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Early Time Courses of Recurrent Venous Thromboembolism and Bleeding during Apixaban or Dalteparin Therapy for Patients with Cancer

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Abstract

Background In patients with acute venous thromboembolism (VTE), the rates of recurrence and major bleeding are highest during the first weeks of anticoagulation. The CARAVAGGIO trial demonstrated noninferiority of apixaban to dalteparin for treatment of cancer-associated VTE without an increased risk of major bleeding. We compared the early time course of VTE recurrence and major bleeding events of apixaban compared with dalteparin at 7, 30, and 90 days of treatment in patients with cancer-associated VTE.

Methods The study design of the CARAVAGGIO trial has been described. Eligible patients were randomly assigned to receive monotherapy with either apixaban or dalteparin for 6 months. The primary efficacy outcome was the incidence of objectively confirmed recurrent VTE. The primary safety outcome was major bleeding.

Results In 1,155 patients, recurrent VTE after 7, 30, and 90 days occurred in 6 (1%), 15 (2.6%), and 27 (4.7%) patients in the apixaban arm versus 5 (0.9%), 20 (3.5%), and 36 (6.2%) patients respectively in the dalteparin arm. By day 7, 30, and 90, major bleeding events had occurred in 3 (0.5%), 9 (1.6%), and 16 (2.8%) patients in the apixaban group versus 5 (0.9%), 11 (1.9%), and 17 (2.9%) patients in the dalteparin group.

Conclusion The frequencies of recurrent VTE and major bleeding events at 7, 30, and 90 days of apixaban compared with dalteparin were similar in patients with cancer-associated VTE. This supports the use of apixaban for the initiation and early phase of anticoagulant therapy in cancer-associated VTE.

Keywords
- anticoagulants
- bleeding
- cancer
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- thrombosis

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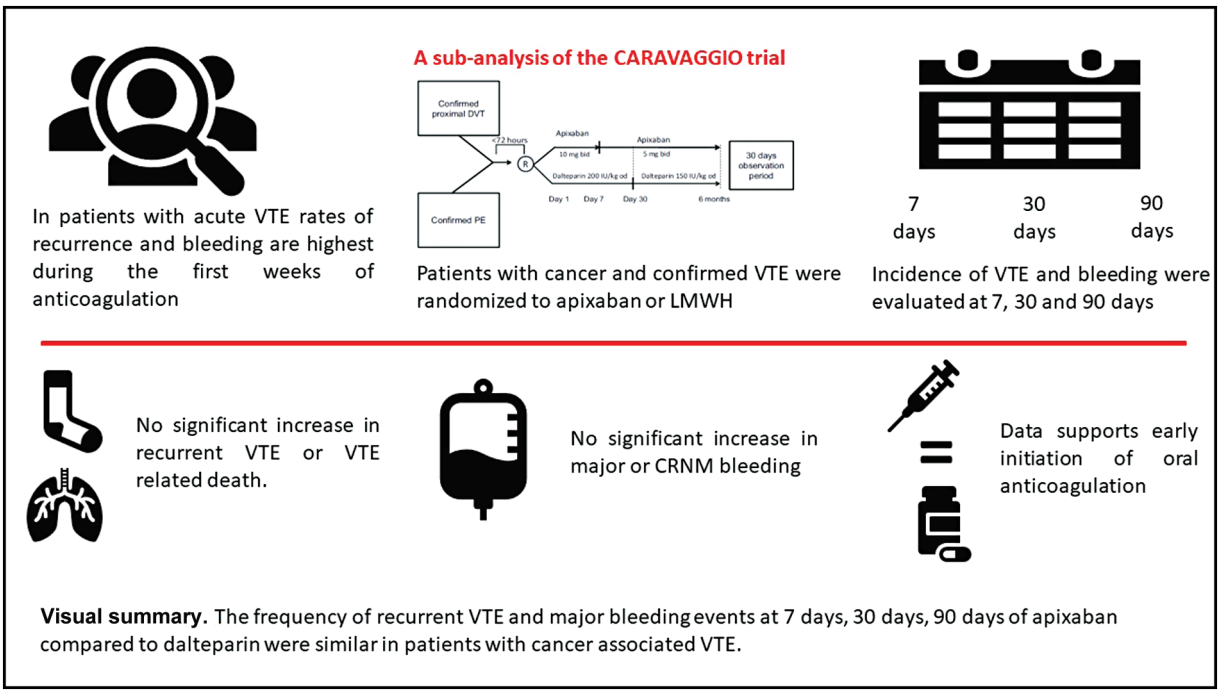

Visual summary. The frequency of recurrent VTE and major bleeding events at 7 days, 30 days, 90 days of apixaban compared to dalteparin were similar in patients with cancer associated VTE.

