	2	11
Site of CRNMB*		
GI		
Oral	0	1
Upper GI	0	2
Lower GI	1	0
Colon and rectum	2	1
Anus	0	3
Hemorrhoidal	0	2
Genitourinary		
Hematuria	1	9
Vagina	0	1
Menorrhagia	0	1
Penis	1	0
Other		
Bronchopulmonary	0	2
Epistaxis	1	1
Bruising	1	1
Hematoma	1	0
Subconjunctival	0	2
Joint effusion	0	1

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.
*Patients could have more than one reason or site of bleed; one patient receiving rivaroxaban had two CRNMBs.

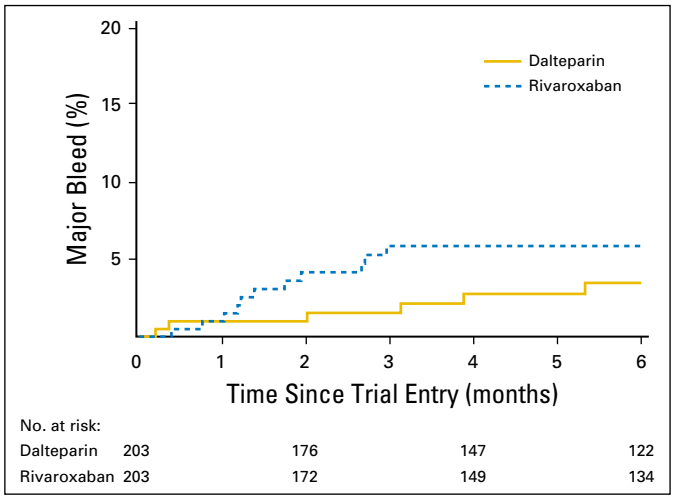

Fig 3. Time to major bleed within 6 months.

In our trial, there were fewer episodes of recurrent VTE associated with rivaroxaban, but there was an increase in bleeding. LMWH accelerates the inhibition by antithrombin of activated factor X in the conversion of prothrombin to thrombin.[18] Rivaroxaban binds directly and reversibly to factor Xa and competitively inhibits factor Xa. It is 10,000-fold more selective for factor Xa than other related serine proteases, and it does not require cofactors (eg, antithrombin) to exert its anticoagulant effect. Rivaroxaban also inhibits both free and clot-bound factor Xa, as well as prothrombinase activity.[19] It is plausible that the enhanced antithrombotic effect of rivaroxaban is associated with a greater perturbation of coagulation, predisposing to more bleeding. Finally, it is recognized that in terms of GI bleeding, rivaroxaban has both a local and systemic effect.[20]

Our trial is not without limitations. Recruitment was slower than anticipated. Our postulates for the number of patients who would be available to participate in the second random assignment were overly optimistic, there was a high mortality rate, and clinicians were choosing not to randomly assign to rivaroxaban versus placebo for many patients. Reducing the sample size required for the first random assignment did not substantially lower the precision of the estimates of the observed outcome rates. The results of our trial reflect only 6 months of treatment and are not generalizable to longer treatment.

Some might consider the SELECT-D trial rather large for a randomized pilot study.[21] However, we consider the study design innovative because it addressed two questions. Although we were unable to answer the question of treatment duration beyond 6 months, we were successful in meeting our primary aim, which was to obtain robust estimates of VTE and bleeding rates for the treatment arms.

In VTE trials, DVT and PE are usually the primary outcome events. We also counted other sites of DVT as primary events. It is not unreasonable to expect anticoagulant therapy to have an effect on such sites. In an exploratory analysis, when only DVT and PE were considered, the rates of recurrent VTE at 6 months were consistent with those in other trials.[3,4,22]

In the recently published Hokusai trial (ClinicalTrials.gov identifier: NCT02073682), patients with cancer with VTE were randomly assigned to either LMWH for at least 5 days followed by the DOAC edoxaban or dalteparin for at least 6 months.[22] The primary outcome was a composite of either recurrent VTE or major bleeding. Edoxaban was found to be noninferior to dalteparin. Over the first 6-month period, the recurrent VTE rate was 6.5% with edoxaban and 8.8% with dalteparin, but rates were 5.6% and 3.2% for major bleeding and 12.3% and 8.2% for CRNMB, respectively. Although there are limitations to between-study comparisons, the results of our trial are consistent with those of this study.

