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ORIGINAL ARTICLE

Effect of polypharmacy on bleeding with rivaroxaban versus vitamin K antagonist for treatment of venous thromboembolism

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Abstract

Background: Polypharmacy, including use of inhibitors of CYP3A4 and P-glycoprotein (P-gp), is common in patients with venous thromboembolism (VTE) and is associated with increased bleeding.

Methods: In 8246 patients included in the EINSTEIN-VTE studies for acute VTE, we evaluated the effect of polypharmacy on bleeding and on the relative differences between rivaroxaban and enoxaparin/vitamin K antagonist (VKA). We assessed the incidence of clinically relevant bleeding (major and clinically relevant nonmajor bleeding) by number of comedications (none, 1–3, ≥4) at baseline, and by use of CYP3A4 and/or P-gp inhibitors. Interaction between rivaroxaban versus enoxaparin/VKA and comedication was assessed by Cox regression analysis with $p_{interaction}$ estimates.

Results: With increasing number of comedications, the incidence of clinically relevant bleeding rose from 5.7% to 13.3% in rivaroxaban recipients and from 9.1% to 11.1% in enoxaparin/VKA recipients. Whereas rivaroxaban was associated with a reduced bleeding risk compared with enoxaparin/VKA in patients without comedication (hazard ratio [HR] 0.6, 95% confidence interval [CI] 0.4–0.9), the risk was similar in patients with ≥4 comedications (HR 1.2, 95% CI 0.97–1.5, $p_{interaction}$ .002). Use of CYP3A4 and/or P-gp inhibitors was associated with a doubled bleeding risk compared with no use, without a difference between rivaroxaban and enoxaparin/VKA.

Conclusion: We conclude that fixed-dose rivaroxaban as compared with enoxaparin followed by dose-adjusted VKA is not associated with an increased bleeding risk in patients with VTE administered polypharmacy in general and CYP3A4 and/or P-gp inhibitors specifically. This implies that the observed increased bleeding risks with polypharmacy and use of CYP3A4 and/or P-gp inhibitors are likely explained by comorbidities and frailty, and not by pharmacokinetic interactions.

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KEYWORDS
coumarins, hemorrhage, polypharmacy, rivaroxaban, venous thromboembolism

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) have become first-choice therapy in the treatment and prevention of venous thromboembolism (VTE) because of their beneficial bleeding risk profile in comparison with vitamin K antagonists (VKAs). In the EINSTEIN deep vein thrombosis (DVT) and pulmonary embolism (PE) program, rivaroxaban was compared with enoxaparin followed by VKAs for the treatment of acute VTE. Rivaroxaban was as efficacious as enoxaparin/VKAs for prevention of symptomatic recurrent VTE (hazard ratio [HR] 0.9, 95% confidence interval [CI] 0.7–1.2).[1] The risk of the composite outcome of major bleeding and clinically relevant nonmajor bleeding was similar for rivaroxaban versus enoxaparin/VKAs (HR 0.9, 95% CI 0.8–1.1).[1] However, the risk of major bleeding was significantly lower among patient randomized to rivaroxaban (HR 0.5, 95% CI 0.4–0.8).[1]

In general, polypharmacy is associated with an increased risk of adverse outcomes, including bleeding and thromboembolic complications, likely reflecting the frailty of patients.[2] The larger the number of concomitant medications, the larger the risk of pharmacokinetic interactions between anticoagulant drugs and concomitant medication. For VKAs, it is known that polypharmacy is associated with an increased bleeding risk.[3,4] For DOACs, similar patterns have been observed in patients with atrial fibrillation.[5,6] Because rivaroxaban is prescribed at a fixed dose without laboratory monitoring, the effect of polypharmacy might be larger for rivaroxaban than for dose-adjusted VKAs.