Introduction

In patients with active cancer-associated venous thromboembolism (VTE), the rates of VTE recurrence and major bleeding (MB) are highest during the first weeks of anticoagulation.[1] This has been seen during treatment with the direct oral anticoagulants (DOACs) as well as with parenteral anticoagulation followed by a vitamin K antagonist (VKA).[2,3]

Unlike VKA, apixaban has a rapid onset of action and in patients with VTE is commenced at a higher dosage for the first 7 days of therapy. The AMPLIFY trial was a randomized, double-blind, 6-month comparison of oral apixaban with conventional therapy (enoxaparin followed by warfarin) in patients with symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE). This study demonstrated noninferiority for apixaban in the treatment of VTE with significantly less MB.[2] This was further evaluated in a sub-set analysis utilizing set time points, demonstrating that the reduction in bleeding risk associated with apixaban begun early (during the first week) in the course of treatment.[1]

The CARAVAGGIO trial demonstrated noninferiority of apixaban to dalteparin for cancer-associated VTE without an increased risk of MB.[4,5] Based on the original publication of the CARAVAGGIO dataset in 2020 and patient preferences for a noninjectable form of therapy, there has been a switch to using apixaban and other DOACs as first-line therapy for cancer-associated VTE.

We sought to evaluate the efficacy and safety of apixaban during the initial high-risk phase of treatment in patients with cancer-associated VTE. Specifically, we performed a prespecified sub-analysis of the time courses of VTE recurrence and bleeding, and to evaluate the incidence after 7, 30, and 90 days of treatment with apixaban compared with dalteparin. These time points have been chosen because (1) the risk that the higher dose of apixaban given during the first 7 days could influence bleeding risk, (2) the dose reduction of apixaban after 7 days could influence the rate of recurrent VTE, (3) the dalteparin dose reduction at day 30 could influence both recurrent VTE and bleeding, and (4) the minimum recommended duration of treatment for VTE is 90 days, a time when anticoagulation is potentially stopped.

Materials and Methods

The study design and methods of the CARAVAGGIO trial (CARAVAGGIO; NCT03045406; https://clinicaltrials.gov/ct2/show/NCT03045406) have been described.[4,5] Briefly, CARAVAGGIO was a multinational, randomized, controlled, investigator-initiated, open-label, noninferiority trial that compared the efficacy and safety of apixaban with dalteparin in patients aged 18 years or older who had a newly diagnosed symptomatic or incidental proximal lower limb DVT or PE. DVT was defined as proximal if it involved the popliteal, femoral, or iliac vein. Incidental PE was defined as involving a segmental or more proximal pulmonary artery.

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

The main patient exclusion criteria were active bleeding or a high risk of bleeding or another contraindication to treatment with apixaban or dalteparin; concomitant thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor) or aspirin over 165 mg daily or dual antiplatelet therapy; creatinine clearance <30 mL/min based on the Cockcroft–Gault equation; acute hepatitis, chronic active hepatitis, liver cirrhosis; or an alanine aminotransferase level three times or more and/or bilirubin level two times or more the upper limit of the normal range.

Eligible patients were randomly assigned to receive monotherapy with either apixaban or dalteparin for 6 months. Patients assigned to the apixaban group received 10 mg of apixaban twice daily for 7 days, followed by 5 mg twice daily thereafter for 6 months. Dalteparin was given subcutaneously at a dose of 200 IU per kilogram once daily for the first month, after which the dose was reduced to 150 IU per kilogram daily. The maximum daily dose allowed for dalteparin was 18,000 IU. Days of drug exposure were calculated from the time of initiating study drug treatment until permanent discontinuation of study drug. Persistence was calculated from one minus the percentage of patients who discontinued the study drug.

