Received: 2 August 2019 | Accepted: 14 October 2019

DOI: 10.1111/jth.14662

ORIGINAL ARTICLE

Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial

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Funding information
The funding support for this trial was Bristol Myers Squibb/Pfizer Alliance.

Abstract

Background: Low-molecular-weight heparin is the guideline-endorsed treatment for cancer-associated venous thromboembolism (VTE). While apixaban is approved for the treatment of acute VTE, limited data support its use in cancer patients.

Objectives: The primary outcome was major bleeding. Secondary outcomes included VTE recurrence and a composite of major plus clinically relevant non-major bleeding (CRNMB).

Patients/Methods: Patients with cancer-associated VTE were randomly assigned to receive either apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for six months or subcutaneous dalteparin (200 IU/kg for one month followed by 150 IU/kg once daily).

Results: Of 300 patients randomized, 287 were included in the primary analysis. Metastatic disease was present in 66% of subjects; 74% were receiving concurrent chemotherapy. Major bleeding occurred in 0% of 145 patients receiving apixaban,

Abstract Presentation: American Society of Hematology Annual Meeting, December 2018

Trial registration number: NCT02585713

Manuscript handled by: Marc Carrier

Final decision: Marc Carrier 14 October 2019

compared with 1.4% of 142 patients receiving dalteparin [P = .138; hazard ratio (HR) not estimable because of 0 bleeding event in apixaban group]. Recurrent VTE occurred in 0.7% of apixaban, compared to 6.3% of dalteparin patients [HR 0.099, 95% confidence interval [CI], 0.013-0.780, P = .0281). Major bleeding or CRNMB rates were 6% for both groups.

Conclusions: Oral apixaban was associated with low major bleeding and VTE recurrence rates for the treatment of VTE in cancer patients.

KEYWORDS

apixaban, bleeding, cancer, dalteparin, venous thromboembolism

1 | INTRODUCTION

Venousthromboembolism (VTE) causes substantial morbidity and mortality in patients with cancer[1-3] Anticoagulant management is challenging for these patients because of an increased propensity for thrombosis recurrence and anticoagulant-associated major bleeding.[4,5] There have been a number of important treatment trials of cancer-associated VTE.[6-11] Most trials have compared vitamin K antagonists with low-molecular-weight heparin (LMWH) and, generally, have shown similar major bleeding and mortality rates. One trial showed a significant reduction of VTE recurrence rates, in favor of dalteparin.[6] Two contemporary trials have compared direct oral anticoagulants, edoxaban, and rivaroxaban, with LMWH in this context.[10,11] Recent guidance/guideline statements have recommended the use of specific direct oral anticoagulants (edoxaban or rivaroxaban) for patients with cancer-associated VTE treatment in the context of low risk of major bleeding and absent drug interactions.[12-14] For patients with an increased bleeding risk, such as intact gastrointestinal and genitourinary cancers or other conditions at risk of bleeding, LMWH remains the preferred anticoagulant.[12]

The disadvantages of LMWH include patient discomfort, cost, lack of a complete antidote, inability to use in severe renal impairment, and thrombocytopenia, with concerns for both bleeding and thrombosis related to heparin-induced thrombocytopenia.

Apixaban, an oral direct factor Xa inhibitor, impairs coagulation by inhibiting the activation of prothrombin to thrombin. A trial, primarily involving non-cancer patients with acute VTE, found that apixaban carries similar efficacy compared to enoxaparin/warfarin with superior safety.[15] Similarly, trials of apixaban in atrial fibrillation have shown good efficacy with superior safety, compared to either warfarin or aspirin.[16,17]

The current trial is a multicenter, randomized, open-label superiority trial that was designed to test the hypothesis that apixaban is associated with a significantly lower rate of major bleeding, compared to dalteparin, in the treatment of patients with active cancer and confirmed acute VTE.

Essentials

- Apixaban is approved for the treatment of acute VTE; however, limited data support its use in cancer patients.
- Patients with acute cancer-associated VTE were randomly assigned to receive apixaban or dalteparin for six months.
- For VTE treatment in cancer, apixaban has good bleeding and VTE recurrence rates compared to dalteparin.
- Oral apixaban had better anticoagulation-related quality-of-life outcomes compared to parenteral dalteparin.

2 | METHODS

The rationale and design of this randomized, open-label, investigator-initiated trial have been published.[18] The primary investigator, in collaboration with the Academic and Community Cancer Research United (ACCRU) research consortium, was responsible for the trial design, protocol development, data collection, statistical analysis, data interpretation, manuscript preparation, and trial oversight. Institutional review boards at each participating center approved the protocol.

2.1 | Patients

Patients, 18 years or older, were eligible for participation if they had confirmed active cancer, defined as any evidence of cancer on cross-sectional or positron emission tomography imaging, metastatic disease, and/or cancer-related surgery, chemotherapy, or radiation therapy within the prior six months. The qualifying thrombus could be an acute lower extremity or upper extremity (jugular, innominate, subclavian, axillary, brachial) deep vein thrombosis (DVT), pulmonary embolism, splanchnic (hepatic, portal, splenic, mesenteric, renal, gonadal), or cerebral vein thrombosis confirmed by appropriate cross-section imaging. Patients had to have a life expectancy exceeding 60 days and an Eastern Cooperative Oncology Group (ECOG) performance status

of 2 or less. Required laboratory criteria included a platelet count ≥50 000/μL, liver function tests (aspartate aminotransferase or alanine aminotransferase) <3-fold the upper limit of normal, international normalized ratio ≤ 1.6, a calculated creatinine clearance ≥30 mL/min using the Cockcroft-Gault formula, and a negative serum or urine pregnancy test result for women of childbearing potential.

