Subgroup Analysis of Patients with Cancer in XALIA: A Noninterventional Study of Rivaroxaban versus Standard Anticoagulation for VTE

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Abstract

Background The noninterventional XALIA study compared rivaroxaban with standard anticoagulation for deep vein thrombosis treatment. This substudy describes the demographics, clinical characteristics, and outcomes of the patients with cancer.

Methods Therapy type, dose, and duration were at the physician's discretion. The cohorts identified were rivaroxaban (rivaroxaban alone or after heparin or fondaparinux for $\leq$48 hours); early switchers (rivaroxaban after heparin or fondaparinux for $>$48 hours to 14 days and/or a vitamin K antagonist [VKA] for 1–14 days); standard anticoagulation (heparin or fondaparinux and a VKA); low-molecular-weight heparin (LMWH) alone; and miscellaneous (other heparins, fondaparinux alone, VKA alone). Primary outcomes were major bleeding, recurrent venous thromboembolism, and all-cause mortality.

Results In XALIA, 587 patients (11.4% of the XALIA cohort) were with cancer: 146 (24.9%) rivaroxaban, 30 (5.1%) early switchers, 141 (24.0%) standard anticoagulation, 223 (38.0%) LMWH, and 47 (8.0%) miscellaneous. Patients with gastrointestinal or lung cancer more commonly received LMWH than rivaroxaban; the opposite occurred in patients with breast or genitourinary cancer. Rates of primary outcome in the rivaroxaban group were as follows: major bleeding, 1.4% ($n = 2$); recurrent venous thromboembolism, 3.4% ($n = 5$); and all-cause mortality, 4.8% ($n = 7$).

Conclusion In XALIA, physicians treated cancer-associated thrombosis with various anticoagulant regimens, most commonly LMWH. In addition, the choice of anticoagulant varied with cancer type. In rivaroxaban-treated patients, rates for the primary outcomes were low, suggesting that patients administered rivaroxaban were a good prognosis group.

Keywords

- cancer-associated thrombosis
- low-molecular-weight heparin
- rivaroxaban
- routine clinical practice
- venous thromboembolism

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Introduction

Rates of venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), are particularly high in patients with cancer, and thrombosis can be an indicator of occult cancer.[1] Agents used to treat cancer, such as chemotherapeutic agents or antiangiogenic agents, have also been shown to increase the risk of thrombosis.[2–4] In cancer-associated thrombosis, treatment with low-molecular-weight heparin (LMWH) was superior to vitamin K antagonists (VKAs) for the prevention of recurrence.[5] Guidelines, therefore, recommend extended (no scheduled stop date) LMWH monotherapy over VKA therapy in this setting.[6] However, many physicians still use a traditional regimen of heparin (LMWH) followed by a VKA to treat VTE in cancer-related thrombosis, for reasons including the high cost of LMWHs over the longer term and injection discomfort for patients.[7]

Direct oral anticoagulants (DOACs) are as effective as standard anticoagulation for the initial treatment of VTE and prevention of VTE recurrence.[8–12] A meta-analysis of six studies and a systematic review study showed that the DOACs are as safe and effective as standard treatment for patients with VTE and cancer.[13] A pooled analysis from the EINSTEIN phase III studies of 1,124 patients with active cancer ($n = 655$) or a history of cancer ($n = 469$) also showed that rivaroxaban had similar efficacy to enoxaparin plus a VKA for preventing VTE recurrence, and rates of major bleeding were lower with rivaroxaban than with enoxaparin/VKA.[14] However, none of the completed studies has directly compared DOACs with LMWH in this setting, and guidelines still advise LMWH over DOACs as the treatment of choice for VTE in patients with cancer.

The noninterventional XALIA phase IV study demonstrated the safety and effectiveness of the single-drug approach with rivaroxaban for the treatment of DVT in routine clinical practice.[15] The findings from XALIA were consistent with those from EINSTEIN DVT and, as with the EINSTEIN phase III studies, several patients with cancer were included in the XALIA study population. This analysis describes the baseline demographics and clinical characteristics, treatment patterns, and outcomes of the patients with known and newly diagnosed cancer in XALIA.

Methods

The methods were as described in the XALIA primary article.[15]

Study Design and Participants

XALIA was a multicenter, international, prospective, noninterventional study of patients with objectively confirmed DVT. Patients received rivaroxaban or standard anticoagulation treatment (initial treatment with unfractionated heparin, LMWH, or fondaparinux, usually overlapping with and followed by a VKA). Patients could be included if they were 18 years or older, with objectively confirmed DVT, and an indication to receive anticoagulation treatment for 3 months or longer. After the approval of rivaroxaban in the PE indication, the protocol was amended to allow the enrolment of patients with DVT and concomitant PE (but not isolated PE).