All outcomes were predefined and identical to those used and described in the original CARAVAGGIO manuscript.[2] The primary efficacy outcome was the incidence of objectively confirmed VTE which included proximal DVT of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, and PE (symptomatic, incidental, or fatal) occurring during the 6-month trial period. The primary safety outcome was MB, defined as overt and associated with a decrease in the blood hemoglobin level of $\geq$2 g/dL, transfusion of two or more units of blood, affecting a critical site, resulting in surgical intervention, or contributing to death, all occurring during the trial-drug period through 72 hours after the last dose was administered. The central adjudication committee determined all major outcomes. Clinically relevant nonmajor bleeding (CRNMB) was defined as acute clinically overt bleeding that does not meet the criteria for MB. It consisted of all bleeding that required medical treatment, investigation, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug, or associated with pain or impairment of activities of daily life.[2]

Statistical Analysis

The CARAVAGGIO study was designed to test the hypothesis that apixaban would be noninferior to dalteparin for the primary efficacy outcome with a prespecified noninferiority margin of 2.00 for the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio.[4] A Cox proportional hazards model that included treatment group and stratification factors as covariates to analyze the time until the first event of the primary outcome during the 6-month trial period was used. Fine and Gray regression models were used to compute the hazard ratio and two-sided 95% CIs for the comparison between apixaban and dalteparin after adjustment for the competing risk of death unrelated to VTE.

For this sub-analysis, the efficacy analyses included data from patients in the intention-to-treat population with a documented outcome status at 7, 30, and 90 days (primary outcome) after randomization. The safety analyses included data obtained at these times from patients during study treatment, defined as the time from the administration of the first dose of study drug until 48 hours after the last dose. Analyses were sub-stratified for the index event (DVT alone, or PE with or without DVT). For safety, the analyses were for MB, CRNMB, and clinically relevant bleeding (a combination of MB or CRNMB). Descriptive comparisons of event rates, relative risks (RRs), and hazard ratios were calculated. Time to event curves were calculated using the Kaplan–Meier method. The calculated CIs for single event rates was based on the Wald asymptomatic confidence limits; RRs, CIs, and *p*-values should be calculated based on the Cochran–Mantel–Haenszel test and stratified by index event.[6]

Results

Patients

The CARAVAGGIO study enrolled 1,170 patients from 119 centers in 11 countries from April 2017 to June 2019; 1,155 patients were included in the modified intention-to-treat analysis (►**Supplementary Fig. S1** [available in the online version]). The demographic and clinical characteristics of the patients were similar in the two treatment groups (►**Supplementary Table S1** [available in the online version]).

Treatment

The median duration of the assigned treatment was 178 days (interquartile range: 106–183) in the apixaban group and 175 days (interquartile range: 79–183) in the dalteparin group ($p = 0.15$). Before permanent discontinuation of a trial drug, 41 patients in the apixaban group and 51 patients in the dalteparin group had received less than 80% of the prescribed treatment. The persistence to apixaban and dalteparin at 90 days and 6 months respectively was: *n* (%): 445 (77.7%) and 410 (71.1%); 364 (63.5%) and 321 (55.6%), respectively.

Efficacy

The primary outcome of recurrent VTE, at 6 months, occurred in 78 patients, 32 of 576 patients (5.6%) in the apixaban group, and 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio: 0.63; 95% CI: 0.37–1.07; $p < 0.001$ for noninferiority; $p = 0.09$ for superiority; ►**Supplementary Table S2** [available in the online version]).

Of the 78 recurrent VTE events, 11 (14.1%) occurred in the first 7 days, 35 (44.8%) in the first 30 days, and 63 (80.7%) in the first 90 days. By day 7, recurrent events occurred in 6 (1.0%) in the apixaban group and 5 (0.9%) in the dalteparin group (RR: 1.21; 95% CI: 0.37–3.93). By day 30, recurrent events occurred in 15 (2.6%) in the apixaban group and 20 (3.5%) in the dalteparin group (RR: 0.75; 95% CI: 0.39–1.46). By day 90, recurrent events occurred in 27 (4.7%) in the apixaban group and 36 (6.2%) in the dalteparin group (RR: 0.75; 95% CI: 0.46–1.23) (►**Fig. 1** and ►**Table 1**). The Kaplan–Meier plot