Patients were excluded from participating if they had received anticoagulant therapy for more than seven days prior to randomization, active bleeding, severe liver disease (known cirrhosis Childs Pugh class B or C) or kidney disease (calculated creatinine clearance must be <30 mL/min), known anticoagulant failure, or prior heparin-induced thrombocytopenia. Patients with brain metastasis were not excluded from trial participation. All patients provided written informed consent for trial participation.

2.2 | Randomization and trial treatment

Patients were randomized at a 1:1 ratio to receive either apixaban or dalteparin.[18] Randomization was performed using an established interactive Web-based system that is used for all clinical trials conducted through the Mayo Clinic Cancer Center and through the ACCRU infrastructure. The dynamic allocation algorithm was used to ensure a balance in marginal distributions of the stratification factors between treatment arms. Stratification factors used in the randomization process included cancer status and venous thromboembolism risk using the Khorana score.[19] Patients randomized to apixaban received 10 mg twice daily for seven days followed by 5 mg twice daily. Those assigned to dalteparin received weight-based subcutaneous therapy at 200 IU/kg once daily for the first month followed by 150 IU/kg for months 2 through 6. A dose-rounding schedule was provided in order to accommodate prefilled syringes (Table S1). Dosing was based on actual body weight with no upper dose limit. Both therapies were to be continued for six months.

2.3 | Temporary anticoagulation adjustment or interruption

For patients requiring an invasive procedure, apixaban was withheld for 48 h for high-bleeding-risk and 24 h for non-high-bleeding-risk procedures.[18,20,21] For patients receiving dalteparin, the last dose was to be reduced to 100 IU/kg and given on the morning of the day prior to the procedure date. Post procedure, DVT prophylaxis was recommended, the first prophylactic dose to be given 24 h after the procedure. Therapeutic anticoagulation was withheld until adequate hemostasis was confirmed and at least 72 hours post procedure.

Each month, patients were evaluated for body weight, platelet count, and creatinine clearance given the impact of these variables on anticoagulant management. For patients receiving dalteparin, a >10% change in body weight triggered a dose adjustment. For patients who developed acute kidney injury (creatinine clearance 15-30 mL/min), dalteparin dosing was reduced by 50% until recovery. For severe kidney injury (creatinine clearance < 15 mL/min) dalteparin was held until recovery. Apixaban dosing was not adjusted during acute kidney injury. For moderate thrombocytopenia (25 000-50 000/μL), dalteparin and apixaban dosing were reduced to prophylaxis doses. For severe thrombocytopenia (<25 000/μL), anticoagulants were held until recovery. For patients requiring a strong CYP3A4 and/or P-glycoprotein inhibitors, apixaban was reduced to 2.5 mg twice daily. The use of strong CYP3A4 inducers was an exclusion criterion for study participation.

2.4 | Outcome measures

The primary safety endpoint included any episode of major bleeding. Major bleeding was defined as overt bleeding plus a hemoglobin decrease of ≥2 g/dL; or transfusion of ≥2 units of packed red blood cells; or intracranial, intraspinal/epidural, intraocular, retroperitoneal, pericardial, intraarticular, intramuscular with compartment syndrome, or fatal bleeding.[22] Clinically relevant non-major bleeding (CRNMB) was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with the health care team, or temporary anticoagulant cessation.[23] Minor bleeding was defined as overt bleeding not meeting criteria for major bleeding or CRNMB. The secondary safety endpoint included a composite of major bleeding and CRNMB.

The secondary efficacy endpoint was any thromboembolic recurrence including DVT, pulmonary embolism (PE), fatal PE, or arterial thromboembolism.[18] A recurrent DVT had to be confirmed by duplex ultrasonography, venography, CT, or MRI. A recurrent PE was confirmed by CT, MR, conventional pulmonary angiography, or VQ imaging. A fatal PE had to be based on objective diagnostic testing, autopsy, or death that could not be attributed to a documented cause and for which PE/DVT could not be ruled out (unexplained death). Incidental VTE recurrence had to be identified on surveillance-related imaging. In order to be classified as a recurrent event, there had to be a new filling defect evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution. An arterial thromboembolism could include myocardial infarction, stroke, transient ischemic attack, or peripheral arterial embolism. Major bleeding and thrombotic events were centrally adjudicated without knowledge of the patient treatment assignment.

2.5 | Surveillance and follow-up

Patients were followed for six months. At monthly intervals, patients underwent either an in-person clinical assessment or a scripted telephone interview to determine interval bleeding or thromboembolic outcomes. Each visit included a standardized assessment of ECOG status, adverse event recording, medication reconciliation, and study drug compliance. Monthly complete blood count, liver function testing, and creatinine were assessed. Patients were instructed using a standardized approach to report symptoms suggestive of

recurrent VTE or bleeding. Appropriate diagnostic imaging and laboratory testing were reviewed for suspected outcome events.