The results of our trial provide evidence that rivaroxaban is an effective alternative to LMWH for the treatment of VTE in cancer. Rivaroxaban reduced the rate of recurrent VTE compared with

LMWH, but at the cost of more bleeding. Oral administration is more convenient than daily subcutaneous injections. It should be used with particular caution in patients with esophageal cancer. At the end of the day, a patient's preference for a specific anticoagulant is based on a careful discussion between patient and physician about the benefits and risks of the treatment alternatives.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Support

Supported by an unrestricted educational grant from Bayer AG, which also provided rivaroxaban and placebo tablets.

Prior Presentation

Presented orally at the American Society of Hematology Annual Meeting, Atlanta, GA, December 9-12, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Honoraria: Bayer AG, Helsinn Healthcare, LEO Pharma, Merck Sharp & Dohme
Research Funding: Bayer AG (Inst)

Andrea Marshall
Research Funding: Bayer AG (Inst)

Jenny Thirlwall
Research Funding: Bayer AG (Inst)

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No relationship to disclose

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No relationship to disclose

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Research Funding: Bayer AG (Inst)

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Research Funding: Roche (Inst), AstraZeneca (Inst), Aeterna Zentaris (Inst), AB Bioscience (Inst), Clovis Oncology (Inst), Bristol-Myers Squibb (Inst), Imgen (Inst), Macrogenics (Inst)
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Acknowledgment

We thank all the co-investigators in the United Kingdom for their commitment throughout the study period, in particular Mojid Khan (MPharm), Robert Grieve, Martin Scott-Brown (MD), and Tom Goodfellow (MD), University Hospitals Coventry and Warwickshire; Veronica Wilkie (FRCGP), University of Worcester; Andrew Entwistle (PhD) and Debs Smith (BA), patient and public involvement (PPI) representatives; Peter Rose (FRCPath), Warwick Hospital; and Jo Grumett (BSc) and Jaclyn Brown (BSc), Warwick Clinical Trials Unit. We also thank all of the patients who participated in the SELECT-D trial and their caregivers and all investigators and their teams from the participating sites (Appendix, Table A4, online only) and members of the UK independent data and safety monitoring committee: Keith Wheatley (PhD), University of Birmingham; Lisa Robinson (FRCPath), Hereford County Hospital; and Ganesh Radhakrishna (FRCR), The Christie National Health Service Foundation Trust. During the trial, one of our PPI representatives, Irene Singleton (BSc), sadly died; Irene gently advised with wise words of a patient.

Appendix

Table A1. Definition of VTE Recurrence

DVT Recurrence	Symptomatic PE Recurrence	Incidental PE Recurrence
Confirmed using CUS: new, noncompressible venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography	New intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of > 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), or a new non–high-probability perfusion defect associated with DVT as documented by CUS or venography	Incidentally diagnosed PE on CT when imaging performed, usually for staging of cancer Fatal PE was based on objective diagnostic testing, autopsy, or death, which could not be attributed to a documented cause and for which PE could not be ruled out (unexplained death)

Abbreviations: CUS, compression ultrasound; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table A2. Bleeding Definitions

Major Bleeding	CRNMB
Acute, clinically overt bleeding accompanied by one or more of the following findings: a decrease in the hemoglobin level of ≥ 20 g/L over a 24-hour period, transfusion of two or more units of packed red cells, bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding), or fatal bleeding[14]	Acute, clinically overt episodes, such as wound hematoma, bruising, GI bleeding, hemoptysis, hematuria, or epistaxis, that did not meet the criteria for major bleeding but were associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study drug, or discomfort or impairment of activities of daily life[9]

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.

