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

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Summary

Background Patients with venous thromboembolism and cancer have a substantial risk of recurrent venous thromboembolism and bleeding during anticoagulant therapy. Although monotherapy with low-molecular-weight heparin is recommended in these patients, in clinical practice many patients with venous thromboembolism and cancer do not receive this treatment. We aimed to assess the efficacy and safety of a single-drug regimen with oral rivaroxaban compared with enoxaparin followed by vitamin K antagonists, in the subgroup of patients with cancer enrolled in the EINSTEIN-DVT and EINSTEIN-PE randomised controlled trials.

Methods We did a subgroup analysis of patients with active cancer (either at baseline or diagnosed during the study), a history of cancer, or no cancer who were enrolled in the EINSTEIN-DVT and EINSTEIN-PE trials. Eligible patients with deep-vein thrombosis (EINSTEIN-DVT) or pulmonary embolism (EINSTEIN-PE) were randomly assigned in a 1:1 ratio to receive rivaroxaban (15 mg twice daily for 21 days, followed by 20 mg once daily) or standard therapy (enoxaparin 1·0 mg/kg twice daily and warfarin or acenocoumarol; international normalised ratio 2·0–3·0). Randomisation with a computerised voice-response system was stratified according to country and intended treatment duration (3, 6, or 12 months). The prespecified primary efficacy and safety outcomes of both the trials and this subanalysis were symptomatic recurrent venous thromboembolism and clinically relevant bleeding, respectively. We did efficacy and mortality analyses in the intention-to-treat population, and bleeding analyses for time spent receiving treatment plus 2 days in the safety population (all patients who received at least one dose of study drug). The EINSTEIN-DVT and EINSTEIN-PE studies are registered at ClinicalTrials.gov, numbers NCT00440193 and NCT00439777.

Findings In patients with active cancer (diagnosed at baseline or during treatment), recurrent venous thromboembolism occurred in 16 (5%) of 354 patients allocated to rivaroxaban and 20 (7%) of 301 patients allocated to enoxaparin and vitamin K antagonist (hazard ratio [HR] 0·67, 95% CI 0·35 to 1·30). Clinically relevant bleeding occurred in 48 (14%) of 353 patients receiving rivaroxaban and in 49 (16%) of 298 patients receiving standard therapy (HR 0·80, 95% CI 0·54 to 1·20). Major bleeding occurred in eight (2%) of 353 patients receiving rivaroxaban and in 15 (5%) of 298 patients receiving standard therapy (HR 0·42, 95% CI 0·18 to 0·99). The overall frequency of recurrent venous thromboembolism in patients with only a history of cancer (five [2%] of 233 patients in the rivaroxaban group *vs* five [2%] of 236 in the standard therapy group; HR 0·98, 95% CI 0·28–3·43) was similar to that of patients without cancer (65 [2%] of 3563 *vs* 70 [2%] of 3594, respectively; HR 0·93, 95% CI 0·66–1·30), but the frequency was increased in patients with active cancer at baseline (six [2%] of 258 *vs* eight [4%] of 204, respectively; HR 0·62, 95% CI 0·21–1·79) and most markedly increased in patients whose diagnosis of cancer was made during the study (ten [10%] of 96 *vs* 12 [12%] of 97, respectively; HR 0·80, 95% CI 0·34–1·88). The overall frequency of major bleeding in patients with only a history of cancer (one [<1%] patient in the rivaroxaban group *vs* four [2%] patients in the standard therapy group; HR 0·23, 95% CI 0·03–2·06) was similar to that of patients without cancer (31 [1%] *vs* 53 [1%], respectively; HR 0·58, 95% CI 0·37–0·91), but was increased in patients with active cancer at baseline (five [2%] *vs* eight [4%], respectively; HR 0·47, 95% CI 0·15–1·45) and was highest in those with cancer diagnosed during the study (three [3%] *vs* seven [7%], respectively; HR 0·33, 95% CI 0·08–1·31).

Interpretation In patients with active cancer and venous thromboembolism, rivaroxaban had similar efficacy to prevent recurrence of venous thromboembolism and reduced the number major bleeding events compared with treatment with enoxaparin and a vitamin K antagonist, although there was no difference between groups for clinically relevant bleeding. Based on these results, a head-to-head comparison of rivaroxaban with long-term low-molecular-weight heparin in patients with cancer is warranted.

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Introduction

The EINSTEIN-DVT[1] and EINSTEIN-PE[2] studies compared rivaroxaban (an oral direct inhibitor of factor Xa) with enoxaparin given with and followed by a vitamin K antagonist for the treatment of deep-vein thrombosis (EINSTEIN-DVT) or pulmonary embolism (EINSTEIN-PE).[1,2] Both studies used an identical design, treatment regimens, outcome definitions and adjudication processes, and a pooled analysis of the two trials showed similar efficacy and a lower incidence of major bleeding events in patients treated with rivaroxaban compared with those treated with enoxaparin and vitamin K antagonist.[3,4] The results of these studies formed the basis for regulatory approval of rivaroxaban for acute and extended treatment of deep-vein thrombosis and pulmonary embolism.

Roughly 10–20% of patients with acute deep-vein thrombosis or pulmonary embolism have either a history of cancer or active cancer.[5–7] Additionally, a diagnosis of previously undetected malignant disease is often made in patients during the first months after acute presentation of unprovoked deep-vein thrombosis or pulmonary embolism.[8–10]

Patients with cancer have a treatment dilemma because anticoagulant treatment with vitamin K antagonists carries not only a residual high risk of recurrent venous thromboembolism but also a high risk of serious bleeding.[11,12] In a meta-analysis of studies comparing standard treatment (low-molecular-weight heparin and vitamin K antagonist) in patients with cancer and venous thromboembolism with long-term low-molecular-weight heparin treatment alone for 3–6 months, patients receiving long-term low-molecular-weight heparin had a relative risk reduction for recurrent venous thromboembolism of more than 50% compared with those receiving standard treatment; however, low-molecular-weight heparin therapy was associated with a statistically non-significant increase in risk of major bleeding.[13] Therefore, patients with cancer and venous thromboembolism are recommended to receive monotherapy with long-term low-molecular-weight heparin.[14–18] However, the level of this recommendation is qualified as 2b (ie, weak with underlying evidence of moderate quality). Consequently, on the basis of medical, economical, and quality-of-life considerations, many physicians still treat patients who have cancer and venous thromboembolism with vitamin K antagonists.