To determine the impact of the two anticoagulation strategies on quality of life, subjects completed a monthly modified Duke Anticoagulation Satisfaction Scale (DASS) instrument (Table S2).[24] In addition, each subject was asked to rate the extent of bruising on a Likert scale (Table S3).

2.6 | Statistical considerations

The trial hypothesis was that apixaban was associated with a significantly lower rate of major bleeding, compared to dalteparin, in the treatment of cancer-associated acute VTE. All patients receiving at least one dose of either apixaban or dalteparin were included in the primary analysis. The study was designed as a superiority trial with 80% power at a one-sided type I error rate of 0.05 to detect a difference in major bleed rate, assuming a six-month cumulative incidence of 6% in the dalteparin arm and 1.4% in the apixaban arm (assuming time to major bleed follows an exponential distribution, these assumptions correspond to a HR of 0.22). The anticipated rates of major bleeding for the dalteparin arm were taken from published randomized trials and a registry of patients with cancer-associated VTE available at the time of trial design.[6,25,26] In the absence of published data specific to cancer patients, major bleeding for the apixaban arm was derived by combining rates from the entire AMPLIFY cohort (0.6%) with a metaanalysis of VTE treatment trials assessing direct oral anticoagulants limited to subjects with underlying cancer (apixaban arm, 2.2%).[15,27] Sample sizes, power estimates, and hazard ratios have been calculated with EAST 6.3 (Cytel Inc). On the basis of these assumptions, a sample size of 300 patients (150 per arm) was required.

The analysis of major bleeding included events occurring during treatment or within seven days of discontinuation. The incidence of major bleeding was estimated using the cumulative incidence function, treating death without major bleeding as the competing risk. Time to major bleeding was the interval from randomization to first major bleed or death, whichever occurred first. The log-rank test was used to compare major bleeding between apixaban and dalteparin. A secondary analysis of the primary safety endpoint was performed in the intention-to-treat patient population using similar methods described for the primary analysis. Analysis of the secondary efficacy endpoint of venous thrombosis recurrence was conducted using these same methods. Responses to patient questionnaires were summarized by arm. Categorical responses were compared using the chi-square test.

3 | RESULTS

3.1 | Patients and treatment

The study was opened from 20 November 2015 to 2 October 2017. Twenty-eight U.S. sites participated (Table S5). Three hundred patients were enrolled/randomized; 150 were allocated to each study arm. The stratification factors were well balanced between treatment arms including the presence of residual disease and Khorana scores. Thirteen patients (five in the apixaban arm and eight in the dalteparin arm) did not start their treatment and were excluded from the primary analysis (Figure 1). Baseline characteristics are shown in

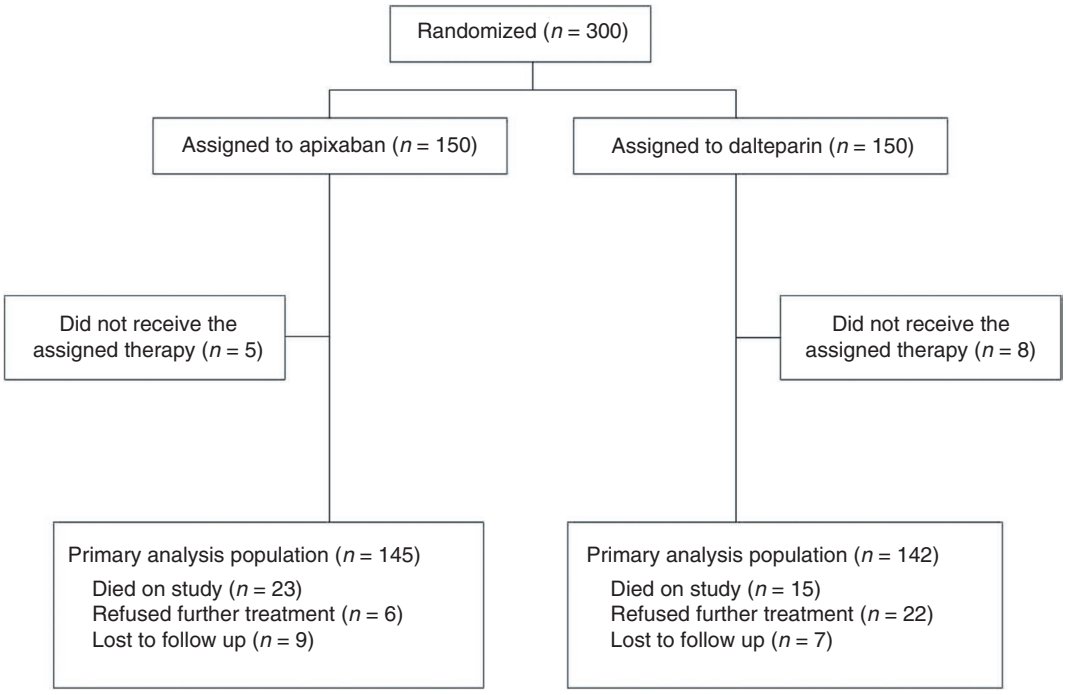

FIGURE 1 Consort diagram. The intention-to-treat analysis defined included all the patients who had undergone randomization and received at least one dose of the assigned treatment

