Rivaroxaban and the EINSTEIN clinical trial programme

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Rivaroxaban, a direct oral anticoagulant, is widely used for the treatment of venous thromboembolism (VTE) in adult patients. The approval of rivaroxaban for the treatment of deep vein thrombosis and pulmonary embolism and the extended secondary prevention of recurrent VTE is based on the results of the EINSTEIN DVT and EINSTEIN PE trials, and the EINSTEIN EXT and EINSTEIN CHOICE trials, respectively. This review provides an updated overview of these completed EINSTEIN studies in adult patients, including results of subanalyses in patients at high risk of recurrent VTE, and discusses the emerging data from the EINSTEIN Junior programme, which is evaluating the use of rivaroxaban for the treatment of paediatric VTE. In the EINSTEIN DVT and EINSTEIN PE trials, rivaroxaban (15 mg twice daily for 21 days, followed by 20 mg once daily thereafter) was shown to be an effective and safe alternative to standard anticoagulation for the treatment of deep vein thrombosis and pulmonary embolism in a broad range of adult patients. These results are supported by increasing amounts of real-world data from patients treated with rivaroxaban in routine clinical practice worldwide. In the EINSTEIN EXT and EINSTEIN CHOICE trials, rivaroxaban was superior to placebo and acetylsalicylic acid, respectively, for the extended treatment of VTE – physicians can now choose between two doses of rivaroxaban (20 mg once daily or 10 mg once daily) for the extended prevention of recurrent VTE, based on a patient's risk of recurrence, bleeding and personal preferences. *Blood Coagul Fibrinolysis* 30:85–95 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

The direct oral anticoagulants (DOACs), which include the Factor Xa inhibitors apixaban, edoxaban and rivaroxaban and the direct thrombin inhibitor dabigatran, are now widely used for the treatment of venous thromboembolism (VTE) [1,2]. The DOACs simplify VTE treatment by offering several well-recognized advantages over parenteral anticoagulants and vitamin K antagonists (VKAs), including oral administration, simple dosing regimens, limited interactions with other medications and food and the lack of a requirement for routine monitoring. The regulatory approval of the DOACs for the treatment and secondary prevention of VTE was based on the results of successful clinical development programmes, which included primary treatment and extended secondary prevention phase III trials [3–11]. Both apixaban and rivaroxaban are approved as single-drug therapies [12,13], whereas dabigatran and edoxaban are approved for administration after initial parenteral anticoagulation for at least 5 days [14,15]. Because of the reduced risk of bleeding and greater convenience for patients and healthcare providers alike, the 2016 American College of Chest Physicians (ACCP) guidelines suggested that DOACs are used in preference to VKAs (and parenteral agents) for the initial and long-term treatment of VTE in most patients [16], except for those with cancer and pregnant/breastfeeding women [16,17]. In patients with cancer-associated thrombosis, the ACCP guidelines advise low molecular weight heparin (LMWH) as first-choice treatment (in preference to DOACs or VKAs), although DOACs and VKAs are suggested treatment options in patients who are not treated with LMWHs [16]. Recent clinical trial data have shown some efficacy benefits of DOACs compared with LMWH in active cancer, albeit at the expense of increased bleeding [18,19]. Recent guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) incorporates these data [20]. The guidance recommends the use of specific DOACs (edoxaban and rivaroxaban) for cancer patients with an acute diagnosis of VTE, a low risk of bleeding and no drug–drug interactions with current systemic therapy. It also recommends that LMWHs constitute an acceptable alternative and that LMWHs are preferable to the two DOACs in patients with an acute diagnosis of VTE and a high risk of bleeding, including those with certain gastrointestinal or urothelial cancers, or specific gastrointestinal abnormalities.

The EINSTEIN clinical development programme has established the efficacy and safety of rivaroxaban for the treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT) and secondary prevention of recurrent VTE in a broad range of patients. The programme

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includes four completed phase III trials in adult patients (EINSTEIN DVT, EINSTEIN PE, EINSTEIN EXT and EINSTEIN CHOICE) and the ongoing EINSTEIN JUNIOR programme [9–11,21–24]. The aim of this review is to provide an updated summary of the key results of the completed EINSTEIN trials, including outcomes in important patient populations, such as fragile patients and patients with renal impairment or cancer, as well as providing an overview of ongoing studies in paediatric patients in the EINSTEIN Junior programme. In addition, real-world evidence on the use of rivaroxaban for VTE treatment will be discussed, highlighting the consistent efficacy and safety profile of rivaroxaban from the randomized controlled trial setting of the EINSTEIN studies to a broad range of patients in routine clinical practice.