Rivaroxaban is subject to oxidative metabolism in the liver. It is a substrate of cytochrome P450 (CYP) 3A4, CYP2J2 and P-glycoprotein (P-gp). P-gp is most likely involved in the renal excretion of rivaroxaban.[7,8] Rivaroxaban exposure is affected by CYP3A4 and P-gp inducers and inhibitors.[7] Drug–drug interactions between rivaroxaban and inhibitors of CYP3A4 and/or P-gp have been fairly well studied, and only systemic concomitant administration of strong inhibitors of both CYP3A4 and P-gp is not recommended because rivaroxaban plasma concentrations may increase to a clinically relevant extent that would lead to increased bleeding risk.[7] All other inhibitors of CYP3A4 and/or P-gp increase rivaroxaban plasma concentrations to a lesser extent and are therefore not contraindicated.

The primary aim of this post hoc analysis was to investigate the impact of systemic use of polypharmacy on clinically relevant bleeding and on the relative differences in bleeding between rivaroxaban and enoxaparin/VKAs for treatment of acute VTE. The secondary aim was to evaluate the effect of concomitant administration of (non-dual strong) inhibitors of CYP3A4 and/or P-gp that may increase rivaroxaban plasma levels but not those of VKAs.

Essentials

- In this post-hoc EINSTEIN-VTE analysis, we evaluated the impact of polypharmacy on bleeding.
- Interaction between rivaroxaban versus enoxaparin/VKA and co-medication was assessed.
- Rivaroxaban vs VKA was not associated with increased bleeding in polypharmacy in general.
- CYP3A4/P-glycoprotein inhibitor use specifically did not affect bleeding in rivaroxaban vs VKA.

2 | METHODS

This study is a post hoc analysis of the EINSTEIN-VTE program, which included the EINSTEIN-DVT (NCT00440193, $n = 3449$)[9] and EINSTEIN-PE (NCT00439777, $n = 4832$)[10] studies conducted between 2007 and 2011. The study design of the EINSTEIN-VTE program and results have been described in detail elsewhere.[9,10] In short, these international, event-driven, open-label, randomized, noninferiority trials compared fixed-dose oral rivaroxaban 15 mg twice daily for 21 days, followed by 20 mg once daily, with standard therapy with enoxaparin followed by adjusted-dose VKA (warfarin or acenocoumarol, international normalized ratio targeted at 2.0–3.0) for the treatment of acute symptomatic VTE. Among other exclusion criteria, patients with a creatinine clearance below 30 ml/min were excluded from participation. Patients were followed up for the intended treatment period of 3, 6, or 12 months and seen at fixed intervals. The principal safety outcome was clinically relevant bleeding, defined as the composite of major bleeding and clinically relevant nonmajor bleeding. Study outcomes were assessed by an independent adjudication committee whose members were unaware of allocation of study medication. The study protocol was approved by the institutional review boards at all participating sites, and all patients provided written informed consent.

2.1 | Concomitant medication

Patients who were treated systemically with a strong inhibitor of both CYP3A4 and P-gp (e.g., azole-antimycotics or protease inhibitors for HIV infection) were excluded from the EINSTEIN-VTE program, whereas all other inhibitors of CYP3A4 and/or P-gp were allowed. At baseline and during the study, data on medication use were collected using an electronic case record form and 100% source verification was carried out. Concomitant medication was coded according to the World Health Organization

Drug Dictionary Version 2005/Q3 and defined via Anatomical-Therapeutic-Chemical codes. Only data for systemically (i.e., intramuscular, intravenous, nasal, oral, rectal, inhalation, subcutaneous, and sublingual) administered medications were included in this analysis.

2.2 | Study population

The study population of this analysis consisted of patients who had received at least one dose of allocated study treatment with either rivaroxaban or enoxaparin/VKAs. Based on the number of concomitant medications at baseline, patients were divided in three groups: no concomitant medication (group 1), one to three concomitant medications (group 2), and four or more concomitant medications (group 3). These cutoffs were chosen in order to have similarly sized groups. Furthermore, patients were grouped in those who used or did not use CYP3A4 and/or P-gp inhibitors.