Table A3. Bleeding Events by Primary Tumor Type

Primary Tumor Type	No. (%)					
	Dalteparin			Rivaroxaban		
	Total	Major Bleeds	CRNMB	Total	Major Bleeds	CRNMB
Total patients	203	6 (3)	7 (3)	203	11 (5)	25 (12)
Bladder	4 (2)	0	1 (25)	10 (5)	1 (10)	5 (50)
Brain	2 (1)	0	0	1 (1)	0	1 (100)
Breast	20 (10)	1 (5)	0	20 (10)	0	2 (10)
Cancer unknown primary	3 (2)	0	0	3 (1)	0	0
Chronic lymphoid leukemia	2 (1)	0	0	1 (1)	0	0
Colorectal	47 (23)	4 (9)	1 (2)	55 (27)	4 (7)	6 (11)
Gallbladder	2 (1)	0	0	2 (1)	0	0
Gastric	7 (3)	0	0	4 (2)	0	0
Gynecologic	7 (3)	0	0	6 (3)	0	0
Kidney	5 (3)	0	0	2 (1)	0	0
Lung	25 (12)	0	2 (8)	22 (11)	1 (5)	2 (9)
Lymphoma	12 (6)	0	0	11 (5)	0	2 (18)
Multiple myeloma	3 (2)	0	0	2 (1)	0	0
Esophageal/gastroesophageal	19 (9)	1 (5)	0	11 (5)	4 (36)	0
Ovarian	18 (9)	0	2 (11)	12 (6)	0	3 (25)
Pancreatic	11 (5)	0	0	19 (9)	0	1 (5)
Prostate	8 (4)	0	1 (13)	13 (7)	0	1 (8)
Sarcoma	0	0	0	2 (1)	0	1 (50)
Other*	5 (3)	0	0	6 (3)	1 (20)	1 (20)
Unknown	3 (2)	0	0	1 (1)	0	0

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.
*Other cancers: anal cancer with major bleed (n = 1); sacral chordoma with CRNMB (n = 1). Patients with CNS tumors (n = 3).

Table A4. SELECT-D Participating Site Teams

Participating Site	Team Members
Basingstoke and North Hampshire Hospital	Jackie Smith, Charlotte Rees
Bradford Royal Infirmary	Janet Bunch, Victoria Drew, Vickie Hawkins, Sam Ackroyd
Bristol Haematology and Oncology Centre	Kay Drury, Jack Teasdale, Vivek Mohan
Castle Hill Hospital	Ceri Fuller, Karen Shepherd, Georgios Bozas
Chelsea and Westminster Hospital	Laletha Agoramoorthy, Thomas Newsom-Davis
Christie Hospital	Jonathan Archer, Jurjees Hasan
Churchill Hospital	Christopher Deane, Nicola Curry
Countess of Chester Hospital	Elizabeth Gallimore, Dale Vimalachandran
County Durham and Darlington National Health Service (NHS) Foundation Trust	Andrea Kay, Susan Wadd, Natalie Picozzi
Ealing Hospital	Sheena Quaid, Olivia Hatcher
Furness General Hospital	Karen Burns, Sarah Moon
Guy's and St Thomas' NHS Foundation	Johanna Young, Beverley Hunt
Heartlands Hospital	James Whitehouse, Neil Smith
Hereford County Hospital	Janine Birch, Sara Willoughby
Hillingdon Hospital	Mariam Nasseri, Amy Guppy
Imperial College Healthcare NHS Trust	Amalia Saucan, Bhavesh Pratap, Alka Shah, Byiravey Pathmanathan, Noura Mohamed, Danielle Power
James Paget University Hospital	Wendy Harrison, Manzoor Mangi
Medway Maritime Hospital	Suzie Reyner, Vijayavalli Dhanapal
Milton Keynes Hospital	Hayley Moss, Sara Greig, Ijaz Mehdi
Mount Vernon Cancer Centre	Christine Brannan, Teresa Young, Marcia Hall
New Cross Hospital	Vanda Carter, Simon Grumett
Newcastle Upon Tyne Hospitals NHS Foundation Trust	Phil Hope, Sophie Alderson, John Hanley
Norfolk and Norwich University Hospital	Victoria License, Adele Cooper, Hamish Lyall
North Cumbria University Hospitals NHS Trust	Patricia Nicholls, Jonathan Nicoll
Northumbria Healthcare NHS Foundation Trust	Catherine Ashbrook-Raby, Charlotte Bomken
Poole Hospital	Louise Heckford, Tamas Hickish
Queen Alexandra Hospital	Sally Louise Evans, Sherilee Cook, Caroline Stemp, Ann O'Callaghan
Queen Elizabeth Hospital Gateshead	Helen Wild, Scott Marshall
Queen's Hospital Burton	Clare Mewies, Helena Cox, Manjusha Keni
Queen's Hospital Romford	Michelle McDonald, Jagadish Akula, Khalid Saja
Raigmore Hospital	Seonaid Arnott, Carol Macgregor
Royal Albert Edward Infirmary	Angela Power, Hiteshkumar Patel
Royal Bournemouth Hospital	Luke Vamplew, Taslima Rabbi, Tom Geldart
Royal Cornwall Hospital	Anne Griffiths, Anna Oakes, Nicholas Ashley, Duncan Wheatley
Royal Hampshire County Hospital	Elizabeth Happle, Katherine Lowndes
The Royal Marsden NHS Foundation Trust	Nadine Nadal, Helen Morgan, Mary Jane Lauigan, Katrin Sainudeen, Ian Chau
Royal Shrewsbury Hospital	Sally Potts, Abel Zachariah
Russells Hall Hospital	Angela Watts, Julie Matthews, Stephen Jenkins
Salisbury District Hospital	Julie Attlee, Louise Bell, Jonathan Cullis
South Tyneside District Hospital	Judith Moore, Ashraf Azzabi
Southport Hospital	Anna Morris, Helen Neville-Webbe
St George's Hospital	Pearl Quartey, James Uprichard
St Helens and Knowsley Teaching Hospitals NHS Trust	Nicola Hornby, David Taylor
St James's University Hospital	Sam Lotfi, Michael Snee
Sunderland Royal Hospital	Paula Newton, Vivienne Hullock, Ashraf Azzabi
University Hospital Coventry	Linda Wimbush, Ruth Manton, Oliver Chapman
Weston General Hospital	Harvey Dymond, Sandra Beech, Serena Hilman
Weston Park Hospital	Aisling Robinson, Jonathan Wadsley
Wexham Park Hospital	Julie-Ann Sinclair, Marcia Hall
Worcestershire Acute Hospitals NHS Trust	Alison Harrison, Hayley Hodson, Helen Tranter, Mark Churn