Rivaroxaban for the treatment of venous thromboembolism in adult patients

Overview of the EINSTEIN DVT and EINSTEIN PE studies

Based on the results of EINSTEIN DVT and EINSTEIN PE, the approved dosing regimen of rivaroxaban for the initial treatment of DVT and PE and prevention of recurrent VTE is 15 mg twice daily (bid) for 21 days, followed by 20 mg once daily (od) for the remainder of the treatment duration [12]. The suggested duration of treatment depends on the risk of recurrent VTE – at least 3 months' therapy should be considered in patients with a VTE provoked by a major transient risk factor (e.g. recent major surgery or trauma) and longer duration of therapy (>3 months) should be considered in patients with a history of recurrent VTE, an unprovoked VTE or a provoked VTE not related to major transient risk factors [12].

EINSTEIN DVT and EINSTEIN PE were both open-label trials that compared rivaroxaban (15 mg bid for 21 days, followed by 20 mg od thereafter) with enoxaparin overlapping with and followed by warfarin for the treatment of VTE [9,10]. Across both studies, the intended duration of treatment was 3, 6 or 12 months in 8, 60 and 32% of patients [9,10], respectively; mean treatment duration was longer in EINSTEIN PE (214 and 216 days for VKA and rivaroxaban, respectively) than EINSTEIN DVT (188 and 194 days for VKA and rivaroxaban, respectively) [25]. In both EINSTEIN DVT and EINSTEIN PE, rivaroxaban was noninferior to enoxaparin/VKA for the treatment of DVT and PE, respectively, and the risk of clinically significant bleeding was similar between treatments (Table 1) [9,10]. In EINSTEIN PE and a pooled analysis of both studies, rates of major bleeding were significantly reduced by ~50% with rivaroxaban compared with enoxaparin/VKA (Table 1) [10,25]. All studies of adult patients discussed within the main text of this article used the ISTH definition of major bleeding (unless stated otherwise) [26]: clinically overt and associated with a decrease in haemoglobin level of at least 2.0 g/dl; if bleeding led to the transfusion of at least 2 U of whole blood or red cells; or if bleeding was intracranial or retroperitoneal, occurred in another critical site, or contributed to death (although definitions of clinically relevant nonmajor bleeding varied between studies). In both studies, the relative efficacy and safety of rivaroxaban versus enoxaparin/VKA was generally consistent irrespective of the intended treatment duration [9,10].

Rivaroxaban for the treatment of venous thromboembolism in high-risk patients: subanalyses of the EINSTEIN DVT and EINSTEIN PE studies

The EINSTEIN pooled analysis included 8282 patients with VTE from EINSTEIN DVT and EINSTEIN PE [25]. This pooled analysis provides important insights into the use of rivaroxaban for the treatment of VTE in patients at high risk of recurrent VTE and/or major bleeding and patients with extremes of bodyweight, in whom physicians may be concerned about over-treating/under-treating with a fixed-dose rivaroxaban regimen. Subgroup analyses across multiple patient subgroups, including: fragile patients [identified by at least one of: age more than 75 years, creatinine clearance (CrCl) < 50 ml/min or body weight ≤50 kg]; patients with prior VTE; patients with renal impairment (CrCl < 50 ml/min); patients with cancer; and patients with low (≤50 kg) or high bodyweight (≥100 kg) showed the consistent efficacy of a fixed dose of rivaroxaban versus enoxaparin/VKA for the prevention of recurrent VTE, with reduced rates of major bleeding (Table 1) [25,27,28,56].

Although the results of the subanalysis in patients with cancer in EINSTEIN DVT and EINSTEIN PE suggested that rivaroxaban is a good alternative to a short course of LMWH overlapping with and followed by VKA for the treatment of cancer-associated thrombosis, a major limitation of these data was that rivaroxaban was not compared with LMWH, the guideline-preferred anticoagulant in patients with cancer. The ongoing CALLISTO programme is further exploring the potential of rivaroxaban for the prevention and treatment of cancer-associated thrombosis [57]. The recently reported select-d trial, (part of the CALLISTO programme [57]), was an open-label, phase III pilot study comparing the efficacy and safety of rivaroxaban (15 mg bid for 21 days followed by 20 mg od) with dalteparin (200 IU/kg od for 30 days followed by 150 IU/kg od) in 406 patients with active cancer and a first VTE [19]. The intended treatment duration in all patients was 6 months. The cumulative VTE recurrence rate at 6 months was lower for patients on rivaroxaban compared with dalteparin [4 versus 11%, respectively; hazard ratio 0.43, 95% confidence interval (CI) 0.19–0.99]; cumulative major bleeding rates at 6 months were low but numerically higher in the rivaroxaban versus dalteparin group (6 versus 4%,