2.3 | Safety outcomes

The outcomes of interest were clinically relevant bleeding (i.e., the composite of major or clinically relevant nonmajor bleeding) and major bleeding. International Society on Thrombosis and Haemostasis criteria were applied to define major and clinically relevant nonmajor bleeding.[11] Bleeding was major if clinically overt and associated with a decrease in hemoglobin level of 2.0 g/dl (1.24 mmol/L) or more, led to transfusion of 2 or more units of red cells, or if it was intracranial or retroperitoneal, in another critical site, or contributed to death. Bleeding was clinically relevant nonmajor if it was overt bleeding that did not meet the criteria for major bleeding but was associated with a medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life. Bleeding episodes were considered for the study treatment period but only during the time from administration of the first dose of study medication to 48 h after the administration of the last dose.

2.4 | Statistical analysis

Bleeding events were reported as cumulative incidences based on Kaplan-Meier survival estimates. The incidences of bleeding events were reported for each concomitant medication group at baseline and were compared between study arms. Cox regression models, stratified by index event (i.e., DVT or DVT ± PE), were used to estimate HRs and their 95% CIs for the comparison of rivaroxaban versus enoxaparin/VKA, separately for the concomitant medication groups. HRs were adjusted for study treatment, sex, age, active cancer, and renal impairment (i.e., creatinine clearance <50 ml/min) at baseline. For the effect of concomitant administration of CYP3A4 and/or P-gp inhibitors on bleeding, Cox regression models were used with CYP3A4 and/or P-gp inhibitors use ("on" vs "off" treatment) as a time-dependent covariate. Therefore, an individual patient could contribute to the time with or without CYP3A4 or P-gp inhibitors in the at-risk period. The exposed patient time for CYP3A4 and/or P-gp inhibitors was defined as start date until end day plus 5 days. Results are reported as incidence rates per 100 patients-years. The *p* values for interaction between study treatment (i.e., rivaroxaban or enoxaparin/VKA) and concomitant medication use were calculated based on a two-sided Wald test, as derived from the Cox model. Statistical Analysis Software (SAS) version 9.4 (SAS Institute) was used to perform analyses.

All authors had access to primary clinical trial data.

2.5 | Data sharing statement

For original data, please contact anthonie.lensing@bayer.com.

3 | RESULTS

The EINSTEIN-VTE program collectively enrolled 8281 patients with acute VTE. Characteristics of these patients have been published elsewhere.[9,10] A total of 8246 patients received at least one dose of the study treatment with either rivaroxaban ($n = 4130$) or enoxaparin/VKA ($n = 4116$) and were included in this analysis (Figure S1). Table 1 summarizes the baseline demographic and clinical characteristics by concomitant medication groups and allocation of study treatment. A total of 1788 patients (21%) did not have concomitant medication (group 1), 3567 patients (43%) used one to three concomitant medications (group 2), and 2891 patients (36%) used four or more concomitant medications (group 3). The mean age ($p < .001$) and the proportion of women ($p < .001$) increased from group 1 to group 3, whereas the median creatinine clearance ($p < .001$) decreased from group 1 to group 3. Antiplatelet therapy use ($p < .001$) and the presence of active cancer ($p < .001$) was highest in group 3. No differences were observed between rivaroxaban and enoxaparin/VKA recipients. Table 2 depicts the patient characteristics at baseline by use of CYP3A4 and/or P-gp inhibitors and allocation of study treatment. Users ($n = 806$) versus nonusers ($n = 7440$) of CYP3A4 and/or P-gp inhibitors were older ($p < .001$), more often female ($p = .04$), and more often used antiplatelet drugs ($p = .002$). All other patient characteristics were comparable between groups, except for a smaller proportion of women ($p = .02$) who received rivaroxaban, compared with enoxaparin/VKAs in users of CYP3A4 and/or P-gp inhibitors.