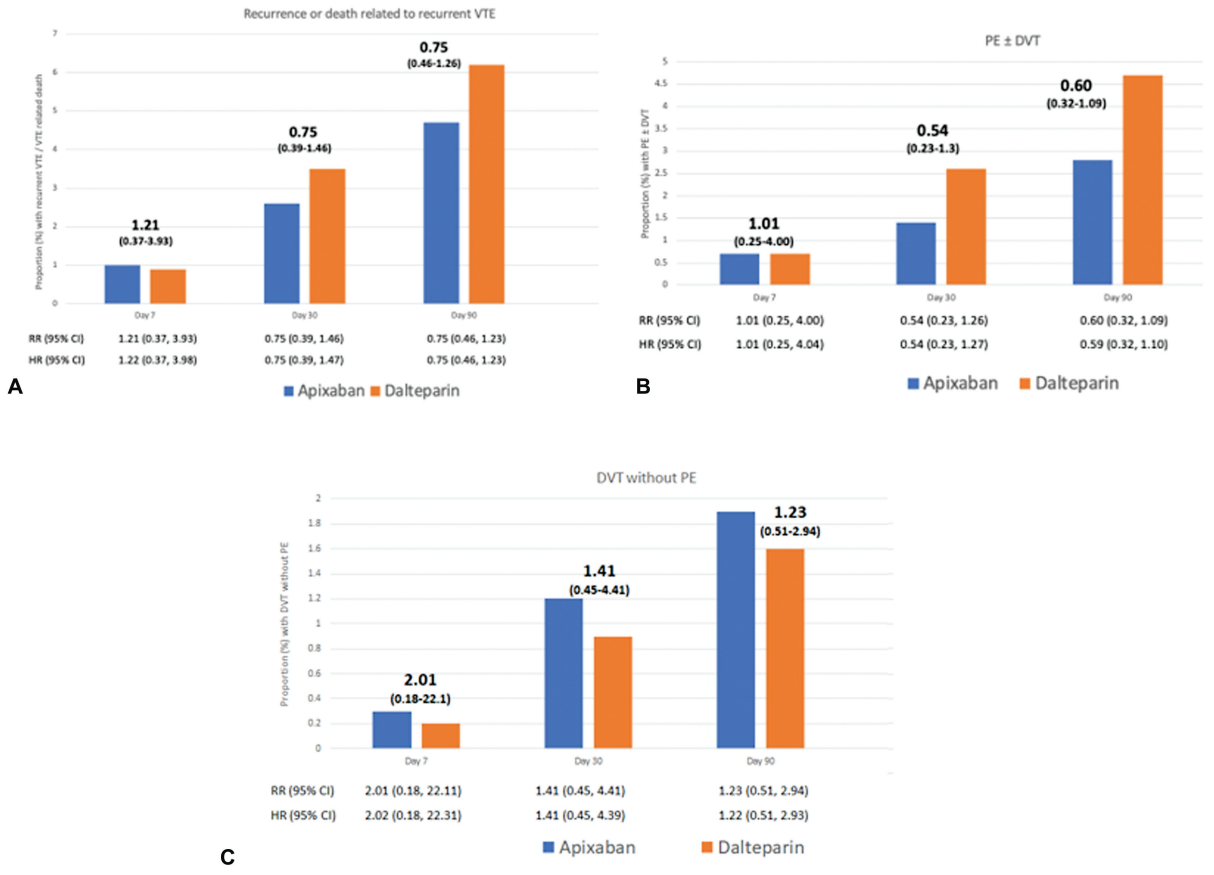

Fig. 1 Primary efficacy outcome for the trial period. (**A**) Proportion of patients with recurrent VTE or VTE-related death. (**B**) Proportion of patients with PE ± DVT. (**C**) Proportion of patients with DVT without PE. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

of time to recurrent VTE or death related to VTE is shown in ►**Fig. 2**.

Bleeding

During the 6 months of treatment, MB occurred in 45 patients, 22 patients who received apixaban (3.8%) and in 23 patients who received dalteparin (4.0%) (RR: 0.82; 95% CI: 0.4–1.69), $p = 0.60$ (►**Supplementary Table S2** [available in the online version]).

Of the total 45 MBs, 8 (17.8%) occurred during the first 7 days; 20 (44.4%) during the first 30 days, and 33 (73.3%) during the first 90 days. By day 7, MB events occurred in 3 (0.5%) in the apixaban group and 5 (0.9%) in the dalteparin group (RR: 0.60; 95% CI: 0.15–2.51). By day 30, MB events occurred in 9 (1.6%) in the apixaban group and 11 (1.9%) in the dalteparin group (RR: 0.82; 95% CI: 0.34–1.98). By day 90, MB events occurred in 16 (2.8%) in the apixaban group and 17 (2.9%) in the dalteparin group (RR: 0.95; 95% CI: 0.48–1.85) (►**Fig. 3** and ►**Table 2**).