The EINSTEIN-DVT and EINSTEIN-PE studies assessed patients with deep-vein thrombosis or pulmonary embolism, and did not exclude patients with cancer. We aimed to analyse the efficacy and safety of rivaroxaban compared with enoxaparin given concurrently with a vitamin K antagonist, followed by vitamin K antagonist alone, in the subgroups of patients in these trials with a history of cancer, active cancer at baseline, and cancer that became symptomatic after randomisation. Additionally, we compared the frequency of events in these patients with those without any history of cancer.

Methods

Study design and participants

In a subgroup analysis, we included patients with cancer from the EINSTEIN-DVT and EINSTEIN-PE trials (two randomised, open-label, phase 3 studies). Patients were potentially eligible for the EINSTEIN-DVT and EINSTEIN-PE studies if they had symptomatic deep-vein thrombosis or pulmonary embolism. The main exclusion criteria were a therapeutic dose of low-molecular-weight heparin, fondaparinux, or unfractionated heparin for more than 48 h before randomisation; more than a single dose of a vitamin K antagonist; treatment of the present episode with thrombectomy, a caval filter, or fibrinolytic therapy; any contraindication listed in the local labelling of enoxaparin, warfarin, or acenocoumarol; a creatinine clearance less than 30 mL/min; pregnancy or breastfeeding; active bleeding or a disorder at high risk for bleeding; or a life expectancy of less than 3 months.[1,2]

The studies were undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocols were reviewed and approved by the institutional review boards of each participating centre. Written informed consent was obtained from all patients.

Randomisation and masking

Randomisation was done separately for patients with deep-vein thrombosis and pulmonary embolism (with or without deep-vein thrombosis), with a computerised voice-response system, and was stratified according to country and the intended treatment duration (3, 6, or 12 months), as decided locally before randomisation. Patients were randomly assigned in a 1:1 ratio to receive rivaroxaban or enoxaparin with a vitamin K antagonist. Patients assigned to rivaroxaban were given 15 mg orally twice daily for 21 days, followed by 20 mg once daily. Rivaroxaban was not subject to dose reductions. Patients assigned to the enoxaparin and vitamin K antagonist group received enoxaparin subcutaneously at a dose of 1·0 mg/kg bodyweight twice daily and either oral warfarin or acenocoumarol (target international normalised ratio [INR] 2·0–3·0), started within 48 h after randomisation. Enoxaparin was discontinued when the INR was 2·0 or more for 2 days consecutively and the patient had received at lease 5 days of enoxaparin treatment. The dose of the vitamin K antagonist was adjusted to maintain an INR of 2·0–3·0.

All suspected outcomes were classified by an independent blinded adjudication committee.

Procedures

Patients were followed up for the intended treatment period (3, 6, or 12 months) at 1 week, 2 weeks, 1 month, and monthly thereafter. At each visit, a checklist was used

to collect information about symptoms and signs of recurrent venous thromboembolism, bleeding, and adverse events. Patients were instructed to report to the study centre immediately if any of these symptoms or signs occurred. In the case of suspected venous thromboembolism, objective testing was required, using ultrasonography or contrast venography for suspected deep vein thrombosis and ventilation-perfusion scanning or spiral CT-angiography for suspected pulmonary embolism.

The presence of cancer was reported on the case report forms by the investigators as only a history of cancer or active cancer at study entry. Additionally, all adverse events related to cancer during treatment were reported. All reported cancers were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). For this analysis, we reviewed all patients with any reported cancer and classified or reclassified them with the following hierarchy: active cancer at baseline, defined as a diagnosis of cancer that occurred within 6 months before enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer;[4] active cancer during the study, defined as a new diagnosis of cancer or recurrence of cancer after randomisation; and a history of cancer, defined as any cancer not meeting the criteria of active cancer (ie, having previously had cancer that was either cured or in remission). This review was done by medical experts (MT, MHP), who were unaware of study treatment allocation and study outcomes and considered the totality of baseline and outcome data obtained from the investigator.

We categorised cancer entities as breast, upper gastrointestinal (including liver and pancreas), lower gastrointestinal, lung, genitourinary tract, brain, haematological system, skin (excluding basal-cell or squamous-cell carcinoma), basal cell or squamous-cell carcinoma, unspecified, other, or combinations. If a patient had a basal-cell or squamous-cell carcinoma of the skin in combination with another type of cancer, the latter category prevailed.

Outcomes

The prespecified primary efficacy outcome of both the trials and this subanalysis was symptomatic recurrent venous thromboembolism (ie, the composite of fatal or non-fatal pulmonary embolism or deep-vein thrombosis). We classified death as due to pulmonary embolism, bleeding, or other established causes or diagnoses. We classified pulmonary embolism as the cause of death if there was objective documentation of the disorder or if death could not be attributed to a documented cause and pulmonary embolism could not be confidently ruled out. The prespecified safety outcome of both the trials and this subanalysis was clinically relevant bleeding, defined as the composite of major and non-major clinically relevant bleeding. Bleeding was defined as major if it was clinically overt and associated with a decrease in haemoglobin concentration of at least 2·0 g/dL; if bleeding led to the transfusion of at least two units of red cells; or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death. Non-major clinically relevant bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study drug, or discomfort or impairment of activities of daily life. We also prespecified to analyse net clinical benefit as a secondary outcome as in the original trials, which was defined as the composite of the primary efficacy outcome and major bleeding (first occurrence of the primary efficacy outcome or major bleeding). Major bleeding and mortality were also secondary outcomes.