3.1 | Bleeding outcomes in relation to number of concomitant medications

Overall, the incidence of bleeding increased with number of concomitant medications (Table 3). The incidence of clinically relevant bleeding increased from 5.7% to 13.3% in rivaroxaban recipients

TABLE 1 Baseline demographic and clinical characteristics by use of concomitant medication and by study treatment group

Characteristic	Number of concomitant medications					
	Group 1: none N = 1788		Group 2: 1–3 N = 3567		Group 3: ≥4 N = 2891	
	Rivaroxaban n = 890	Enoxaparin/VKA n = 898	Rivaroxaban n = 1767	Enoxaparin/VKA n = 1800	Rivaroxaban n = 1473	Enoxaparin/VKA n = 1418
Age, mean (SD)	49 (16)	50 (16)	55 (17)	55 (17)	64 (15)	64 (15)
Female sex, *n* (%)	293 (33)	296 (33)	787 (45)	841 (47)	756 (51)	773 (55)
Weight in kg, mean (SD)	81 (18)	82 (19)	82 (18)	82 (18)	84 (20)	84 (20)
BMI in kg/m^2, median (IQR)	26 (24–30)	26 (24–30)	27 (24–31)	27 (24–30)	28 (25–32)	28 (25–32)
Creatinine clearance in ml/min, median (IQR)	106 (86–132)	108 (87–134)	101 (76–129)	100 (77–126)	82 (60–112)	83 (61–113)
Etiology of DVT or PE, *n* (%)						
Unprovoked	625 (70)	627 (70)	1079 (61)	1121 (62)	901 (61)	880 (62)
Recent surgery or trauma	127 (14)	147 (16)	338 (19)	323 (18)	287 (20)	256 (18)
Active cancer[a]	25 (3)	24 (3)	76 (4)	57 (3)	131 (9)	115 (8)
Medication use, *n* (%)						
Aspirin	–	–	61 (4)	70 (4)	300 (20)	293 (21)
Any antiplatelet therapy	–	–	77 (4)	80 (4)	349 (24)	351 (25)
CYP3A4 and/or P-gp inhibitor	–	–	46 (3)	51 (3)	161 (11)	160 (12)
Comorbidities[b], *n* (%)						
Cardiac disease	48 (5)	33 (4)	169 (10)	145 (8)	387 (26)	351 (25)
Pulmonary disease	81 (9)	91 (10)	275 (16)	296 (16)	505 (34)	420 (30)
Study treatment duration, *n* (%)						
3 months	73 (8)	85 (10)	151 (9)	152 (8)	108 (7)	86 (6)
6 months	530 (60)	526 (59)	1063 (60)	1069 (59)	864 (59)	866 (61)
12 months	287 (32)	287 (32)	553 (31)	579 (32)	501 (34)	466 (33)

Abbreviations: BMI, body mass index; CYP3A4, cytochrome P450 3A4; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; P-gp, P-glycoprotein; SD, standard deviation; VKA, vitamin K antagonist.

[a]Active cancer is defined as a diagnosis of cancer that occurred within 6 months before enrollment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer.

[b]Cardiac disease and pulmonary disease were defined as patients having at least one medical history record with stop date later than date of randomization or ongoing after study and the primary path of its MedDRA Lowest Level Term is "Respiratory, thoracic and mediastinal disorders" or "Cardiac disorders" MedDRA System Organ Class groups.

TABLE 2 Baseline demographic and clinical characteristics by use of CYP3A4 and/or P-gp inhibitors and by study treatment group

Characteristic	Concomitant use of CYP3A4 and/or P-gp inhibitors			
	None N = 7440		≥1[c] N = 806	
	Rivaroxaban n = 3735	Enoxaparin/VKA n = 3705	Rivaroxaban n = 395	Enoxaparin/VKA n = 411
Age, mean (SD)	56 (17)	56 (17)	63 (16)	63 (16)
Female sex, *n* (%)	1641 (44)	1675 (45)	195 (49)	235 (57)
Weight in kg, mean (SD)	83 (19)	82 (19)	82 (19)	82 (20)
BMI in kg/m^2, median (IQR)	27 (24–31)	27 (2–31)	27 (24–31)	28 (25–32)
Creatinine clearance in ml/min, median (IQR)	98 (73–126)	98 (74–126)	83 (60–112)	84 (61–113)
Etiology of DVT or PE, *n* (%)				
Unprovoked	2367 (63)	2367 (64)	238 (60)	261 (64)
Active cancer[a]	192 (5)	165 (5)	40 (10)	31 (8)
Medication use, *n* (%)				
Aspirin	309 (8)	301 (8)	52 (13)	62 (15)
Any antiplatelet therapy	364 (10)	358 (10)	62 (16)	73 (18)
Comorbidities[b], *n* (%)				
Cardiac disease	472 (13)	413 (11)	132 (33)	116 (28)
Pulmonary disease	729 (20)	667 (18)	132 (33)	140 (34)
Study treatment duration, *n* (%)				
3 months	305 (8)	306 (8)	27 (7)	17 (4)
6 months	2236 (60)	2227 (60)	221 (56)	234 (57)
12 months	1194 (32)	1172 (32)	147 (37)	160 (39)