Cancer Reporting and Classification

In XALIA, the investigators reported cancer by marking checkboxes on the case report forms (CRFs). Patients with cancer were therefore defined as having either known cancer or cancer that was newly diagnosed at study entry. Cancers were categorized as breast, central nervous system, gastrointestinal, genitourinary tract, lung, hematological system, melanoma, or other. The cancer type was also recorded using a checkbox system. If patients had more than one type of cancer, multiple checkboxes could be marked.

Procedures

Treatment, dose, and duration were at the attending physician's discretion. For the purpose of this substudy, we defined the following treatment cohorts: rivaroxaban cohort (patients treated with rivaroxaban alone or who received heparin or fondaparinux for $\leq$48 hours before switching to rivaroxaban, consistent with the approach in EINSTEIN DVT);[9] early switchers cohort (patients treated with rivaroxaban who received heparin or fondaparinux for >48 hours to 14 days or a VKA for 1–14 days before changing to rivaroxaban); standard anticoagulation cohort (patients treated with heparin or LMWH or fondaparinux overlapping with and followed by a VKA); LMWH-alone cohort; and miscellaneous cohort (patients treated with other heparins, fondaparinux alone, or a VKA alone). The observation period ended 12 months from the date of the final patient enrolment; therefore, each patient was followed up for at least 12 months.

Outcomes

The primary outcomes were as in XALIA: major bleeding, recurrent VTE, and all-cause mortality. Major bleeding was defined as overt bleeding associated with a fall in hemoglobin of $\geq$20 g/L; a transfusion of two or more units of packed red blood cells or whole blood; critical site bleeding (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal); or fatal bleeding. Recurrent VTE was defined as the new onset of symptoms confirmed by diagnostic testing; only symptomatic VTE was considered in this study. Death was classified as being VTE-related, bleeding-related, or from other causes. Secondary outcomes were major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction, unstable angina, acute coronary syndromes); other symptomatic thromboembolic events (Budd-Chiari syndrome, retinal-vein thrombosis, sinus-vein thrombosis, portal-vein thrombosis, catheter-associated thrombosis, upper-limb thrombosis [if initial DVT was not an upper-limb thrombosis]); and other adverse events (AEs).

Statistical Analysis

A descriptive analysis was conducted and the crude rates for the primary outcomes of the five treatment cohorts of

patients with cancer were recorded. Due to imbalances in clinical characteristics of the treatment groups, this analysis was purely observational and no direct comparisons were conducted. Treatment patterns by type of cancer and type of cancer treatment were also described. All analyses considered only outcomes occurring on treatment (i.e., events were assigned to the treatment [rivaroxaban or standard anticoagulation] which was given initially after the index event; the stopping of this first medication was considered as the stopping of study medication). The rationale for considering only events occurring on treatment was to focus on events occurring under the newly introduced drug; for example, if a patient switched to rivaroxaban on day 10 due to a bleeding event occurring earlier (e.g., on day 5), we considered that such an event should not be assigned to the early switcher group, as it is not related to the newly introduced drug.

Role of the Funding Source

Bayer AG and Janssen Research and Development, the XALIA study funders, gathered, maintained, and extracted data. The authors had responsibility for data interpretation and writing the article. All authors had access to the raw data. The corresponding author had final responsibility to submit for publication. The study is registered at www.clinicaltrials.gov (NCT01619007).

Results

Baseline Demographics and Clinical Characteristics

The total enrolment for XALIA between June 26, 2012, and March 31, 2014, was 5,142 patients; 6 patients did not take study medication and were excluded from the analysis. Of the remaining 5,136 patients, 587 (11.4%) had known or newly diagnosed cancer at baseline.

Of the 587 patients with cancer, 146 patients (24.9%) received rivaroxaban, 30 (5.1%) were early switchers, 141 (24.0%) received standard anticoagulation, 223 (38.0%) received LMWH alone, and 47 (8.0%) were in the miscellaneous cohort. Of the 30 early switchers with cancer, 27 (90.0%) were switchers from heparin or fondaparinux and 3 (10.0%) were switchers from a VKA. The flow of patients through the study is shown in ►**Fig. 1**; baseline demographics and clinical characteristics for patients with cancer are shown for the five treatment cohorts in ►**Table 1**. The median treatment duration for patients with cancer was 152 days (interquartile range [IQR]: 86–278 days) with rivaroxaban versus 164 days (IQR: 86–269 days) with LMWH (►**Table 2**).

Reasons for Initial VTE Therapy Choice

Reasons for the choice of initial VTE treatment among patients with cancer are shown in ►**Table 3**; more than one reason could be cited for this choice. In the rivaroxaban cohort, the living conditions and age of the patient were the most frequently specified reasons; guidelines, comorbidities, and drug availability were also commonly selected. For the early switcher patients, medical/hospital guidelines were the most common reason, and for the other three cohorts, the most frequently cited reason was comorbidities.