TABLE 1 Baseline demographics and clinical characteristics by treatment arm

	Apixaban (N = 150)	Dalteparin (N = 150)	P value
Age (years)	64.4 (11.3)	64.0 (10.8)	.4857
Female gender (%)	78 (52.0%)	77 (51.3%)	.9080
Creatinine clearance 30-50 mL/min, n (%)	14 (9.3%)	14 (9.3%)	1.0000
Platelet count 50-100 000/mm^3, *n* (%)	10 (6.7%)	13 (8.7%)	.5150
Body weight, mean (SD)	84.8 (23.2)	86.8 (20.5)	.1712
<60 kg, *n* (%)	19 (12.9%)	13 (8.8%)	.2528
>120 kg, *n* (%)	10 (6.8%)	8 (5.4%)	.6161
Qualifying thrombus *n*, (%)			
Any pulmonary embolism (PE)	81 (55.1%)	75 (50.7%)	.4463
Any deep vein thrombosis (DVT)	71 (48.3%)	70 (47.3%)	.8632
PE only	64 (43.5%)	57 (38.5%)	.3804
PE with DVT	17 (11.6%)	18 (12.2%)	.8739
DVT only	54 (36.7%)	52 (35.1%)	.7747
Lower extremity DVT	46 (31.3%)	50 (33.8%)	.6479
Upper extremity DVT	25 (17.0%)	21 (14.2%)	.5048
Cerebral VT	2 (1.4%)	0 (0.0%)	.1545
Splanchnic VT	12 (8.2%)	27 (18.2%)	.0106
Missing	3 (2.0%)	2 (1.4%)	
Anticoagulated prior to randomization, *n* (%)	89 (60.5%)	82 (55.4%)	.3713
ECOG score			
0	60 (40.0%)	62 (41.3%)	.3199
1	70 (46.7%)	76 (50.7%)	
2	20 (13.3%)	12 (8.0%)	
Distant metastasis	96 (65.3%)	97 (66.0%)	.9906
Concurrent systemic cancer therapy	108 (73.5%)	110 (74.3%)	.8672
Solid tumor *n* (%)			
Brain	3 (2.0%)	5 (3.4%)	.2566
Breast	16 (10.9%)	12 (8.1%)	
Colorectal	18 (12.2%)	29 (19.6%)	
Ears, nose, and throat	3 (2.05)	1 (0.7%)	
Genitourinary	13 (8.7%)	14 (9.3%)	
Gynecologic	14 (9.5%)	15 (10.1%)	
Lung	32 (21.8%)	19 (12.8%)	
Melanoma	0 (0.0%)	4 (2.7%)	
Neuroendocrine	2 (1.4%)	3 (2.0%)	
Pancreatic/hepatobilliary	23 (15.6%)	24 (16.2%)	
Sarcoma	3 (2.0%)	1 (0.7%)	
Thyroid	0 (0.0%)	1 (0.7%)	
Upper gastrointestinal	7 (4.8%)	4 (2.7%)	
Other	0 (0.0%)	1 (0.7%)	
Hematologic malignancy *n* (%)			
Leukemia	1 (0.7%)	3 (2.0%)	.7051
Lymphoma	10 (6.8%)	6 (4.1%)	
Multiple myeloma	2 (1.4%)	5 (3.4%)	
Other	0 (0.0%)	1 (0.7%)	
Previous venous thrombosis	8 (5.4%)	12 (8.1%)	.3625
Family history of thrombosis	3 (2.0%)	7 (4.8%)	.1981
Recent hospitalization (within 3 months)	68 (46.3%)	61 (41.2%)	
Recent surgery (within 3 months)	24 (16.3%)	37 (25.0%)	.0659
Race			
White	140 (93.3%)	138 (92.0%)	.2618
Black or African American	6 (4.0%)	11 (7.3%)	
Asian	2 (1.3%)	0 (0.0%)	
American Indian or Alaska Native	1 (0.7%)	0 (0.0%)	
Not reported: patient refused or not available	0 (0.0%)	1 (0.7%)	
Unknown: patient unsure	1 (0.7%)	0 (0.0%)	
Ethnicity			
Hispanic or Latino	1 (0.7%)	0 (0.0%)	.2611
Non-Hispanic	146 (97.3%)	147 (98.0%)	
Not reported	2 (1.3%)	0 (0.0%)	
Unknown	1 (0.7%)	3 (2.0%)	
Prior miscarriage	7 (4.9%)	5 (3.5%)	.7282
Trauma (within 3 months)	3 (2.0%)	3 (2.0%)	.9933
Tumor status			
Resected with no residual	16 (10.9%)	18 (12.5%)	.8428
Resected with known residual	36 (24.5%)	40 (27.8%)	
Unresected	78 (53.1%)	72 (50.0%)	
Recurrent	17 (11.6%)	14 (9.7%)	
Missing	3 (2%)	6 (4%)	

Table 1. A little more than half of randomized patients had a pulmonary embolism as the qualifying VTE. For those patients randomized to the apixaban arm, 86 (60.1%) patients received LMWH prior to starting apixaban. For those pretreated with LMWH, the mean duration of treatment prior to starting study drug was 3.6 days.