Abbreviations: BMI, body mass index; CYP3A4, cytochrome P450 3A4; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; P-gp, P-glycoprotein; SD, standard deviation; VKA, vitamin K antagonist.

[a]Active cancer is defined as a diagnosis of cancer that occurred within 6 months before enrollment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer.

[b]Cardiac disease and pulmonary disease were defined as patients having at least one medical history record with stop date later than date of randomization or ongoing after study and the primary path of its MedDRA Lowest Level Term is "Respiratory, thoracic and mediastinal disorders" or "Cardiac disorders" MedDRA System Organ Class groups.

[c]Defined as any use before the minimum of study treatment end day +2 days and bleeding event.

TABLE 3 Risk of bleeding for rivaroxaban versus enoxaparin/VKA by concomitant medication groups

Concomitant medication group	Rivaroxaban no. = 4130			Enoxaparin/VKA no. = 4116			Adjusted HR (95% CI)
	Events	*N*	%	Events	*N*	%	
Clinically relevant bleeding[a]							
Group 1: none	51	890	5.7	82	898	9.1	0.6 (0.4–0.9)
Group 2: 1–3	141	1767	8.0	172	1800	9.6	0.8 (0.7–1.02)
Group 3: ≥4	196	1473	13.3	158	1418	11.1	1.2 (0.97–1.5)
$p_{interaction}$							.002
Major bleeding							
Group 1: none	7	890	0.8	14	898	1.6	0.5 (0.2–1.3)
Group 2: 1–3	8	1767	0.5	25	1800	1.4	0.3 (0.1–0.7)
Group 3: ≥4	25	1473	1.7	33	1418	2.3	0.7 (0.4–1.2)
$p_{interaction}$							.25

Abbreviations: CI, confidence interval; HR, hazard ratio; VKA, vitamin K antagonist.

[a]Clinically relevant bleeding was defined as the composite of major or clinically relevant nonmajor bleeding.

compared with from 9.1% to 11.1% in enoxaparin/VKA recipients (p = .002 for interaction between allocated study treatment and number of concomitant medications). Figure 1A shows the cumulative incidence of clinically relevant bleeding over time by concomitant medication and randomized treatment. In patients without concomitant medications rivaroxaban was associated with less bleeding than enoxaparin/VKA, and in the group of patients with the most concomitant medications of ≥4 the bleeding risk was similar between the two treatment arms. For major bleeding, a similar pattern as for all clinically relevant bleeding was observed, yet the p value for interaction between the study treatment groups was not significant (p = .25). Figure 1B shows the cumulative incidence of major bleeding over time by concomitant medication group and allocation of study treatment.