Table 1 Summary of available clinical evidence from randomized controlled trials and routine clinical practice on the use of rivaroxaban for the treatment of deep vein thrombosis and pulmonary embolism and secondary prevention of recurrent venous thromboembolism

						Recurrent VTE		Major bleeding[a]	
Study name	Type of study	Patient population	Treatment	*N*	Treatment duration	%	HR (95% CI) or *P* value	%	HR (95% CI) or *P* value
Rivaroxaban for the initial treatment of VTE									
EINSTEIN DVT [9]	Phase III RCT	Patients with DVT	Enoxaparin/VKA	1718	187.5 days[b]	3.0	0.68	1.2	0.65
			Rivaroxaban	1731	193.6 days[b]	2.1	(0.44–1.04)	0.8	(0.33–1.30)
EINSTEIN PE [10]	Phase III RCT	Patients with PE ± DVT	Enoxaparin/VKA	2413	214.3 days[b]	1.8	1.12	2.2	0.49
			Rivaroxaban	2419	216.3 days[b]	2.1	(0.75–1.68)	1.1	(0.31–0.79)
EINSTEIN pooled [25]	Pooled analysis of EINSTEIN DVT + EINSTEIN PE	Patients with VTE	Enoxaparin/VKA	4131	203.8 days[b]	2.3	0.89	1.7	0.54
			Rivaroxaban	4151	207.6 days[b]	2.1	(0.66–1.19)	1.0	(0.37–0.79)
EINSTEIN pooled	RCT subgroup analysis	Fragile patients with VTE[c] [25]	Enoxaparin/VKA	782	187.2[b]	3.8	0.68	4.5	0.27
			Rivaroxaban	791	196.8[b]	2.7	(0.39–1.18)	1.3	(0.13–0.54)
		Patients with prior VTE [25]	Enoxaparin/VKA	819	252.6[b]	3.1	0.45	1.7	0.51
			Rivaroxaban	791	259.0[b]	1.4	(0.22–0.91)	0.9	(0.21–1.27)
		Patients with VTE and CrCl 30–49 ml/min [26]	Enoxaparin/VKA	313	NR	3.2	1.05	3.9	0.23
			Rivaroxaban	323		3.4	(0.44–2.47)	0.9	(0.06–0.81)
		Patients with VTE and active cancer[d] [27]	Enoxaparin/VKA	301	178–181 days[e]	6.6	0.67	5.0	0.42
			Rivaroxaban	354	180–182 days[e]	4.5	(0.35–1.30)	2.3	(0.18–0.99)
		Patients ≤50 kg with VTE [28]	Enoxaparin/VKA	92	180 days[e]	2.2	2.47	4.4	0.24
			Rivaroxaban	75	181 days[e]	6.7	(0.47–12.89)	1.3	(0.03–2.20)
		Patients ≥100 kg with VTE [28]	Enoxaparin/VKA	695	183 days[e]	2.0	1.12	1.2	0.76
			Rivaroxaban	698	184 days[e]	2.3	(0.55–2.30)	0.9	(0.26–2.19)
select-d [19]	Pilot phase III RCT	Patients with VTE and active cancer	LMWH	203	5.8 months[e]	11[f]	–	4[f]	–
			Rivaroxaban	203	5.9 months[e]	4[f]		6[f]	
MERCURY PE [29]	Phase IV, US-based, randomized multicentre study	Patients with low-risk PE, defined by HESTIA criteria	Standard anticoagulation (treated according to local protocol)	63	89 days[e]	0	–	0	–
			Rivaroxaban (early discharge from emergency department)	51	91 days[e]	0		0	
XALIA [30]	RWE – multicentre, prospective NIS	Patients with DVT[g] (safety population)	Standard anticoagulation[h]	2149	190 days[e]	2.6	0.67	2.3	0.41
			Rivaroxaban	2619	181 days[e]	1.4	(0.44–1.03)	0.7	(0.24–0.70)
		Patients with DVT[g] (PSA population)	Standard anticoagulation[h]	2010	NR	2.3	0.91	2.1	0.77
			Rivaroxaban	2505		1.4	(0.54–1.54)	0.8	(0.40–1.50)
		Patients with DVT[g]	Early switchers[i] [54]	368	190 days[e]	2.2	–	1.4	–
XALIA [31]	RWE – multicentre, prospective NIS; subgroup analysis	Patients with DVT[g] and cancer	LMWH	223	164 days[e]	4.5	NR	3.6	NR
			Parenteral anticoagulation/ VKA	141	214 days[e]	4.3		5.0	
			Rivaroxaban	146	152 days[e]	3.4		1.4	
			Early switchers[i]	30	196 days[e]	3.3		0	
			Miscellaneous	47	141 days[e]	4.3		4.3	
XALIA-LEA [32]	RWE – multicentre, prospective NIS	Patients with VTE (safety population)	Standard anticoagulation[h]	402	NR	8.3[j]	0.33	8.2[j]	0.35
			Rivaroxaban	1285		2.6[j]	(0.17–0.67)[k]	2.7[j]	(0.18–0.69)[k]
XALIA pooled [33]	RWE – pooled analysis of XALIA + XALIA-LEA	Patients with VTE (PSS population)	Standard anticoagulation[h]	2543	NR	4.5[j]	0.85	3.9[j]	0.65
			Rivaroxaban	3902		2.5[j]	(0.54–1.32)	1.7[j]	(0.39–1.08)
REMOTEV [34]	RWE – single centre, prospective NIS	Patients with VTE (safety population)	LMWH/fondaparinux	69	NR	11.6	NR	4.3	NR
			VKA	96		3.1		3.1	
			Rivaroxaban	280		1.4		1.1	
Dresden NOAC Registry [35]	RWE – German multicentre, prospective registry	Patients with VTE starting treatment within 14 days of index VTE	Rivaroxaban	418	206 days[e]	1.9	–	3.8	–
SWIVTER [36]	RWE –Swiss, multicentre registry	Patients with VTE (enrolled population)	Standard anticoagulation[h]	1645	NR	3.3[l]	0.36	2.4[l]	0.20
			Rivaroxaban	417		1.2[l]	(0.14–0.90)	0.5[l]	(0.05–0.83)
		Patients with VTE (PSA population)	Standard anticoagulation[h]	417		2.1[l]	0.55	0.5[l]	1.00
			Rivaroxaban	417		1.2[l]	(0.18–1.65)	0.5[l]	(0.14–7.07)