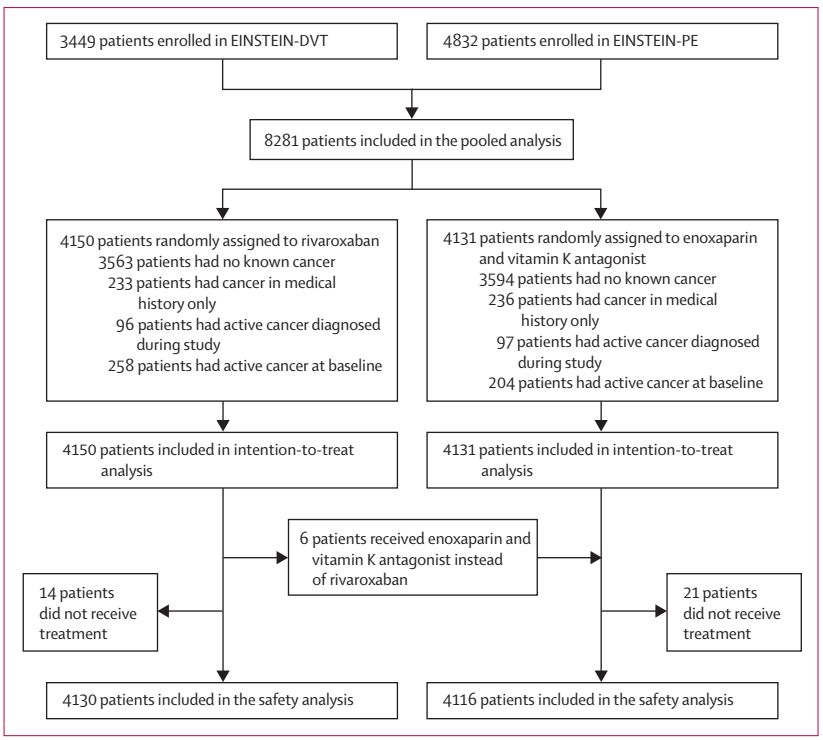

Figure 1: **Study design**

Statistical analysis

For both the subgroup analysis and trials, we did efficacy and mortality analyses on an intention-to-treat basis with a Cox proportional hazards model, stratified according to the qualifying deep-vein thrombosis or pulmonary embolism and the intended duration of treatment, adjusted for age, as a continuous variable. Schoenfeld-residual plots and log(–log) plots showed that the proportionality assumption was met (appendix). Bleeding analyses were done similarly, but for all randomly assigned patients for the time they had received study drug, plus 2 days.[1,2] We analysed bleeding outcomes in the safety population (all patients who received at least one

See Online for appendix

	No known cancer		Cancer in medical history only		Active cancer at baseline		Active cancer diagnosed during the study	
	Rivaroxaban (n=3563)	Enoxaparin and vitamin K antagonist (n=3594)	Rivaroxaban (n=233)	Enoxaparin and vitamin K antagonist (n=236)	Rivaroxaban (n=258)	Enoxaparin and vitamin K antagonist (n=204)	Rivaroxaban (n=96)	Enoxaparin and vitamin K antagonist (n=97)
Sex								
Male	1973 (55%)	1931 (54%)	120 (52%)	123 (52%)	152 (59%)	109 (53%)	57 (59%)	51 (53%)
Female	1590 (45%)	1663 (46%)	113 (48%)	113 (48%)	106 (41%)	95 (47%)	39 (41%)	46 (47%)
Age								
<65 years	2378 (67%)	2394 (67%)	80 (34%)	80 (34%)	109 (42%)	77 (38%)	39 (41%)	39 (40%)
65–75 years	708 (20%)	707 (20%)	74 (32%)	97 (41%)	80 (31%)	77 (38%)	26 (27%)	33 (34%)
>75 years	477 (13%)	493 (14%)	79 (34%)	59 (25%)	69 (27%)	50 (25%)	31 (32%)	25 (26%)
Planned treatment duration								
3 months	303 (9%)	297 (8%)	11 (5%)	13 (6%)	19 (7%)	12 (6%)	2 (2%)	3 (3%)
6 months	2098 (59%)	2159 (60%)	144 (62%)	133 (56%)	168 (65%)	127 (62%)	60 (63%)	51 (53%)
12 months	1162 (33%)	1138 (32%)	78 (33%)	90 (38%)	71 (28%)	65 (32%)	34 (35%)	43 (44%)
Creatinine clearance								
Missing	34 (1%)	26 (1%)	4 (2%)	2 (1%)	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
≥80 mL/min	2481 (70%)	2523 (70%)	99 (42%)	113 (48%)	125 (48%)	97 (48%)	43 (45%)	54 (56%)
50 to <80 mL/min	804 (23%)	800 (22%)	89 (38%)	91 (39%)	98 (38%)	71 (35%)	39 (41%)	30 (31%)
<50 mL/min	244 (7%)	245 (7%)	41 (18%)	30 (13%)	34 (13%)	35 (17%)	13 (14%)	12 (12%)
Fragility*								
No	2975 (83%)	2979 (83%)	146 (63%)	169 (72%)	175 (68%)	132 (65%)	63 (66%)	69 (71%)
Yes	588 (17%)	615 (17%)	87 (37%)	67 (28%)	83 (32%)	72 (35%)	33 (34%)	28 (29%)
Body-mass index	28·2 (5·8)	28·2 (5·7)	27·7 (5·0)	28·9 (5·7)	27·4 (5·4)	26·7 (4·6)	27·8 (5·4)	27·8 (5·8)
Recurrent or metastatic cancer	..	..	..	..	49 (19%)	52 (25%)	18 (19%)	25 (26%)
Chemotherapy	..	..	..	..	74 (29%)	62 (30%)	14 (15%)	19 (20%)
Total duration of initial LMWH treatment (days)†	1·0 (0·9–1·4)	7·4 (5·8–10·2)	1·0 (0·0–1·4)	7·6 (6·0–10·0)	1·0 (0·5–1·3)	7·4 (5·3–9·7)	1·0 (0·5–1·3)	7·0 (5·5–9·6)
Total treatment duration (days)	183 (179–273)	182 (178–267)	183 (180–311)	182 (178–347)	182 (132–187)	181 (97–187)	180 (59–186)	178 (36–243)
Mean proportion of time spent with international normalised ratio								
<2·0	..	23%	..	22%	..	21%	..	20%
2·0–3·0	..	62%	..	63%	..	57%	..	59%
>3·0	..	16%	..	16%	..	23%	..	22%
Overall compliance ≥80%	3315 (93%)	3333 (93%)	222 (95%)	220 (93%)	239 (93%)	195 (96%)	84 (88%)	90 (93%)