Abbreviation: SELECT-D, Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism

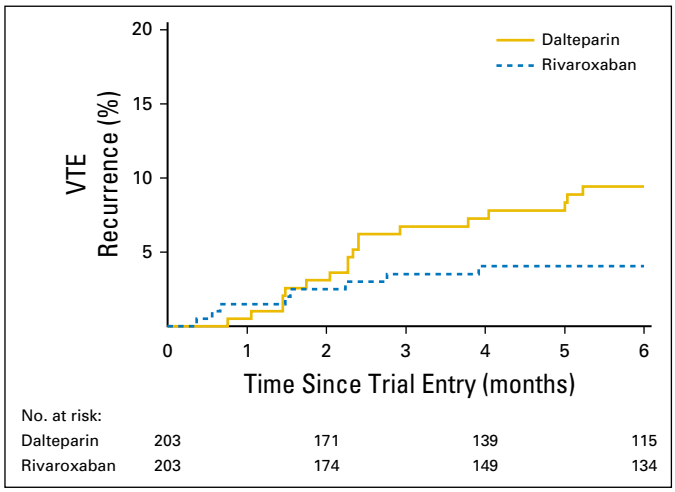

Fig A1. Competing risk analysis. The 6-month cumulative incidence for venous thromboembolism (VTE) recurrence, allowing for the competing risk of death, was 9% (95% CI, 6% to 14%) for dalteparin and 4% (95% CI, 2% to 7%) for rivaroxaban.

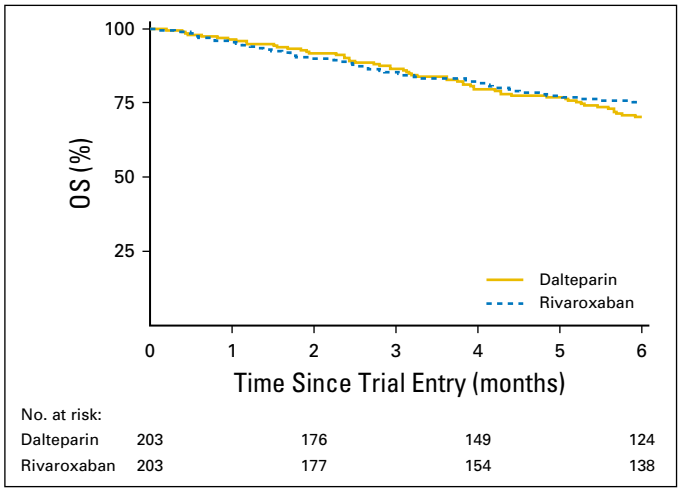

Fig A2. Overall survival (OS) within 6 months.