During the 6 months of treatment, MB or CRNMB occurred in 126 patients, 70 patients who received apixaban (12.2%) and in 56 patients who received dalteparin (9.7%) (RR: 1.16; 95% CI: 0.77–1.75). (►**Supplementary Table S2** [available in the online version]).

Of the total 126 bleeding events, 24 (19.0%) occurred during the first 7 days; 58 (46.0%) during the first 30 days, and 89 (70.6%) during the first 90 days. Bleeding events occurred in 14 (2.4%) in the apixaban group and 10 (1.7%) in the dalteparin group (RR: 1.40; 95% CI: 0.63–3.14) by day 7, 30 (5.2%) in the apixaban group and 28 (4.8%) in the dalteparin group (RR: 1.08; 95% CI: 0.65–1.78) by day 30, and in 46 (8.0%) in the apixaban group and 43 (7.4%) in the dalteparin group (RR: 1.07; 95% CI: 0.72–1.60) by day 90. When stratified by anatomical site at day 90, there were more genitourinary bleeds observed with apixaban compared with dalteparin and conversely more upper gastrointestinal bleeds with dalteparin than with apixaban (see ►**Supplementary Table S3** [available in the online version]).

The Kaplan–Meier plot of time to recurrent VTE, MB, and CRNMB is shown in ►**Fig. 1**. The Kaplan–Meier plot of MB and CRNMB is shown in ►**Fig. 2**. ►**Table 2** also details the number and proportion of patients with CRNMB events.

Discussion

It is well documented that patients with VTE events have the highest risk of VTE recurrence or VTE-related death within 3 months of initial VTE event.[3,7,8] Similarly, the risk of anticoagulation-related bleeding is highest within the first 3 months of therapy.[3,9,10] During this period of time, the risks of recurrent VTE and bleeding are even greater in patients with active cancer.[11] Clinical trials generally focus

Table 1 Recurrence or death related to venous thromboembolism after 7, 30, and 90 days

	Recurrent VTE				DVT without PE				PE ± DVT			
	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)
Day 7	6 (1.0)	5 (0.9)	1.21 (0.3–3.93)	1.22 (0.37–3.98)	2 (0.3)	1 (0.2)	2.01 (0.18–22.11)	2.02 (0.18–22.31)	4 (0.7)	4 (0.7)	1.01 (0.25–4.00)	1.01 (0.25–4.04)
Day 30	15 (2.6)	20 (3.5)	0.75 (0.39–1.46)	0.75 (0.39–1.47)	7 (1.2)	5 (0.9)	1.41 (0.45–4.41)	1.40 (0.45–4.39)	8 (1.4)	15 (2.6)	0.54 (0.23–1.26)	0.54 (0.23–1.27)
Day 90	27 (4.7)	36 (6.2)	0.75 (0.46–1.23)	0.75 (0.46–1.23)	11 (1.9)	9 (1.6)	1.23 (0.51–2.94)	1.22 (0.51–2.93)	16 (2.8)	27 (4.7)	0.60 (0.32–1.09)	0.59 (0.32–1.10)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; RR, relative risk.

Note: For patients who had more than one event, only the first event was countered. Percentages are calculated on total number of mITT patients in each treatment group. The apixaban-to-dalteparin hazard ratio adjusted for the competing risk of death unrelated to event was computed with associated two-sided 95% confidence interval by resorting to the Fine and Gray regression model using treatment group, symptomatic versus unsuspected VTE, and active cancer versus history of cancer as covariates. Stratum reported in the first column is the reference for HR calculation. For landmark analysis at each time point, only patients with an event of interest within specified time from randomization are considered as events in the analysis. Patients reporting an event after given days from randomization are considered as censored.

on longer term VTE recurrence and bleeding complications and therefore often omit capturing and/or reporting the important earlier data. The clinical consequences of early bleeding may impact anticancer treatment as well as the intensity and the duration of anticoagulation therapy. The results of this sub-analysis of the original CARAVAGGIO trial therefore provide clarity on the risk of VTE recurrence, death related to VTE recurrence, and MB and CRNMB complications within the first 7, 30, and 90 days of VTE diagnosis and commencement of either oral apixaban or subcutaneous dalteparin in patients with cancer.