Data are n (%), mean (SD), or median (IQR). LMWH=low-molecular-weight heparin. *Fragility was defined as one or more of the following criteria: age older than 75 years, calculated creatinine clearance less than 50 mL/min, or low bodyweight (≤50 kg). †Including prerandomisation treatment.

***Table 1*: Demographic and treatment characteristics**

dose of study medication). Because this analysis was a subgroup analysis, we did no formal sample size calculation. However, the prespecified threshold for the upper limit of the 95% CI of the hazard ratio (HR) for the primary efficacy analysis of the pooled EINSTEIN-DVT and EINSTEIN-PE studies to accept non-inferiority was 1·75.[1,2] We calculated p values for interaction using the Wald test. The occurrence of recurrent venous thromboembolism, mortality, and major bleeding are presented as absolute percentages. We calculated absolute risk differences (ARD) and their 95% CIs as weighted absolute risk differences for the rivaroxaban group minus the enoxaparin and vitamin K antagonist group using the Mantel–Haenszel asymptotic method, with the weights based on sample sizes per strata (qualifying deep-vein thrombosis or pulmonary embolism, intended duration of treatment, age <60 years *vs* ≥60 years). In this analysis, we describe outcomes for defined patient groups with cancer (ie, active cancer; at baseline, diagnosed during the study, or both combined), a history of cancer, and no known cancer. We calculated the mean time during which the INR was below, within, or above the therapeutic range after the discontinuation of enoxaparin, with correction for interruptions in the administration of vitamin K antagonists or the use of concomitant heparins.[4] We did a prespecified analysis to estimate the effects of age, bodyweight, renal function, presence of metastases or recurrent cancer, or use of chemotherapy on recurrent

venous thromboembolism and major bleeding. We tested the effects of age, bodyweight, and renal function on occurrence of recurrent venous thromboembolism and major bleeding by including these factors as three categories in the Cox proportional hazards models as a single covariate (Wald test for trend with one degree of freedom). Calculations were done with the statistical software package SAS version 9.2.

The EINSTEIN-DVT and EINSTEIN-PE studies are registered at ClinicalTrials.gov, numbers NCT00440193 and NCT00439777.

Role of the funding source

Bayer HealthCare Pharmaceuticals and Janssen Research and Development, the funders of the EINSTEIN-DVT and EINSTEIN-PE studies, gathered, maintained, and extracted data. The authors had responsibility for interpreting the data and writing the article. MHP, AWAL, PP, and PSW had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between March 22, 2007, and March 12, 2011, 8281 patients (3449 in the EINSTEIN-DVT trial and 4832 in the EINSTEIN-PE trial) were enrolled at 314 sites in 38 countries; 4150 patients were randomly assigned to receive rivaroxaban and 4131 were randomly assigned to receive standard therapy. Of the 655 (8%) patients with any active cancer, 462 (6%) presented with the diagnosis at baseline, and 193 (2%) were diagnosed with cancer during the study. A further 469 (6%) patients had a history of cancer but not active cancer and 7157 (86%) never had any cancer (figure 1). Patients with any cancer were older, more had renal impairment, and they were more often classified as fragile compared with patients without any cancer (table 1). Within the four defined groups (ie, active cancer at baseline, active cancer diagnosed during the study, history of cancer, and no known cancer), the demographic characteristics of the patients were similar for those treated with rivaroxaban and those treated with enoxaparin and vitamin K antagonist. Review of cancer diagnoses resulted in reclassification of 38 patients in the rivaroxaban group and 20 in the standard-therapy group; 14 patients with active basal-cell or squamous-cell carcinoma of the skin remained in the cancer group, because they were not excluded a priori.

Treatment characteristics for the four groups are given in table 1. Compared with patients without cancer or those with a history of cancer, patients with active cancer at baseline or diagnosed during the study had a lower proportion of INR values in the therapeutic range (2·0–3·0) and a higher proportion of INR values above 3·0.

The overall frequency of recurrent venous thromboembolism in patients with only a history of cancer was similar to that of patients without cancer, but the frequency was increased in patients with active cancer at baseline and most markedly increased in patients whose diagnosis of cancer was made during the study (table 2).

Recurrent venous thromboembolism occurred in 36 (5%) of 655 patients with active cancer (at baseline or presenting during the study) compared with 145 (2%) of 7626 patients with no active cancer (adjusted HR 3·12, 95% CI 2·14–4·54). In patients with active cancer, recurrent venous thromboembolism occurred in similar frequency in the two treatment groups (table 3). Of the 16 events in the rivaroxaban group, 13 occurred while patients were still receiving assigned treatment; in the enoxaparin and vitamin K antagonist group, 20 events were recorded of which 16 occurred while patients were receiving treatment.