3.2 | Primary outcome

The median treatment duration was 5.78 months for apixaban and 5.65 months for dalteparin groups. The primary outcome of major bleeding up to six months occurred in 0 of 145 patients (0%) assigned

to apixaban [95% CI not estimable (NE) and 2 of 142 patients (1.4%) (95% CI, 0.6%-6.6%) assigned to dalteparin (*P* = .138; HR and 95% CI not estimable because of no bleeding event in the apixaban arm] (Table 2). The major bleeding events in the dalteparin arm included one retroperitoneal and one intracranial bleed. Both major bleeds events occurred while on treatment. The time to the occurrence of primary-outcome events is shown in Figure 2. The results remained the same for an intention-to-treat analysis, where all 300 randomized patients were included in the analysis (Figure S2 and S3).

3.3 | Secondary outcomes

The secondary composite efficacy endpoint included the combined outcomes of venous and arterial thromboembolism. Recurrent VTE occurred in one patient (0.7%) in the apixaban group and nine (6.3%) in the dalteparin group (difference in risk −5.6 percentage points; HR0.099, 95% CI, 0.013-0.780, *P* = .0281) (Table 2). Six of the VTE events occurred on treatment. The remaining four occurred within three days of going off treatment. Of the recurrent VTE events, five were symptomatic. There was one arterial thrombosis in each treatment group. These events occurred in patients who also suffered concurrent venous thrombi and were thus already accounted for.

For the secondary composite bleeding endpoint (major or CRNMB), nine (6%) patients in each arm had an event, with a HR of 0.931, 95% CI, 0.43-2.02, *P* = .88 (Table 2). The time to the occurrence of secondary-outcome events is shown in Figure 3.

There were 23 deaths (16%) in the apixaban arm and 15 deaths (11%) in the dalteparin arm, HR 1.40 (95% CI, 0.82-2.43, *P* = .3078). There were no deaths attributed to either major bleeding or thromboembolism.

The qualifying thrombus for trial inclusion was an upper extremity, splanchnic, or cerebral vein thrombotic event in 87 patients (29%; Table 1). Of the two patients in the dalteparin arm with major bleeding, the qualifying thrombus was an upper extremity DVT in one patient. Of the nine dalteparin-treated patients with recurrent VTE, the qualifying thrombus was splanchnic vein thrombosis in three patients. The qualifying thrombus for the VTE recurrence in the apixaban arm was a lower extremity DVT.

During the trial, there were 83 invasive procedures performed (45 in the apixaban group and 38 in the dalteparin group). Of these, 36 (43%) were considered major surgeries. Within the 30-day interval following the procedures, there were no VTE or major bleeding events.

3.4 | Quality of life assessment

At baseline, there were no significant differences in any of the questions comparing the two treatment arms (Table 3). By the first month, excess bruising, stress, worry and irritation, difficulty, burden, and frustration taking anticoagulants were all significantly higher for those patients randomized to receive dalteparin. Overall burden and negative impact on overall quality of life

TABLE 2 Clinical outcomes during treatment period

	Apixaban (N = 145)	Dalteparin (N = 142)	Hazard ratio (95% CI)	P value
Primary safety endpoint				
Major bleed	0 (0.0)	2 (1.4)	0.0 (0.0-)	.138
Secondary safety endpoint				
Bleeding *n* (%)				
Clinically relevant non-major bleed	9 (6.2)	7 (4.2)		
Major plus CRNMB	9 (6.2)	9 (6.3)		.8816
Secondary efficacy endpoint*				
Venous thromboembolism *n* (%)	1 (0.7%)	9 (6.3%)	0.099 (0.013-0.78)	.0281
Pulmonary embolism	0 (0.0)	1 (0.7%)		
Lower extremity DVT	0 (0.0)	4 (2.8%)		
Upper extremity DVT	0 (0.0)	2 (1.4%)		
Splanchnic VT	0 (0.0)	2 (1.4%)		
Cerebral VT	1 (0.7%)	0 (0.0%)		
Arterial thrombosis *n* (%)	1 (0.7%)	1 (0.7%)		
Mortality *n* (%)	23 (16)	15 (11)		.3078

Abbreviations: CI, confidence interval; CRNMB, clinically relevant non-major bleeding; DVT, deep vein thrombosis; VT, vein thrombosis.

*Arterial thrombotic events occurred in patients suffering concurrent VTE and were thus already accounted for.