3.2 | Bleeding outcomes in relation to use of CYP3A4 and/or P-gp inhibitors

In total, 806 of all 8246 (9.8%) patients used at least one CYP3A4 and/or P-gp inhibitor (Table 2), most commonly clarithromycin (n = 159), verapamil (n = 139), diltiazem (n = 121), amiodarone (n = 98), and fluoxetine (n = 86; Table 4). The distribution of use of CYP3A4 and/or P-gp inhibitors was comparable for patients who received rivaroxaban or enoxaparin/VKA. In both study treatment groups, the incidence of clinically relevant bleeding was approximately twice as high during use of CYP3A4 and/or P-gp inhibitors compared with no use (32.0 vs 16.0 per 100 patient-years [py] for rivaroxaban and 37.9 vs 18.0 per 100 py for enoxaparin/VKAs; Table 5). There was no significant interaction between allocated study treatment and use of CYP3A4/P-gp inhibitors ($p_{interaction}$ = .64). The incidence of major bleeding only, during use of CYP3A4 and/or P-gp inhibitors versus no use, was almost twice as high in the rivaroxaban group (2.7 vs 1.6 per 100 py), compared with three times as high in the enoxaparin/VKA group (8.4 vs 2.8 per 100 py; Table 5). There was no significant interaction between allocated study treatment and use of CYP3A4/P-gp inhibitors for major bleeding ($p_{interaction}$ = .35).

4 | DISCUSSION

In this study among 8246 patients with acute VTE randomized to rivaroxaban or enoxaparin/VKAs, we confirmed that use of concomitant medication, in general and CYP3A4/P-gp inhibitors specifically, was associated with an increased risk of bleeding. The effect of concomitant medication on bleeding was larger in patients treated with rivaroxaban (rise from 6% in patients without comedication to 13% in those with ≥4) than in patients treated with enoxaparin/VKA (rise from 9% to 11%, p-interaction .002). In patients without comedication, rivaroxaban was associated with less bleeding then enoxaparin/VKAs and in the group of ≥4 comedication bleeding risk was similar. Similarly, the use of CYP3A4 and/or P-gp inhibitors was associated with an approximate doubled risk of clinically relevant bleeding to a similar extent in both rivaroxaban and enoxaparin/VKA recipients. This is remarkable because CYP3A4 or P-gp inhibitors are not involved in the metabolism of VKAs and the dose of VKAs was adjusted to maintain the target international normalized ratio range of 2.0 to 3.0. These observations imply that the observed rise in