	No known cancer			Cancer in medical history only			Active cancer at baseline			Active cancer diagnosed during the study		
	Riva-roxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)	Riva-roxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)	Riva-roxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)	Riva-roxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)
Intention-to-treat population	3563	3594	..	233	236	..	258	204	..	96	97	..
Safety population	3546	3582	..	231	236	..	257	202	..	96	96	..
Recurrent venous thromboembolism*	65 (2%)	70 (2%)	0·93 (0·66–1·30)	5 (2%)	5 (2%)	0·98 (0·28–3·43)	6 (2%)	8 (4%)	0·62 (0·21–1·79)	10 (10%)	12 (12%)	0·80 (0·34–1·88)
Major bleeding†	31 (1%)	53 (1%)	0·58 (0·37–0·91)	1 (<1%)	4 (2%)	0·23 (0·03–2·06)	5 (2%)	8 (4%)	0·47 (0·15–1·45)	3 (3%)	7 (7%)	0·33 (0·08–1·31)
Clinically relevant bleeding†	315 (9%)	341 (10%)	0·92 (0·79–1·07)	25 (11%)	22 (9%)	1·16 (0·65–2·05)	30 (12%)	27 (13%)	0·82 (0·48–1·38)	18 (19%)	22 (23%)	0·81 (0·43–1·52)
Mortality*	33 (1%)	42 (1%)	0·77 (0·49–1·22)	5 (2%)	4 (2%)	1·12 (0·30–4·22)	38 (15%)	36 (18%)	0·82 (0·52–1·30)	20 (21%)	17 (18%)	1·30 (0·67–2·52)
Net clinical benefit*	100 (3%)	122 (3%)	0·82 (0·63–1·06)	9 (4%)	9 (4%)	0·98 (0·39–2·48)	12 (5%)	19 (9%)	0·50 (0·24–1·03)	13 (14%)	19 (20%)	0·61 (0·30–1·25)

Data are n (%) or HR (95% CI). HR=hazard ratio. *Percentage based on intention-to-treat population. †Percentage based on safety population.

Table 2: **Recurrent venous thromboembolism, major bleeding, mortality, and net clinical benefit**

	Rivaroxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)	ARD (95% CI)	p value*
Intention-to-treat population	354	301	..	..	..
Safety population	353	298	..	..	..
Recurrent venous thromboembolism†	16 (5%)	20 (7%)	0·67 (0·35 to 1·30)	−1·7% (−5·2 to 1·8)	0·24
Major bleeding‡	8 (2%)	15 (5%)	0·42 (0·18 to 0·99)	−3·0% (−5·9 to 0·0)	0·047
Clinically relevant bleeding‡§	48 (14%)	49 (16%)	0·80 (0·54 to 1·20)	−2·7% (−8·3 to 3·0)	0·28
Mortality†	58 (16%)	53 (18%)	0·93 (0·64 to 1·35)	−1·6% (−7·4 to 4·2)	0·70
Net clinical benefit†	25 (7%)	38 (13%)	0·54 (0·33 to 0·90)	−5·3% (−9·9 to −0·7)	0·018

Data are n (%) or HR (95% CI). HR=hazard ratio. *Calculated from the Cox models. †Percentage based on intention-to-treat population. ‡Percentage based on safety population. §Composite of major bleeding and non-major clinically relevant bleeding.

***Table 3*: Recurrent venous thromboembolism, bleeding, mortality, and net clinical benefit in patients with active cancer**

The overall frequency of major bleeding in patients with only a history of cancer was similar to that of patients without cancer, but was increased in patients with active cancer at baseline and was highest in those with cancer diagnosed during the study (table 2). Major bleeding occurred in 23 (4%) of 651 patients with active cancer compared with 89 (1%) of 7595 patients with no active cancer (adjusted HR 2·87; 95% CI 1·80–4·58). In patients with active cancer, there were fewer major bleeding events in patients treated with rivaroxaban, compared to those treated with enoxaparin and a vitamin K antagonist (table 3). In patients with active cancer, three of the eight major bleeding events in the rivaroxaban group and nine of the 15 major bleeding events in the enoxaparin and vitamin K antagonist group were related to cancer.

Clinically relevant bleeding occurred in 97 (15%) of 651 patients with active cancer (at baseline or diagnosed during the study) compared with 703 (9%) of 7595 patients with no active cancer (HR 1·73; 95% CI 1·39–2·14). In patients with active cancer, clinically relevant bleeding was similar between the two groups (table 3).

111 (17%) of 655 patients with active cancer died compared with 84 (1%) of 7626 patients without active cancer (adjusted HR 13·48; 95% CI 10·06–18·05). In patients with active cancer, 58 (16%) of 354 patients died in the rivaroxaban group and 53 (18%) of the 301 patients in the enoxaparin and vitamin K antagonist group died (HR 0·93; 95% CI 0·64 to 1·35; weighted ARD −1·6%, 95% CI −7·4 to 4·2). In patients with active cancer at baseline, the number of patients who died was similar between the two treatment groups (table 3).

The composite outcome of recurrent venous thromboembolism and major bleeding (net clinical benefit) occurred in 63 (10%) of 655 patients with active cancer (at baseline or diagnosed during the study) compared with 240 (3%) of 7626 patients with no active cancer (adjusted HR 3·08; 95% CI 2·32–4·10). In patients with active cancer, there were fewer adverse outcomes for patients treated with rivaroxaban compared with patients treated with enoxaparin and a vitamin K antagonist (table 3).

Table 4 shows the frequency of recurrent venous thromboembolism and major bleeding by cancer subtype. Although most of the subgroups have few patients, most events seem to concentrate in patients with lung cancer, upper gastrointestinal cancer, genitourinary tract cancer, and haematological malignancies.