The results of this sub-analysis showed that apixaban was comparable to dalteparin in terms of efficacy and safety in the initiation phase when high-dose apixaban was given (first 7 days), the phase of higher dose low-molecular-weight heparin (first 30 days), and the recommended minimum duration of anticoagulation treatment phase (3 months). Specifically, it highlights the similar rates of VTE recurrence, death related to VTE, and MB and CRNMB events at all time points between the two anticoagulants. The low rates of early recurrence and bleeding complications were comparable between both treatment groups and parallel that seen in previous trials.[2,4]

These results provide reassurance to clinicians about the safety and efficacy of early commencement of oral anticoagulation for patients with cancer presenting with an acute VTE event. Although not statistically significant, there were numerically more CRNMB in the apixaban group and these were mainly bleeding from the upper airway (from nose to larynx) and genitourinary tract, the latter presenting with hematuria. In the first 7 days, there were 12 CRNMB events in the apixaban group and 5 in the dalteparin group; although this difference was not statistically significant, in practice, clinicians should consider this prior to starting apixaban 10 mg twice a day for 7 days in those at higher risk of bleeding (e.g., renal impairment, anemia, or genital/oral cancer etc.). Conversely, there were more upper GI bleeds with dalteparin (►**Supplementary Table S3** [available in the online version]).

One previous sub-analysis of the CARAVAGGIO study examined MB using the International Society on Thrombosis and Haemostasis and European Medicines Agency definitions, CRNMB, severity of bleeding (categorized into four categories), and patients' bleeding risk factors.[12] This sub-analysis showed that the bleeding rates, severity of presentation, and clinical course of MB were similar in both groups. There was one critical site bleeding and no fatal bleeding in the apixaban arm while the dalteparin arm had five critical site bleedings and two fatal bleedings. A total of 36.4 and 56.5% of patients with MB required hospitalization in the apixaban and dalteparin arms, respectively. Drug interruption was required in 63.6 and 69.5% of patients with MB in the apixaban and dalteparin arms, respectively.

The trend toward lower rates of VTE recurrence and/or death related to VTE by day 30 and specifically by day 90 may be linked to the reduced dosage of dalteparin beyond this time. The trial protocol stipulated that dalteparin was given subcutaneously at a dose of 200 IU per kilogram once daily

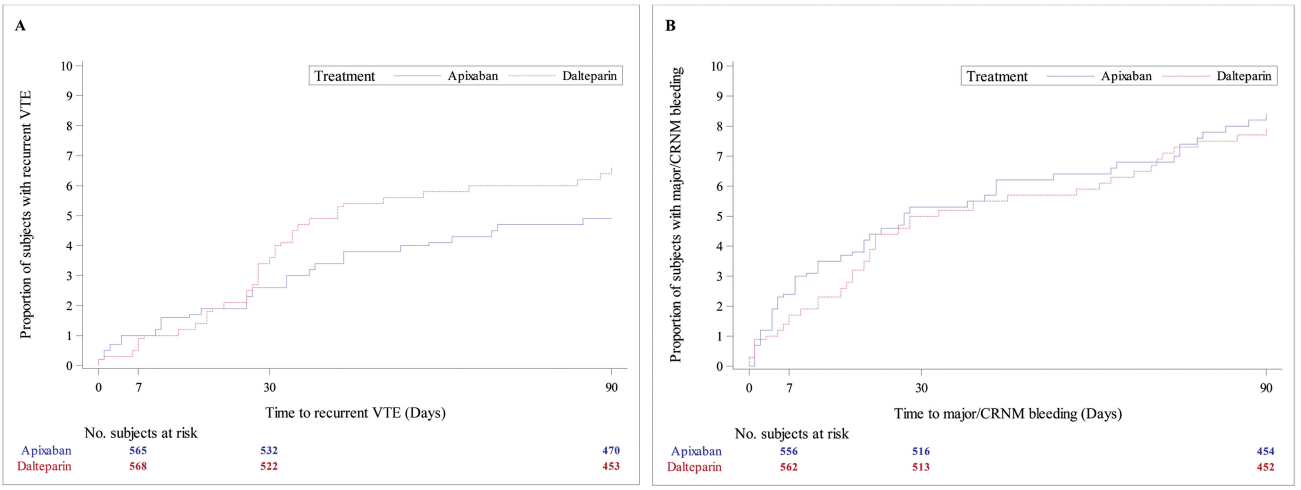

Fig. 2 Kaplan–Meier cumulative event rates for recurrent VTE/VTE-related death (**A**). Kaplan–Meier cumulative event rates for major and CRNM bleeds until day 90 (**B**). CRNM, clinically relevant nonmajor; VTE, venous thromboembolism.