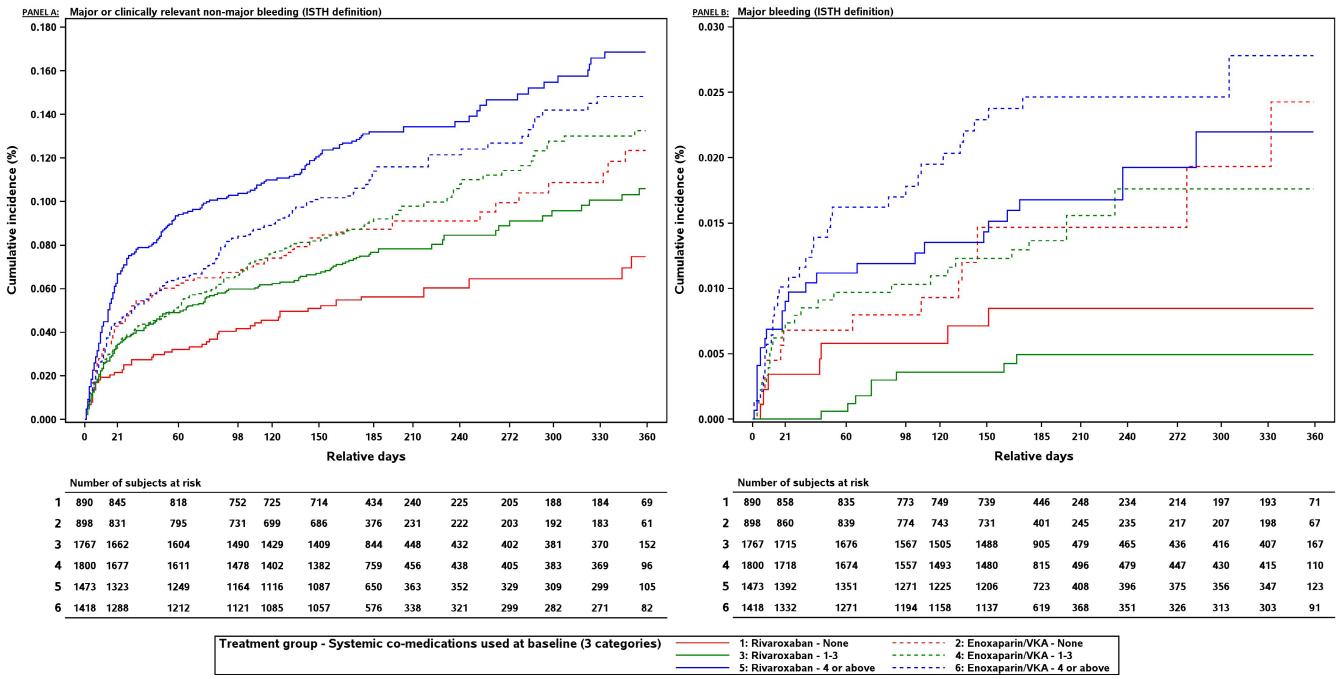

FIGURE 1 Cumulative incidence of clinically relevant bleeding* and major bleeding by concomitant medication group and study treatment group. * Clinically relevant bleeding was defined as the composite of major or clinically relevant non-major bleeding. Abbreviation: VKA: vitamin K antagonist

TABLE 4 Types of CYP3A4 and/or P-gp inhibitors used in the at-risk period

Drug containing CYP3A4 and/or P-gp inhibitor, *n* (%)	Rivaroxaban *N* = 4130	Enoxaparin/VKA *N* = 4116
Cardiac drugs		
Amiodarone	57 (1.4)	41 (1.0)
Diltiazem	56 (1.4)	65 (1.6)
Dronedarone	0 (0)	2 (0)
Quinidine	1 (0)	2 (0)
Verapamil/trandolapril	12 (0.3)	9 (0.2)
Verapamil	58 (1.4)	60 (1.5)
Antibiotics		
Chloramphenicol	1 (0)	2 (0)
Clarithromycin	77 (1.9)	82 (2.0)
Erythromycin	10 (0.2)	11 (0.3)
Norfloxacin	23 (0.6)	23 (0.6)
Telithromycin	2 (0)	10 (0.2)
Antifungals (systemic only)		
Fluconazole	32 (0.8)	25 (0.6)
Itraconazole	2 (0)	2 (0)
Ketoconazole	1 (0)	2 (0)
Miconazole	3 (0.1)	2 (0)
Voriconazole	0 (0)	2 (0)
Psychotropic drugs		
Fluoxetine	37 (0.9)	49 (1.2)
Fluoxetine/olanzapine	0 (0)	1 (0)
Fluvoxamine	5 (0.1)	8 (0.2)
Nefazodone	1 (0)	0 (0)
Miscellaneous		
Amoxicillin/clarithromycin/pantoprazole	0 (0)	1 (0)
Aprepitant	4 (0.1)	2 (0)
Bicalutamide	7 (0.2)	8 (0.2)
Ciclosporin	3 (0.1)	5 (0.1)
Cimetidine	14 (0.3)	9 (0.2)
Imatinib	1 (0.0)	2 (0)
Mifepristone	0 (0)	1 (0)
Ritonavir/lopinavir	1 (0)	0 (0)
Tacrolimus	2 (0)	6 (0.1)

Abbreviation: VKA, vitamin K antagonist.

bleeding risk with rivaroxaban with increasing comedications could explained by a combination of a direct pharmacokinetic interaction as well as frailty and comorbidities associated with comedication use. In patients with monitored VKA therapy, direct pharmacokinetic interactions are unlikely and the rise in bleeding risk is likely to be explained more by frailty only. Indeed, patients with more comedication were older, more often had renal impairment, active cancer, and used antiplatelet therapy (Table 1), which are all factors associated with increased bleeding risk.