In patients with active cancer, the HRs for recurrent venous thromboembolism and major bleeding were generally similar for subgroups according to age, bodyweight, creatinine clearance, presence of recurrent or metastatic cancer, and chemotherapy (figure 2). For both treatments groups individually, decreasing bodyweight was not associated with an increased rate of major bleeding (figure 2).

By contrast, there was no significant difference in the rivaroxaban group in the proportion of patients who had a major bleeding event with decreasing renal function (p_{trend}=0·92), but in patients treated with enoxaparin and a vitamin K antagonist, there were significantly more major bleeding events with decreasing renal function (p_{trend}=0·01).

Discussion

This subgroup analysis in patients with acute venous thromboembolism showed similar efficacy of a single-drug approach with oral, fixed-dose rivaroxaban to the combination of subcutaneous enoxaparin and INR-titrated therapy with vitamin K antagonist in patients with cancer, and consistent results across all important clinical subgroups. The increased risk of recurrent venous thromboembolism and major bleeding, and increased mortality in patients with active cancer compared with those without active cancer, is consistent with previous reports,[11,12] and underlines the importance of separate analyses for patients with and without cancer. Rivaroxaban had a significant advantage compared with enoxaparin and vitamin K antagonist in patients with active cancer with regard to major bleeding and net clinical benefit, consistent with the overall result of the pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies.[4]

The number of patients with active cancer either at baseline or diagnosed during the study differed slightly from the numbers reported previously in the main study publications.[1,2,4] Although the trial investigators were asked to indicate in the case report form the presence of active cancer (defined as cancer that occurred within 6 months before enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer) and history of cancer, during case review for this analysis we noted that in several patients a misclassification had occurred that had not been identified during the monitoring and electronic querying processes. That is, some patients were not classified as having active

	Cancer in medical history only		Active cancer at baseline		Active cancer diagnosed during the study	
	Rivaroxaban	Enoxaparin and vitamin K antagonist	Rivaroxaban	Enoxaparin and vitamin K antagonist	Rivaroxaban	Enoxaparin and vitamin K antagonist
All cancer sites						
Recurrent VTE	5/233 (2%)	5/236 (2%)	6/258 (2%)	8/204 (4%)	10/96 (10%)	12/97 (12%)
Major bleeding	1/231 (<1%)	4/236 (2%)	5/257 (2%)	8/202 (4%)	3/96 (3%)	7/96 (7%)
Breast						
Recurrent VTE	0/40	0/45	0/27	1/26	0/5	0/4
Major bleeding	0/39	1/44	0/27	0/26	0/5	0/4
Endocrine						
Recurrent VTE	0/5	0/3	0/2	0/1	0/2	0/4
Major bleeding	0/5	0/3	0/2	0/1	0/2	0/4
Upper gastrointestinal (including liver or pancreas)						
Recurrent VTE	1/10	0/5	0/17	0/5	2/12	2/9
Major bleeding	0/10	0/5	0/17	1/5	0/12	2/9
Lower gastrointestinal						
Recurrent VTE	0/14	0/22	0/24	0/20	0/18	1/8
Major bleeding	0/14	1/22	1/24	0/20	1/18	1/8
Lung						
Recurrent VTE	0/3	0/3	0/21	1/13	2/13	5/17
Major bleeding	0/3	0/3	0/21	0/13	0/13	2/17
Genitourinary tract						
Recurrent VTE	1/83	0/68	3/74	0/69	4/15	2/27
Major bleeding	0/82	1/69	2/74	7/69	0/15	1/27
Brain						
Recurrent VTE	0/0	0/1	1/4	0/3	0/1	1/2
Major bleeding	0/0	0/1	0/4	0/3	0/1	0/2
Haematological						
Recurrent VTE	1/10	1/12	1/42	0/25	1/12	1/7
Major bleeding	0/10	0/12	1/42	0/25	2/12	1/6
Skin (excluding squamous-cell or basal-cell carcinoma)						
Recurrent VTE	1/22	1/23	0/6	0/2	0/4	0/1
Major bleeding	0/22	0/23	1/6	0/2	0/4	0/1
Squamous-cell or basal-cell carcinoma						
Recurrent VTE	1/31	0/39	0/8	2/6	0/0	0/0
Major bleeding	0/31	1/39	0/8	0/6	0/0	0/0
Combinations						
Recurrent VTE	0/8	2/9	0/17	1/21	0/1	0/1
Major bleeding	1/8	0/9	0/17	0/21	0/1	0/1
Other or unspecified						
Recurrent VTE	0/9	1/8	0/15	2/11	1/2	0/2
Major bleeding	0/9	0/8	0/15	0/11	0/2	0/2

Data are n/N (%) or n/N. VTE=venous thromboembolism.

Table 4: **Recurrent venous thromboembolism and major bleeding in patients with cancer, by cancer site**

cancer but received cancer treatment during the 6-month period before randomisation or had recurrent or metastatic cancer. Hence, we decided to reclassify all patients with any cancer, which resulted in a reclassification of 38 patients in the rivaroxaban group and 20 in the standard-therapy group. Finally, 14 patients with (active) basal-cell or squamous-cell carcinoma of the skin remained in the cancer group, because they were not excluded a priori. However, these patients were a minority in the active cancer group and only a few events occurred in these patients (table 4).