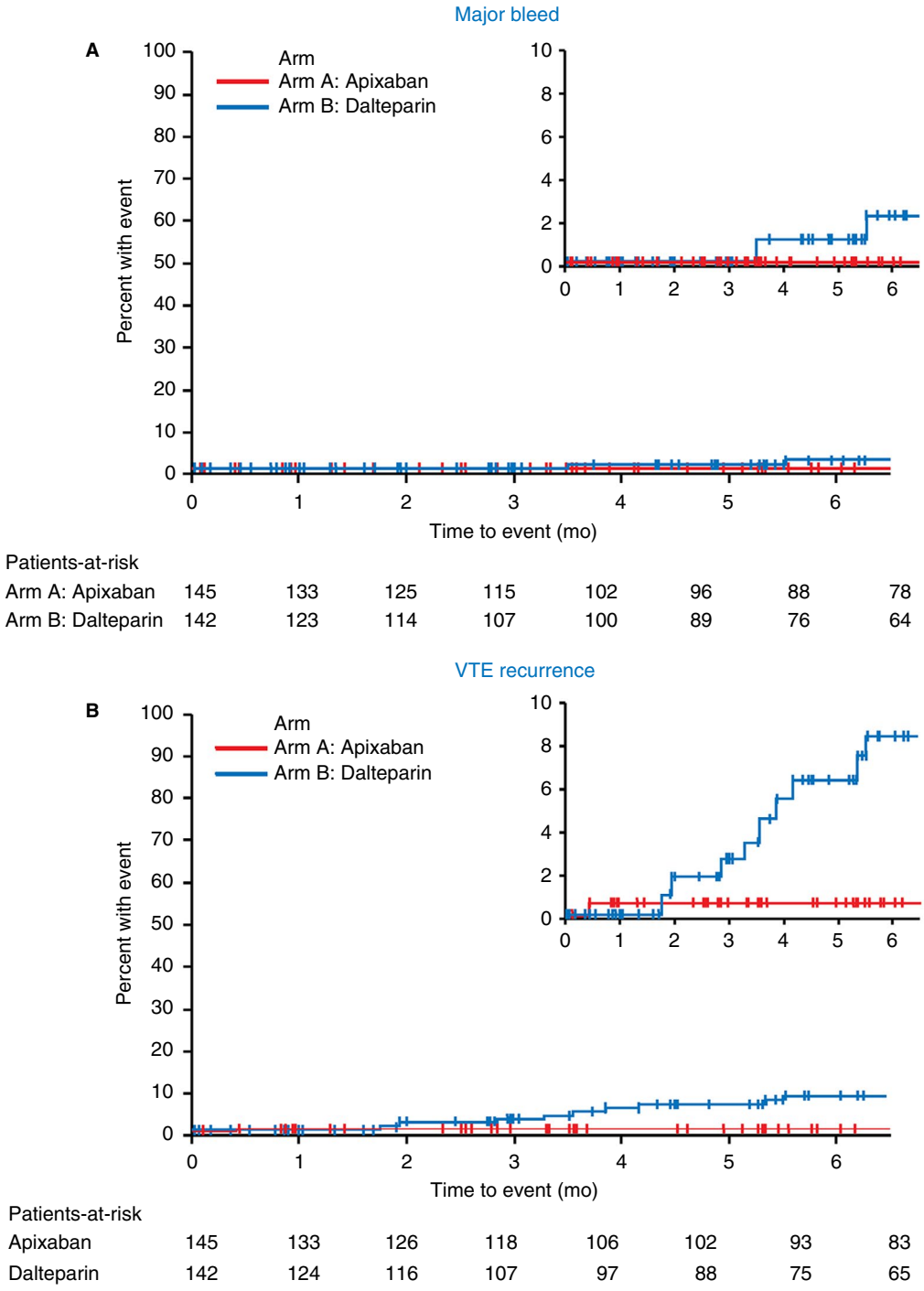

FIGURE 2 Major bleeding and venous thromboembolism recurrence. Panel A, The primary outcome was major bleeding. Panel B, The secondary efficacy outcome was the cumulative incidence of recurrent venous thrombosis. The inset of both panels shows the same data on an enlarged *y* axis

also were significantly higher for dalteparin subjects. Measures of confidence, that the anticoagulant would protect the individual's health, favored dalteparin at month 1. Overall satisfaction with their anticoagulant favored the apixaban arm. Bruising, reported on a Likert scale (0-10), also favored apixaban at all time intervals ($P < .002$).

During the trial, there were patients in both arms who refused further treatment (Figure 1). More patients randomized to dalteparin stopped therapy relative to the apixaban arm (22 vs. 6; $P = .0012$; Table S4, Figure S1).

4 | DISCUSSION

The CLOT trial remains the milestone of cancer-associated VTE therapy, against which contemporary trials have been compared.[6] There