for the first month, after which the dose was reduced to 150 IU per kilogram daily. In contrast, apixaban was maintained at 5 mg twice daily beyond week 2 of administration. While not statistically significant, there is a clear divergence in Kaplan–Meier analysis beyond 30 days. This is similar to what was seen in the original AMPLIFY study comparing apixaban to conventional therapy.[2]

The higher dose of apixaban at the time of commencement of anticoagulation was not associated with increased rates of MB or CRNMB events. Similarly, the continued treatment dose of apixaban had similar rates of bleeding complications to the maintenance dose of dalteparin. In patients with cancer, who have a baseline heightened bleeding risk compared with healthy controls, these data are reassuring.

In line with the original CARAVAGGIO trial, this subanalysis has several limitations. First, to avoid the use of parenteral placebo for 6 months, it was an open-label trial. The numbers of VTE recurrences, however, were similar in the two treatment groups, and all suspected trial outcome events were centrally adjudicated in a blinded manner. Second, due to safety concerns, patients with brain tumors,

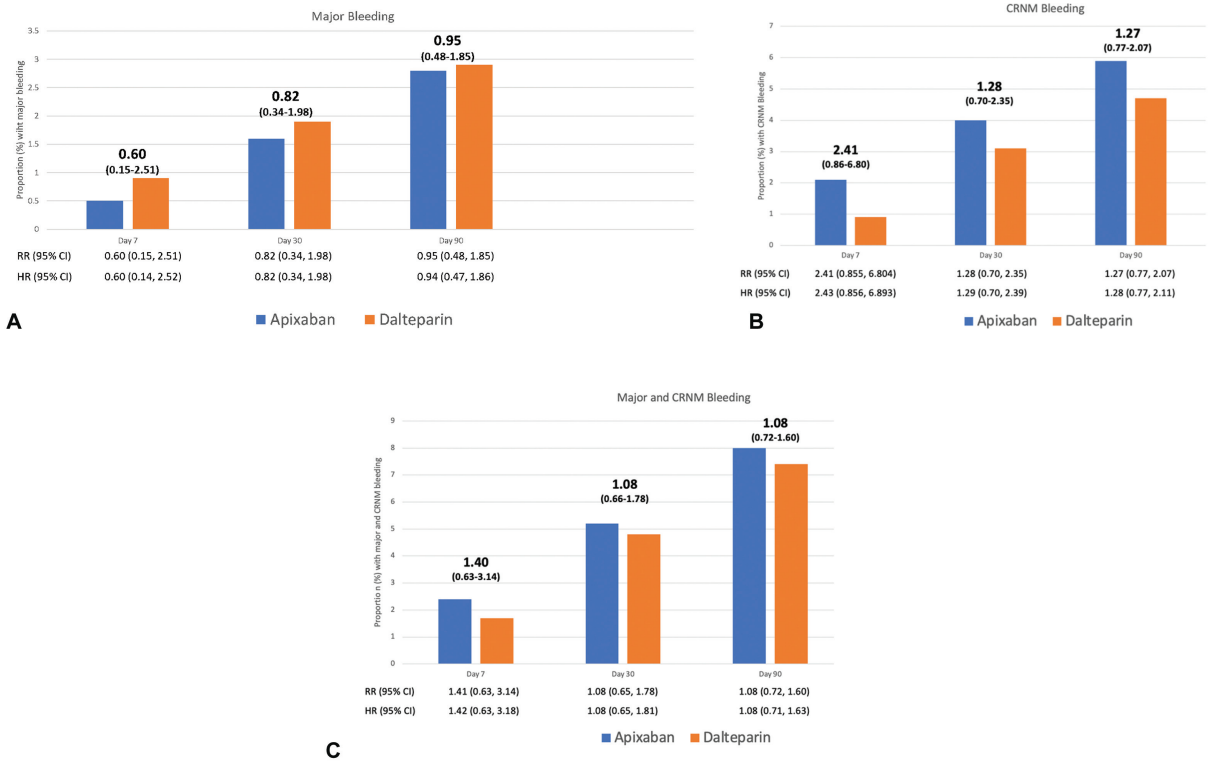

Fig. 3 Bleeding events. Proportion of patients who had major bleeding (**A**), clinically relevant nonmajor (CRNM) bleeding (**B**), and major bleeding and CRNM bleeding (**C**).