The suggestion that rivaroxaban can be given at the same dose in all patients without laboratory monitoring has raised concern. Therefore, we did subgroup analyses for both efficacy and safety in patients with active cancer for age, bodyweight, renal function, presence of metastases or recurrent cancer, and use of chemotherapy. The HRs for recurrent venous

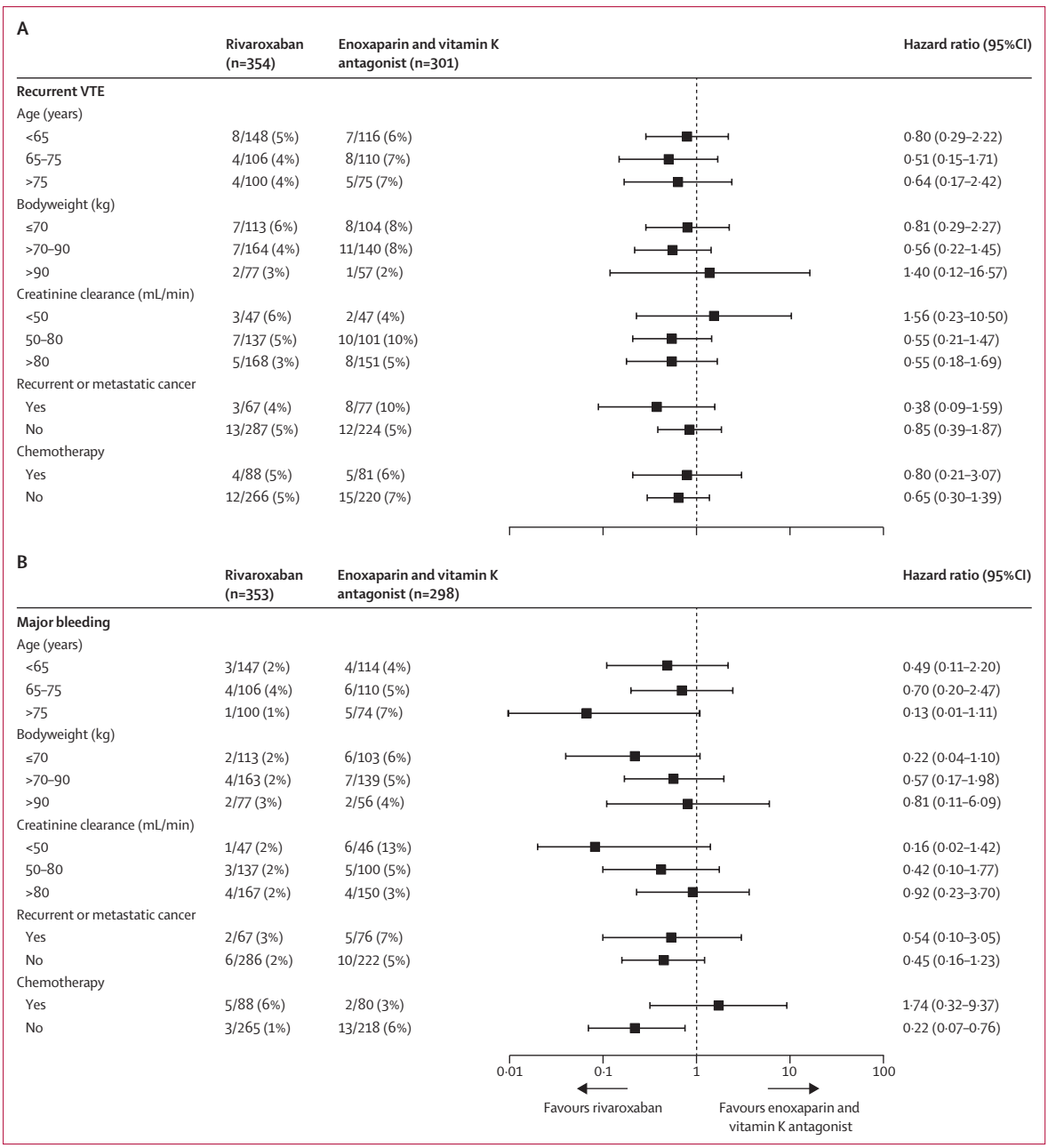

***Figure 2*: Forest plots of recurrent venous thromboembolism (A) and major bleeding (B) among patients with active cancer**

thromboembolism and major bleeding between both treatment arms were generally similar in these subgroups. As noted in a separate analysis of the EINSTEIN data,[19] there were more major bleeding events reported in patients with decreasing renal function who received enoxaparin and vitamin K antagonist, but not in those receiving rivaroxaban. Fixed-dosed rivaroxaban did not result in an increase of major bleeding with decreasing bodyweight. These results are consistent with the pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies.[3,4]

Some limitations of our study should be noted. Firstly, the EINSTEIN-DVT and EINSTEIN-PE studies used an open-label design that could have biased assessment of outcomes. Nevertheless, we made efforts to reduce investigator bias, including the requirement to use objective and validated tests to confirm suspected recurrent venous thromboembolism and the use of an independent adjudication committee, whose members were blinded to treatment assignment, to adjudicate outcome events.

Second, in the enoxaparin and vitamin K antagonist group, the choice of vitamin K antagonist was limited to

acenocoumarol or warfarin, which might not have been the vitamin K antagonist of choice for some participating centres. However, INR monitoring was intensive and required assessment at least once a month. Although the time spent in therapeutic INR range was lower for patients with active cancer in this study, the reported percentage of time in therapeutic range (57%) and below therapeutic range (20%) for these patients compared favourably with that reported by Lee and colleagues[15] (46% and 30%, respectively).

Third, patients with cancer included in the study might have been less ill than were those excluded because patients with a life expectancy of less than 3 months or requiring long-term treatment with subcutaneous low-molecular-weight heparin (as judged by their treating physician) were not eligible for the EINSTEIN studies.[13–18] Additionally, patients diagnosed with cancer after randomisation were retrospectively reclassified to the cancer group during the study. However, unless rivaroxaban or enoxaparin with vitamin K antagonist could have differential effects on a new diagnosis of cancer during the trial, the principle of randomisation was maintained with an intention-to-treat approach to the analysis. Indeed, the noted frequency of active cancer during the study was 2% in both treatment groups, hence there was no indication for such a differential effect. Furthermore, we did not adjust for other risk factors for venous thromboembolism such as male sex and body-mass index. However, these risk factors were balanced within each subgroup and did not substantially affect recurrent venous thromboembolism during anticoagulant treatment (table 1).