Type of Cancer and Cancer Treatment Patterns

The most common type of cancer in the rivaroxaban, early switcher, standard anticoagulation, and miscellaneous cohorts was genitourinary cancer (38/146 [26.0%] in the rivaroxaban group, 12/30 [40.0%] in the early switchers, 53/141 [37.6%] in the standard anticoagulation cohort, and 15/47 [31.9%] in the miscellaneous cohort; ►**Table 4**). The most common type of cancer in the LMWH group was gastrointestinal (57/223 [25.6%]). ►**Table 5** shows the proportion of patients who had received, or were currently receiving, chemotherapy or hormone treatment, with the LMWH group having the highest proportion of patients receiving ongoing treatment for cancer (99/223 [44.4%]).

Primary Outcomes

Results for the primary outcomes in patients with cancer are shown in ►**Fig. 2**. The rates of major bleeding were 1.4% (2/146) in the rivaroxaban group, 5.0% (7/141) with standard anticoagulation, 3.6% (8/223) with LMWH, and 4.3% (2/47) in the miscellaneous cohort; no major bleeding events occurred in the early switchers with cancer. The rates of recurrent VTE were 3.4% (5/146) in the rivaroxaban group, 3.3% (1/30) in the early switchers, 4.3% (6/141) in the standard anticoagulation group, 4.5% (10/223) in the LMWH cohort, and 4.3% (2/47) in the miscellaneous cohort. All-cause mortality occurred in 4.8% (7/146) of patients in the rivaroxaban group, 4.3% (6/141) of patients in the standard anticoagulation group, 24.7% (55/223) of patients in the LMWH group, and 14.9% (7/47) of patients in the miscellaneous cohort; there were no deaths in the early switchers cohort. A detailed breakdown of the primary outcomes is shown in ►**Table 6**.

Secondary Outcomes

Major Adverse Cardiovascular Events

Treatment-emergent major adverse cardiovascular events occurred in 0.7% (1/146) of the rivaroxaban cohort, 0.7% (1/141) of the standard anticoagulation cohort, and 0.9% (2/223) of the LMWH cohort; no events occurred in the early switcher or miscellaneous cohorts.

Other Symptomatic Thromboembolic Events

There were no other symptomatic thromboembolic events in any of the treatment cohorts.

Other Adverse Events

In the rivaroxaban group, 45.9% (67/146) of patients had at least one treatment-emergent AE. Of the early switchers, 60.0% (18/30) of patients had at least one AE. The proportion in the standard anticoagulation group was 49.6% (70/141), 60.5% (135/223) in the LMWH group, and 44.7% (21/47) in the miscellaneous group.

Discussion

As cancer therapies evolve and patients with tumors live longer, any additional information regarding the treatment of cancer-associated diseases such as thrombosis in this