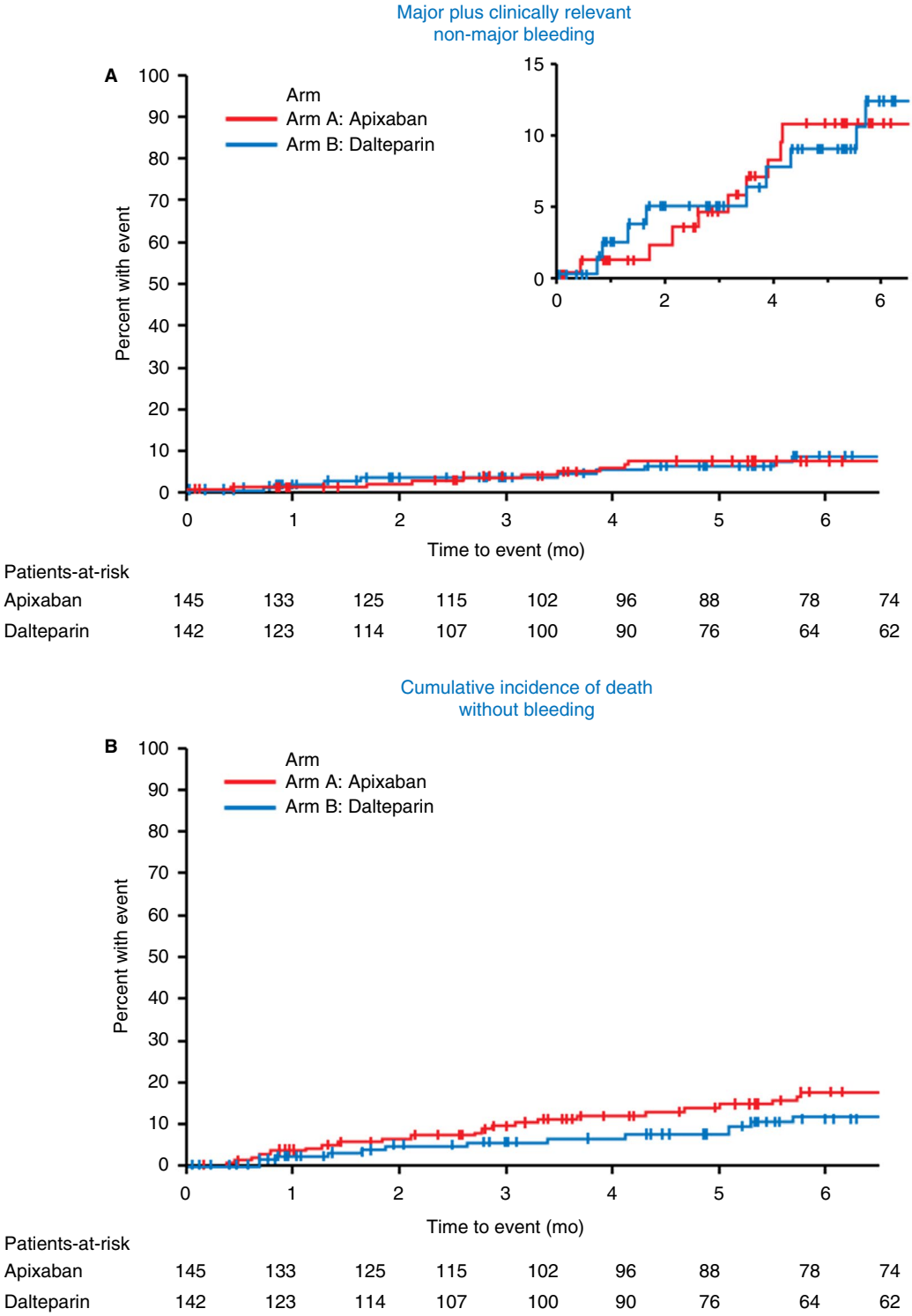

FIGURE 3 Major plus clinically relevant non-major bleeding and mortality. Panel A, The secondary safety outcome was the cumulative incidence major bleeding or clinically relevant non-major bleeding. Panel B, Overall mortality at six months is provided. The inset for panel A shows the same data on an enlarged *y* axis

are now three trials, including the present one, to support the hypothesis that the direct oral anticoagulants provide a promising alternative to LMWH for these patients.[10,11] Striking a balance between the quest for improved efficacy and maintaining safety remains a priority. In the current trial, bleeding rates for apixaban-treated cancer patients were low and compared favorably to HOKUSAI VTE Cancer and SELECT-D.[10,11] Major bleeding was similar to that reported for patients without cancer. In the AMPLIFY trial, which enrolled primarily non-cancer patients, published rates of major and CRNMB rates for apixaban treatment were 0.6% and 4.3%, respectively.[15]

TABLE 3 Quality of life survey

Cycle*	Fear of bleeding limited participation in vigorous activities	Fear of bleeding limited participation in activities of daily life	Concern for excessive bruising	Limited my diet	Added stress to my life	Was difficult to carry out	Caused me a great deal of worry	Caused me a great deal of irritation	Caused me a great deal of frustration	Was a burden to me	Negatively impacted my quality of life	Confidence that the drug protected me from clots	I am satisfied with my blood thinner
0	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
1	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors dalteparin	Favors apixaban
2	Neutral	Neutral	Neutral	Neutral	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Favors apixaban	Neutral	Neutral	Favors apixaban
3	Neutral	Neutral	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban
4	Neutral	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban
5	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Neutral
6	Neutral	Neutral	Favors apixaban	Neutral	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Favors apixaban	Neutral	Neutral	Neutral

Note: Yellow highlighted boxes pictorially denote "Favors Apixaban." Red highlighted boxes denote "Favors Dalteparin." White boxes denote those questions where there were no significant differences between arms.

*The designation of "Favors" was applied when differences reached a P value < .05.