A final limitation was the absence of a formal sample size calculation. However, the upper limit of the 95% CI of the observed HR in patients with active cancer was 1·30, which compared favourably with the a-priori specified threshold for non-inferiority (ie, 1·75) for the primary analysis of the pooled EINSTEIN studies.[3,4]

What implications do our results have for clinical practice? Compared with vitamin K antagonists, rivaroxaban has a short half-life,[20,21] which facilitates temporary interruptions for procedures or periods of thrombocytopenia. Rivaroxaban does not need routine laboratory monitoring of coagulation, whereas with vitamin K antagonist even intensive INR monitoring results in a time in therapeutic range that is often less than optimum. Rivaroxaban has no relevant food interactions, and drug interactions with chemotherapeutic and other anticancer agents are expected to be small, with no requirement for a rivaroxaban dose adaptation.[22] Thus, frequently used drugs for cancer treatment that inhibit P-glycoprotein transport or the cytochrome P450 3A4 pathway (eg, ciclosporin, tacrolimus, tamoxifen, lapatinib, nilotinib, sunitinib, and imatinib) increase rivaroxaban concentrations only modestly, whereas drugs that induce P-glycoprotein transport or the cytochrome P450 3A4 pathway (eg, dexamethasone, doxorubicin, and vinblastine) decrease rivaroxaban concentrations only modestly.

Although a comparison with long-term low-molecular-weight heparin was not investigated in the EINSTEIN studies, it is clear that, by contrast with low-molecular-weight heparins, rivaroxaban does not require parenteral administration or weight-adjusted dosing, has no risk of heparin-induced thrombocytopenia, and could have, especially when compared with enoxaparin, a lower risk of accumulation in patients with renal impairment, which is not uncommon among patients with cancer.[4,19,23] Finally, in the general population of the EINSTEIN studies, patient-reported satisfaction and quality of life was better in the rivaroxaban-treated patients than in the group treated with enoxaparin and vitamin K antagonist, although we have not yet examined whether this is the same in patients with active cancer.[24,25] Hence, it can be expected that quality of life will also be improved with rivaroxaban compared with long-term injected low-molecular-weight heparin.

We believe that in patients with active cancer and venous thromboembolism, rivaroxaban can be considered as an alternative in those cases in which the attending physician would have given therapy including a vitamin K antagonist rather than long-term low-molecular-weight heparin. Based on these results in patients with cancer, a head-to-head comparison of rivaroxaban with long-term low-molecular-weight heparin is warranted.

***Panel*: Research in context**

Systematic review

We searched PubMed using the terms "deep vein thrombosis", "pulmonary embolism", "venous thromboembolism", "cancer", and "anticoagulant treatment", without any restrictions.

Interpretation

In patients with cancer with venous thromboembolism, long-term monotherapy with low-molecular-weight heparin is recommended. However, the level of this recommendation is qualified as 2b (ie, weak with underlying evidence of moderate quality). Consequently, on the basis of medical, economic, and quality-of-life considerations, many physicians still give patients with cancer and venous thromboembolism long-term therapy with vitamin K antagonists. This analysis of the EINSTEIN-DVT and EINSTEIN-PE studies addressed the efficacy and safety of rivaroxaban versus enoxaparin and vitamin K antagonist in the subgroups of patients with a history of cancer, active cancer at baseline, and active cancer diagnosed during the study. The data showed that in patients with active cancer and venous thromboembolism, rivaroxaban had similar efficacy and improved safety compared with enoxaparin and vitamin K antagonist, consistent with the overall result of the pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies. Therefore, rivaroxaban could be considered as an alternative in those cases in which the attending physician would have given standard therapy of a short course of a low-molecular-weight heparin with a vitamin K antagonist, rather than long-term low-molecular-weight heparin, although a head-to-head comparison between long-term low-molecular-weight heparin and rivaroxaban is still required.

Contributors

MHP, AWAL, PP, and PSW created the initial draft version of this manuscript. MHP and MT performed the reclassification of patients with cancer. ÁFP performed statistical analysis. All authors participated in writing and review of the article and accept full responsibility for its overall content.

Declaration of interests

MHP has received research support and honoraria, and has participated in advisory boards for Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Daiichi Sankyo, LEO Pharma, ThromboGenics, and Pfizer. AWAL, MT, ÁFP, and SDB are employees of Bayer HealthCare Pharmaceuticals. TAB has received honoraria from Bayer HealthCare, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, Amgen Australia, and GlaxoSmithKline. RML and JR have received honoraria in connection with patient recruitment and follow-up in the EINSTEIN study. BLD has received honoraria from Bayer and Daiichi Sankyo. JB-W has participated in scientific advisory boards for and received speaker's honoraria and research support from Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Novartis, LEO Pharma, and other manufacturers of anticoagulants. ATC has served on advisory boards for Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, Portola, and Sanofi, and has received consulting fees, lecture fees, support for manuscript preparation, and payment for the development of educational presentations from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. MJK has received research support from Pfizer, Bayer, and Daiichi Sankyo, and has participated in scientific advisory boards Pfizer, Leo, Bayer, and Boehringer Ingelheim. PSW has received research support from Bristol-Myers Squibb/Pfizer; has participated on scientific advisory boards for Bayer Schering Pharma, Pfizer, and Boehringer Ingelheim; and has received honoraria from Bayer Schering Pharma, Pfizer, and bioMérieux. PP has acted as a consultant for Bayer Pharma, Daiichi Sankyo, Pfizer, Boehringer Ingelheim, and Sanofi-Aventis.

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