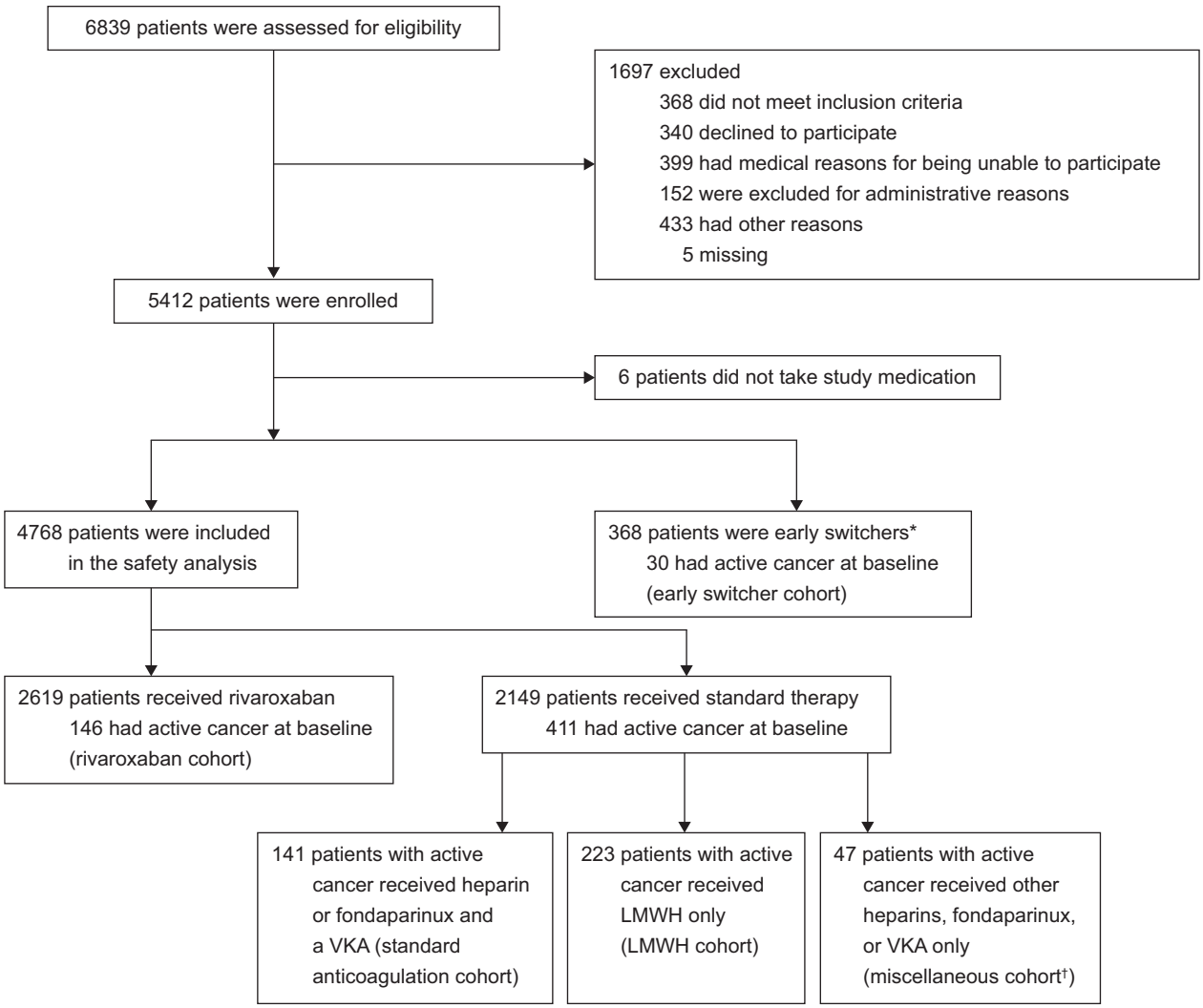

Fig. 1 Flow of patients through the study. A total of 5,142 patients were enrolled in XALIA; 6 patients were excluded as they did not take study medication. Of the remaining 5,136 patients, 587 (11.4%) had known or newly diagnosed cancer at baseline. Patients with cancer were administered various anticoagulant treatment regimens, with the LMWH-treated patients comprising the largest of the five study cohorts. *Early switchers were those patients treated with rivaroxaban who received heparin or fondaparinux for >48 hours to 14 days or a VKA for 1–14 days before changing to rivaroxaban. †Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a VKA alone. LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

clinically challenging group of patients is a valuable addition to real-world practice and improving patient outcomes. In XALIA, patients with known or newly diagnosed cancer at baseline more frequently received parenteral treatment than rivaroxaban therapy. Some patients with cancer (early switchers) were switched to rivaroxaban after an initial period of treatment with standard anticoagulation. The largest of the five anticoagulation treatment cohorts was the LMWH group, in accordance with current guidelines for cancer-associated thrombosis.[6] These results suggested that, as expected, physicians were generally cautious in prescribing a newer therapy to patients with cancer, in particular when chemotherapy or hormone therapy was still ongoing. However, they were more willing to treat patients with rivaroxaban or to switch some of the patients to rivaroxaban after initial treatment with parenteral agents when chemotherapy was ended less than 6 months before the acute DVT. In addition, many patients treated with standard anticoagulation received VKAs, despite the guideline recommendations to treat cancer-associated thrombosis with LMWH; the prescription of DOACs is advised as an alternative to VKAs.[6] Commonly cited reasons for VTE therapy choices included medical or hospital guidelines, age of patient, availability of therapy, and the presence of comorbidities.

Patients with gastrointestinal cancer most often received LMWH; however, for other sites, other treatments were more common. In the rivaroxaban group, the most common sites of cancer were genitourinary or breast, and the proportion of patients receiving rivaroxaban for these cancer types was higher than with LMWH. The LMWH group had the highest proportion of patients receiving ongoing hormone therapy or chemotherapy during the study—this may reflect the stage of the disease and may have contributed to the higher rates of recurrent VTE and mortality observed in this

Table 1 Baseline demographics and clinical characteristics of patients with cancer at baseline