Our results are consistent with studies in atrial fibrillation and VTE that evaluated bleeding risks with rivaroxaban[5] and apixaban[6] (which are both substrates for CYP3A4 and P-gp), and dabigatran etexilate[12] (substrate for P-gp only). In these studies, polypharmacy and use of CYP3A4 and/or P-gp inhibitors were overall associated with increased bleeding rates, but all three DOACs were at least as safe as standard treatment with (enoxaparin)/VKA therapy.[5,6,12]

Our study has several limitations and strengths. First, our study was a post hoc analysis of the EINSTEIN-VTE program. However, data on concomitant medication use were collected prospectively and a 100% source verification was performed. Also, randomization occurred without knowledge or influence of use of concomitant medication and all bleeding events were adjudicated

TABLE 5 Risk of bleeding for rivaroxaban versus enoxaparin/VKA by concomitant use of CYP3A4 and/or P-gp inhibitors

Concomitant use of CYP3A4 and/or P-gp inhibitors[b]	Rivaroxaban n = 4130				Enoxaparin/VKA n = 4116				Adjusted HR (95% CI)
	Events	N	Patient years at risk	Events per 100 patient years (95% CI)	Events	N	Patient years at risk	Events per 100 patient years (95% CI)	
Clinically relevant bleeding[a]									
None	356	3963	2117	16.8 (15.1–18.7)	371	3944	2057	18.0 (16.3–20.0)	0.9 (0.8–1.1)
≥1	32	377	100	32.0 (21.9–45.1)	41	394	108	37.9 (27.2–51.4)	0.8 (0.5–1.3)
$p_{interaction}$									0.636
Major bleeding									
None	37	3964	2245	1.6 (1.2–2.3)	62	3946	2178	2.8 (2.2–3.7)	0.6 (0.4–0.9)
≥1	3	395	111	2.7 (0.6–7.9)	10	411	119	8.4 (4.0–15.4)	0.3 (0.1–1.1)
$p_{interaction}$									0.351

Abbreviations: CI, confidence interval; CYP3A4, cytochrome P450 3A4; HR, hazard ratio; P-gp, P-glycoprotein; VKA, vitamin K antagonist.

[a]Concomitant use of CYP3A4 or P-gp inhibitors is defined as any use before the minimum of study treatment end day +2 days and bleeding event.

[b]Clinically relevant bleeding was defined as the composite of major or clinically relevant nonmajor bleeding.

by a central committee whose members were unaware of randomized allocation, as well as concomitant medication. In addition, according to the study protocol, patients randomized to enoxaparin/VKAs were intensively monitored by the international normalized ratio, diminishing the potential effects of drug interactions. Second, although the EINSTEIN-VTE program included a large number of patients, the number of patients in some subgroups of interest were relatively small. Hence, we divided use of concomitant medication into three groups only to maintain statistical power for our analyses. Specifically, we did not have enough power to analyze patients administered two or more CYP3A4/P-gp inhibitors.[5] Third, as corresponding rivaroxaban plasma levels of the patients in our study at the time of CYP3A4 and/or P-gp inhibitor intake were not measured, we are unable to relate rivaroxaban plasma concentration to bleeding events during use of CYP3A4 and/or P-gp inhibitors.[13,14] Therefore, we performed a time-dependent drug exposure analysis for concomitant inhibitor use and observed no difference or interaction between rivaroxaban and enoxaparin/VKA.

We conclude that fixed-dose rivaroxaban as compared with enoxaparin followed by dose-adjusted VKA is not associated with an increased bleeding risk in patients with VTE and polypharmacy, in general and for CYP3A4 and/or P-gp inhibitors specifically. We observed an interaction between allocated treatment and comedication, in which rivaroxaban leads to less bleeding in those without comedication and in those with the highest number of comedications rivaroxaban loses this advantage over VKAs and is associated with a similar bleeding risk. We speculate that the overall observed increased bleeding risks with polypharmacy and use of CYP3A4 and/or P-gp inhibitors is mostly explained by comorbidities and frailty than by drug–drug interactions.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Ingrid M. Bistervels, Anthonie W. A. Lensing, and Michiel Coppens designed the study. Martin Gebel performed the statistical analysis. Ingrid M. Bistervels and Roisin Bavalia wrote the first draft of the manuscript. Martin Gebel, Anthonie W. A. Lensing, Saskia

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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