Given the efficacy and safety data now available, guidance/guideline statements now recommend the use of specific direct oral anticoagulants for this indication.[12-14]

Determining the role of direct oral anticoagulants in the treatment of acute VTE in cancer patients requires a growing dataset of comparable trials. For this purpose, there are important similarities across these three cancer trials with direct oral anticoagulants. First, the clinical characteristics of participating patients were similar. Metastatic disease at presentation was comparable for the current trial (65.3%), HOKUSAI VTE Cancer (52.5%), and SELECT-D (58%); concurrent chemotherapy use was similar (73.5%, 71%, and 72%, respectively). Tumor types were also similar, with colorectal, lung, pancreas, and gynecologic cancers representing prevalent cancer types for each trial. Second, pulmonary embolism was a qualifying event in more than half of subjects in each of these trials. Leg DVT constituted the majority of the remainder of the qualifying events for each trial. Third, each trial included dalteparin as a common comparator LMWH. Bleeding complications in the dalteparin arm were comparable across these three trials.[10,11]

In order to mimic real-world oncology practices, the current trial permitted enrollment of patients with thrombosis involving the upper extremity deep veins, splanchnic veins, and cerebral venous sinuses. In a recent study, acute VTE involving these locations represented >40% of subjects with active cancer. Sensitivity analyses suggested that these patients had similar study outcomes to those with proximal DVT and PE.[28] In the current study, one-third of the recurrent VTE in the dalteparin arm involved patients with splanchnic vein thrombosis as the qualifying thrombus for study enrollment. Despite this broad sampling, the VTE recurrence rates for dalteparin-treated patients in the current study were similar to those reported for previous trials (range 6%-10.5%). In the HOKUSAI Cancer VTE trial, recurrent VTE occurred in 7.9% of edoxaban-treated patients and 11.3% in the dalteparin arm.[10] In the SELECT-D trial, rates were 4% for rivaroxaban and 11% for dalteparin groups.[11] In the current trial, recurrent VTE rates were significantly lower for patients receiving apixaban compared to dalteparin.

Mortality rates did not differ significantly by treatment arm (apixaban 16% vs. dalteparin 11%; P = .31). There were no deaths related to either recurrent thromboembolism or major bleeding. The observed mortality rates were not anticipated, on the basis of tumor type and stage, with two-thirds of subjects having metastatic disease. This study was not powered to determine survival differences. To date, there have been no treatment trials of cancer-associated acute VTE that have shown a survival advantage based on anticoagulant assignment.[6-11] Loss of subjects to death undermines the accumulation of bleeding and thrombotic events and underscores the complexity of designing clinical trials in this population. Indeed, the competing risks of early mortality may have influenced the primary and secondary outcomes of this and other similar trials.

A unique aspect of the current trial included a prescribed approach to periprocedural anticoagulation management.[18-20] Implementation of this strategy yielded successful periprocedural

management for 83 subjects, without major bleeding or thromboembolic complications.

An important feature of this current study are the monthly anticoagulation satisfaction and bruise surveys. By the first month, there were a number of features that favored oral apixaban over parenteral dalteparin therapy. Parenteral therapy added stress, anxiety, and frustration to overall anticoagulant management and negatively impacted overall quality of life. As such, patients assigned to dalteparin were 3-fold more likely to abandon therapy, compared to those assigned apixaban. Given the increasing emphasis on shared decision making, these data may be useful when discussing treatment options with patients. The burden of cancer and associated treatment alone can be overly challenging for patients and their families. Anticoagulation delivery need not be onerous in order to impact positively outcomes that can only be realized if patients continue to take the medication. As such, providing an oral alternative to parenteral therapy has the potential to improve compliance and outcomes.

There are several noteworthy trial limitations. First, the sample was relatively small, at 300 total patients. Thirteen patients did not receive study medications, in part because of dissatisfaction with study drug allocation. This sample size was based on a power calculation using assumptions for major bleeding for dalteparin and apixaban. The study did not meet its predefined primary outcome because of the lower-than-anticipated major bleeding rates for both treatment arms. The VTE recurrence and mortality rates were also lower than anticipated for both arms. The reasons for these low event rates are unclear and not clearly explained by cancer characteristics. Second, there was 6% patient loss (16/300) to follow-up. Third, the study included fewer patients with upper gastrointestinal malignancy compared to the HOKUSAI Cancer VTE trial.[10] While patients with upper GI malignancy were neither excluded nor discouraged from trial participation, this finding may have influenced the major bleeding rates.

These trial results, when combined with HOKUSAI and SELECT D, add support to the hypothesis that direct oral anticoagulants provide a safe and effective alternative to LMWH for cancer patients with acute VTE. Results of the ongoing CARAVAGGIO trial, which has a similar design yet larger patient sample, are eagerly awaited for the continued test of this hypothesis.

ACKNOWLEDGMENTS

This work was supported by a grant from the Bristol Myer Squibb Pfizer Alliance.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

RDM, WEW, JGLR, and CLL designed the research methods; RDM, WEW, JGLR, TZ, AA, AT, UP, DA, KG, CK, JPB, RALF, SH, CJL, DEH, PV, and CLL helped with patient recruitment. RDM, WEW, JGLR, TZ, and CLL analyzed the results and made significant contributions to the initial manuscript draft. RDM, WEW, JGLR, TZ, AA, AT, UP, DA, KG, CK, JPB, RALF, SH, CJL, DEH, PV, and CLL analyzed the results and made critical revisions to the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: McBaneRII, WysokinskiWE, LeRademacherJG, et al Apixaban and dalteparin in active malignancy associated venous thromboembolism: The ADAM VTE trial*J Thromb Haemost*2020;18:411–421. https://doi.org/10.1111/jth.14662