Characteristic	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[a] ($n = 47$)
Age, y, mean (SD)	69.3 (11.9)	70.4 (10.6)	70.4 (10.7)	68.0 (12.7)	70.0 (12.7)
Age category					
< 60 y	29 (19.9)	4 (13.3)	22 (15.6)	52 (23.3)	6 (12.8)
≥ 60 y	117 (80.1)	26 (86.7)	119 (84.4)	171 (76.7)	41 (87.2)
Male	76 (52.1)	15 (50.0)	73 (51.8)	105 (47.1)	25 (53.2)
Weight					
< 50 kg	5 (3.4)	0 (0.0)	1 (0.7)	12 (5.4)	2 (4.3)
≥ 50–70 kg	29 (19.9)	8 (26.7)	42 (29.8)	77 (34.5)	12 (25.5)
> 70– < 90 kg	55 (37.7)	12 (40.0)	53 (37.6)	71 (31.8)	12 (25.5)
≥ 90 kg	25 (17.1)	6 (20.0)	28 (19.9)	29 (13.0)	9 (19.1)
Missing	32 (21.9)	4 (13.3)	17 (12.1)	34 (15.2)	12 (25.5)
First available CrCl					
< 30 mL/min	3 (2.1)	2 (6.7)	10 (7.1)	6 (2.7)	1 (2.1)
30– < 50 mL/min	14 (9.6)	5 (16.7)	13 (9.2)	15 (6.7)	6 (12.8)
50– < 80 mL/min	33 (22.6)	7 (23.3)	42 (29.8)	54 (24.2)	10 (21.3)
≥ 80 mL/min	44 (30.1)	9 (30.0)	36 (25.5)	67 (30.0)	14 (29.8)
Missing	52 (35.6)	7 (23.3)	40 (28.4)	81 (36.3)	16 (34.0)
Index diagnosis					
DVT only	135 (92.5)	21 (70.0)	121 (85.8)	197 (88.3)	37 (78.7)
DVT with PE	11 (7.5)	9 (30.0)	20 (14.2)	26 (11.7)	10 (21.3)
Previous VTE	41 (28.1)	10 (33.3)	38 (27.0)	26 (11.7)	12 (25.5)
Known thrombophilic condition	5 (3.4)	0 (0.0)	8 (5.7)	6 (2.7)	1 (2.1)
Previous major bleeding episode	4 (2.7)	5 (16.7)	9 (6.4)	14 (6.3)	2 (4.3)

Abbreviations: CrCl, creatinine clearance; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Note: Data are *n* (%) unless stated otherwise.
[a]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a VKA alone.

group, because some cancer treatments are associated with increased risks of thromboembolic events.[16–18]

For the primary outcomes of major bleeding, recurrent VTE, and all-cause mortality, the rates were lower in patients treated with rivaroxaban than with standard anticoagulation, LMWH, and miscellaneous cohorts (with the exception of all-cause mortality in the standard anticoagulation cohort, which was lower than in the rivaroxaban cohort). However, the study population was very heterogeneous and these comparisons were unadjusted, meaning that the results were impacted by

Table 2 Treatment duration in patients with cancer

Treatment duration (d)	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[a] ($n = 47$)
Median	152	196	214	164	141
IQR	86–278	94–358	112–431	86–269	64–365
Mean (SD)	190.6 (161.2)	237.0 (195.1)	291.1 (214.2)	191.0 (145.6)	211.1 (192.9)
Min–max	1–749	1–859	1–898	2–751	1–714

Abbreviations: IQR, interquartile range; LMWH, low-molecular-weight heparin; SD, standard deviation; VKA, vitamin K antagonist.
Note: Data are days unless stated otherwise.
[a]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a VKA alone.

Table 3 Reason for choice of initial VTE treatment in patients with cancer[a]

Reason[a]	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[b] ($n = 47$)
Availability of drug	35 (24.0)	1 (3.3)	11 (7.8)	9 (4.0)	3 (6.4)
Comorbidities	38 (26.0)	9 (30.0)	70 (49.6)	170 (76.2)	25 (53.2)
Distance to treating physician	17 (11.6)	1 (3.3)	3 (2.1)	5 (2.2)	2 (4.3)
Medical or hospital guidelines	39 (26.7)	15 (50.0)	52 (36.9)	61 (27.4)	10 (21.3)
Patient's age	50 (34.2)	8 (26.7)	26 (18.4)	25 (11.2)	11 (23.4)
Patient's living condition	53 (36.3)	5 (16.7)	17 (12.1)	20 (9.0)	9 (19.1)
Price of drug	5 (3.4)	1 (3.3)	9 (6.4)	4 (1.8)	7 (14.9)
Type of health insurance	1 (0.7)	1 (3.3)	2 (1.4)	2 (0.9)	1 (2.1)
Other	20 (13.7)	4 (13.3)	13 (9.2)	18 (8.1)	10 (21.3)

Abbreviations: LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Note: Data are *n* (%) unless stated otherwise.
[a]More than one reason could be selected by the physician for each patient.
[b]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a VKA alone.