Table 2 Bleeding after 7, 30, 90 days

	Major bleeding				CRNM bleeding				Major and CRNM bleeding			
	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)	Apixaban	Dalteparin	RR (95% CI)	HR (95% CI)
Day 7	3 (0.5)	5 (0.9)	0.60 (0.15–2.51)	0.60 (0.14–2.52)	12 (2.1)	5 (0.9)	2.41 (0.86–6.80)	2.43 (0.86–6.89)	14 (2.4)	10 (1.7)	1.41 (0.63–3.14)	1.42 (0.63–3.18)
Day 30	9 (1.6)	11 (1.9)	0.82 (0.34–1.97)	0.82 (0.34–1.98)	23 (4.0)	18 (3.1)	1.28 (0.70–2.35)	1.29 (0.70–2.39)	30 (5.2)	28 (4.8)	1.08 (0.65–1.78)	1.08 (0.65–1.81)
Day 90	16 (2.8)	17 (2.9)	0.95 (0.48–1.85)	0.94 (0.47–1.86)	34 (5.9)	27 (4.7)	1.27 (0.77–2.07)	1.28 (0.77–2.11)	46 (8.0)	43 (7.4)	1.08 (0.72–1.60)	1.08 (0.71–1.63)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; RR, relative risk.
Note: For patients who had more than one event, only the first event was countered. Percentages are calculated on total number of mITT patients in each treatment group. The apixaban-to-dalteparin hazard ratio adjusted for the competing risk of death unrelated to event was computed with associated two-sided 95% confidence interval by resorting to the Fine and Gray regression model using treatment group, symptomatic versus unsuspected VTE, and active cancer versus history of cancer as covariates. Stratum reported in the first column is the reference for HR calculation. For landmark analysis at each time point, only patients with an event of interest within specified time from randomization are considered as events in the analysis. Patients reporting an event after given days from randomization are considered as censored.

known cerebral metastases, or acute leukemia were excluded from enrolment, consequently these results cannot be extrapolated to these patient groups. Third, the results of this time point analysis have not been adjusted for the study center, unlike the initial analysis of the CARAVAGGIO trial and this may account for the slight differences in results. Fourth, the small patient numbers result in measures of effect with wide CIs and this limits the interpretation of the data in various cohorts including those with DVT without PE, patients with PE $\pm$ DVT, and those with reduced renal function. The main strength of this analysis is that the data originate from a randomized controlled trial, undertaken in a broad range of patients with active cancer, and the study outcomes were blindly adjudicated by a central adjudication committee.

In conclusion, sub-analysis of the CARAVAGGIO trial found that apixaban was comparable to dalteparin at all time points, within the limits of uncertainty shown in the results. Specifically, there was no increase in recurrent VTE, VTE-related death, or bleeding events at 7 days, 30 days, 90 days, and 6 months. This supports early initiation of oral anticoagulation. Oral versus subcutaneous anticoagulation has the advantage of ease of administration and outpatient delivery, which may improve patients' quality of life—an important consideration in patients with cancer.

What is known about this topic?

- The rates of recurrence and bleeding are highest during the first weeks of anticoagulation.
- These risks are even greater in patients with cancer.

What does this paper add?

- This article highlights the safety and efficacy of apixaban compared with dalteparin at all major time points for cancer-associated VTE.
- Data provide reassurance about early commencement of oral anticoagulation therapy.

Authors' Contribution

A.T.C. was responsible for study design, data review, and writing and reviewing the manuscript. K.J.C. was responsible for data review, and writing and reviewing of the manuscript. R.A. was responsible for data and manuscript review. All authors had access to the data and had final responsibility for the decision to submit for publication.

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Conflict of Interest

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