the baseline clinical characteristics of the treatment group and therefore cannot be compared directly. Furthermore, the heterogeneity of the study population could potentially have impacted treatment selection. Better-prognosis patients may have been more likely to be administered rivaroxaban, increasing the likelihood of lower outcome rates for this cohort. All-cause mortality was highest by a substantial margin in the patients treated with LMWH, with death occurring in a quarter of all patients; the most common cause of death in the latter group was cancer (87.3% [48/55] of all deaths in the group), suggesting that patients with more advanced-stage cancer were administered LMWH. VKA use (standard anticoagulation group) was associated with the highest rate of major bleeding of the five cohorts, with similar rates of VTE recurrence to patients receiving LMWH only. This is of interest, because cancer-associated thrombosis is often treated with VKAs. Rates for all three primary outcomes were higher in the rivaroxaban cohort for patients with cancer than in the respective groups in the primary XALIA analysis (1.4 vs. 0.7% for major bleeding, 3.4 vs. 1.4% for recurrent VTE, and 4.8 vs. 0.5% for mortality); similarly, patients in this substudy who received standard anticoagulation, LMWH alone, or miscellaneous treatment had higher rates for all three primary outcomes versus the standard anticoagulation treatment group in the main XALIA population.[15] This was similar to the findings of a substudy of patients with cancer versus those without cancer from the EINSTEIN DVT and EINSTEIN PE studies,[14] and in other earlier studies,[19,20] where the presence of cancer was also

Table 4 Known or newly diagnosed cancer at baseline

Cancer type	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[a] ($n = 47$)
Breast	32 (21.9)	10 (33.3)	25 (17.7)	34 (15.2)	13 (27.7)
CNS	5 (3.4)	0 (0.0)	4 (2.8)	6 (2.7)	1 (2.1)
Gastrointestinal	20 (13.7)	4 (13.3)	19 (13.5)	65 (29.1)	8 (17.0)
Genitourinary	38 (26.0)	12 (40.0)	53 (37.6)	57 (25.6)	15 (31.9)
Hematological	12 (8.2)	0 (0.0)	13 (9.2)	22 (9.9)	3 (6.4)
Lung	5 (3.4)	1 (3.3)	10 (7.1)	23 (10.3)	5 (10.6)
Musculoskeletal	3 (2.1)	0 (0.0)	1 (0.7)	3 (1.3)	0 (0.0)
Melanoma	6 (4.1)	0 (0.0)	6 (4.3)	6 (2.7)	0 (0.0)
Other	33 (22.6)	4 (13.3)	20 (14.2)	21 (9.4)	7 (14.9)

Abbreviations: CNS, central nervous system; LMWH, low-molecular-weight heparin.
Note: Data are *n* (%) unless stated otherwise.
[a]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a vitamin K antagonist alone.

Table 5 Chemotherapy and hormone therapy in patients with any cancer

Chemotherapy or hormone therapy in patients with any cancer	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[a] ($n = 47$)
Previous therapy	33 (22.6)	11 (36.7)	38 (27.0)	44 (19.7)	14 (29.8)
$<$ 6 mo before acute DVT	9 (6.2)	3 (10.0)	14 (9.9)	29 (13.0)	7 (14.9)
$\geq$ 6 mo before acute DVT	24 (16.4)	8 (26.7)	24 (17.0)	15 (6.7)	7 (14.9)
Ongoing	21 (14.4)	3 (10.0)	25 (17.7)	99 (44.4)	16 (34.0)

Abbreviations: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin.
Note: Data are *n* (%) unless stated otherwise.
[a]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a vitamin K antagonist alone.

associated with higher incidence rates for the primary outcomes. These findings highlight the importance of subanalyses of patients with and without cancer. In the early switchers cohort, primary outcome rates were either very low or no events occurred, although the sample size for this group (30 patients) was very small. For the secondary outcomes, rates of major adverse cardiovascular events were very low in all cohorts and no events occurred in the early switchers or the miscellaneous cohort; no other symptomatic thromboembolic events occurred in any of the treatment groups.

In terms of implications for clinical practice, the current study provides information on how physicians consider treatment selection, and how outcomes in cancer-associated thrombosis with a particular therapy are affected by the prognosis of the patient population. Furthermore, the low rates for the primary outcomes with rivaroxaban in patients with cancer-associated thrombosis in XALIA, and the fact that the observations were consistent with the findings from the analysis of patients with cancer and VTE in the EINSTEIN studies, should be reassuring to clinicians.

There were some limitations with this analysis: the small number of patients with cancer, particularly in the early switcher group, means that the results must be interpreted with caution (e.g., in the EINSTEIN studies, 651/8,246 [7.9%] patients had active cancer in the safety analyses).[14] The imbalances in baseline clinical characteristics between treatment cohorts coupled to the small sample size also meant that direct comparisons between treatment cohorts were not appropriate; hence, our data are presented as descriptive only. In addition, XALIA was an open-label study, which raised the possibility of bias in investigator reporting of events; however, this was alleviated by the use of objective diagnostic methods and by the adjudication of all events by the Adjudication Committee, which was blinded to the treatment choice. We collected information on the presence of cancer, but detailed information on activity of cancer is not available; however, based on data for cancer treatment (►**Table 5**), we can assume that the majority of patients had active cancer. Additionally, information relating to cancer stage was not collected, which

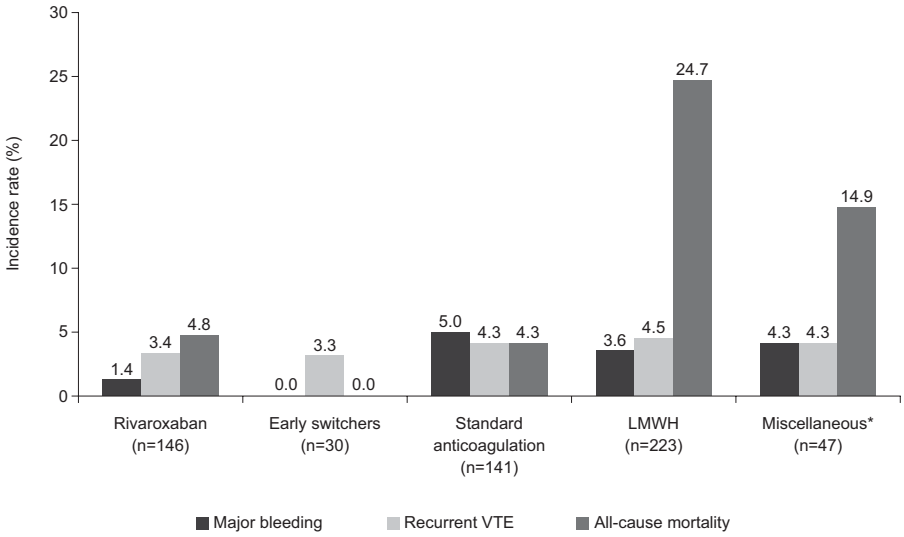

Fig. 2 Primary outcomes in patients with cancer by treatment group. Outcomes are unadjusted for imbalances in clinical characteristics at baseline, and cannot be directly compared between treatment cohorts. *Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a VKA alone. LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 6 Treatment-emergent clinical outcomes in patients with cancer

Outcome	Rivaroxaban ($n = 146$)	Early switchers ($n = 30$)	Standard anticoagulation ($n = 141$)	LMWH ($n = 223$)	Miscellaneous[a] ($n = 47$)
Safety					
Major bleeding episode (adjudicated)					
Any	2 (1.4)	0 (0.0)	7 (5.0)	8 (3.6)	2 (4.3)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal	0 (0.0)	0 (0.0)	3 (2.1)	4 (1.8)	0 (0.0)
CNS (intracranial, subdural, subarachnoid, or cerebral)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs					
Any treatment-emergent AE	67 (45.9)	18 (60.0)	70 (49.6)	135 (60.5)	21 (44.7)
Any serious AE emerging during treatment	28 (19.2)	4 (13.3)	42 (29.8)	103 (46.2)	15 (31.9)
Any AE resulting in discontinuation of study drug	15 (10.3)	1 (3.3)	8 (5.7)	41 (18.4)	3 (6.4)
Any AE leading to or prolonging hospitalization	22 (15.1)	8 (26.7)	35 (24.8)	70 (31.4)	10 (21.3)
Effectiveness					
Recurrent VTE	5 (3.4)	1 (3.3)	6 (4.3)	10 (4.5)	2 (4.3)
Type of recurrent VTE					
Fatal PE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death in which PE could not be ruled out	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)
Nonfatal PE	2 (1.4)	0 (0.0)	2 (1.4)	4 (1.8)	0 (0.0)
Recurrent DVT plus PE	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Recurrent DVT	0 (0.0)	1 (3.3)	3 (2.1)	5 (2.2)	2 (4.3)
Other	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other					
Major adverse cardiovascular events	1 (0.7)	0 (0.0)	1 (0.7)	2 (0.9)	0 (0.0)
Other thromboembolic events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All-cause mortality	7 (4.8)	0 (0.0)	6 (4.3)	55 (24.7)	7 (14.9)
Cause of death					
VTE-related death					
PE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PE not ruled out	2 (1.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Bleeding related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer related	4 (2.7)	0 (0.0)	5 (3.5)	48 (21.5)	7 (14.9)
Cardiovascular disease	1 (0.7)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)
Other	0 (0.0)	0 (0.0)	1 (0.7)	3 (1.3)	0 (0.0)

Abbreviations: AE, adverse event; CNS, central nervous system; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.
Note: Data are n (%) unless stated otherwise.
[a]Miscellaneous cohort included patients treated with other heparins, fondaparinux alone, or a vitamin K antagonist alone.

may have impacted the outcomes and therapeutic decisions depending on the distribution of early- and late-stage cancers between the treatment groups. An implicit criterion for inclusion in the study was also life expectancy beyond around 3 months, as patients were required to have an indication for at least 12 weeks of anticoagulant treatment. Therefore, this also impacted mortality outcomes as patients with shorter life expectancies were excluded.

This was consistent with what was done in the EINSTEIN DVT study. Finally, values for approximately one-third of creatinine clearance measurements were missing (in cases where measurements were not recorded on the CRF, concerted efforts were made to determine whether the measurements had not been taken, or they had been taken but not recorded on the CRF by the investigator). Therefore, safety data must be assessed cautiously, as both LMWH and rivaroxaban are renally excreted; however, as we have discussed previously, this is not unexpected in a noninterventional study.[21]

In summary, this substudy of the noninterventional XALIA study provides evidence that physicians treat cancer-associated thrombosis with different anticoagulant regimens. The most commonly prescribed treatment regimen was LMWH. The high mortality in the LMWH cohort suggests that physicians administer LMWH to patients with the most advanced cancer. Rivaroxaban and standard anticoagulation are used in patients with better prognosis and the early switchers comprise an intermediate prognosis group of patients. Switching to rivaroxaban after parenteral anticoagulation for several days can also be seen as a careful treatment approach to patient populations who were excluded from the pivotal randomized trials. Finally, it would be of interest in the future to conduct studies in populations with well-matched baseline characteristics to enable direct comparisons of rivaroxaban to LMWH in patients with cancer-associated thrombosis.

Contributions of Authors

W.A. created the initial draft of this report. W.A., L.G.M., S.H., R.K., and A.G.G.T. were members of the Adjudication Committee. M.G. performed the statistical analysis. All authors participated in writing and review of the report and accept full responsibility for its overall content.

Conflict of Interest

W.A. has received speaker's honoraria from, and participated in scientific advisory boards for, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and has received research support from Bayer. L.G.M. has received consultancy fees from Bayer and Daiichi Sankyo, and research support from Boehringer Ingelheim, Janssen-Cilag Ltd, and Pfizer Inc. S.H. has received consultancy fees from Aspen Pharmacare, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer Inc., and Sanofi SA. R.K. has received consultancy fees from Bayer, Berlin-Chemie Menarini, Daiichi Sankyo, Lundbeck Ltd, and Servier Laboratories Ltd, and speaker's honoraria from Bayer, Bristol-Myers Squibb, and Daiichi Sankyo. D.M., J.S., M.v.E. and M.G. are employees of Bayer AG. A.G.G.T. has received speaker's honoraria and consultancy fees from, and participated in scientific advisory boards for, Bayer and Janssen Research & Development, LLC.

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References

1 Young A, Chapman O, Connor C, Poole C, Rose P, Kakkar AK. Thrombosis and cancer. Nat Rev Clin Oncol 2012;9(08):437–449
2 Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008;300(19):2277–2285
3 Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol 2011;29(25):3466–3473
4 Tully CM, Apolo AB, Zabor EC, et al. The high incidence of vascular thromboembolic events in patients with metastatic or unresectable urothelial cancer treated with platinum chemotherapy agents. Cancer 2016;122(05):712–721
5 Louzada ML, Majeed H, Wells PS. Efficacy of low- molecular-weight- heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. Thromb Res 2009;123(06):837–844
6 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149(02):315–352
7 Piatek C, O'Connell CL, Liebman HA. Treating venous thromboembolism in patients with cancer. Expert Rev Hematol 2012;5(02): 201–209
8 Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287–1297
9 Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499–2510
10 Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369(09):799–808
11 Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361(24):2342–2352
12 Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369(15): 1406–1415
13 Vedovati MC, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. Chest 2015;147(02):475–483
14 Prins MH, Lensing AWA, Brighton TA, et al. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1 (01):e37–e46

15 Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016;3(01):e12–e21
16 Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001;98(05):1614–1615
17 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5 (03):632–634
18 Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer 2007;110(10): 2339–2346
19 Prandoni P, Lensing AWA, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100(10):3484–3488
20 Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000;18(17):3078–3083
21 Ageno W, Mantovani LG, Haas S, et al. Real life studies and good clinical practice - Authors' reply. Lancet Haematol 2016;3(04): e160–e161