Table 1 (*continued*)

Study name	Type of study	Patient population	Treatment	*N*	Treatment duration	Recurrent VTE		Major bleeding[a]	
						%	HR (95% CI) or *P* value	%	HR (95% CI) or *P* value
RIETE registry [37]	RWE – multicentre, international registry	Patients with PE starting treatment:			Rivaroxaban				
		<48 h from index VTE		591	167 days[b]	0.37[m,n]/0[n,o]	–	2.20[n]	–
		3–7 days from index VTE		402	194 days[b]	0.92[m,n]/0[n,o]	–	2.31[n]	–
		≥8 days from index VTE		525	211 days[b]	0[m,n]/0.33[n,o]	–	0.65[n]	–
Mayo clinic thrombophilia database [38–40]	RWE – prospective registry	Patients with VTE and active cancer	LMWH	121	174 days[p]	1.7	*P* = 0.45	5.8	*P* = 0.20
			Rivaroxaban	135	219 days[p]	2.8		2.2	
Mantha *et al.* [41]	RWE – prospective cohort study	Patients with VTE and active cancer	Rivaroxaban	200	NR	4.4[f]	–	2.2[f]	–
Peacock *et al.* [42]	RWE – retrospective analysis of EMR from US DOD healthcare system	Patients with VTE	Rivaroxaban	9638	NR	NR	–	2.47[n]	–
		Patients with DVT	Rivaroxaban	5426	NR	NR	–	2.74[n]	–
		Patients with PE ± DVT	Rivaroxaban	4212	NR	NR	–	2.18[n]	–
Coleman *et al.* [43]	RWE – retrospective analysis of US healthcare claims database	Patients with VTE starting treatment within 30 days of index VTE (PSA population)	Warfarin	32 244	6.2 months[b]	3.5	0.81	1.0	0.79
			Rivaroxaban	13 609	6.2 months[b]	2.8	(0.73–0.90)	0.8	(0.65–0.96)
Sindet-Pederson *et al.* [44]	RWE – retrospective analysis of Danish healthcare registries	Patients with VTE starting treatment within 7 days of VTE diagnosis	VKAs	6907	NR	3.13[q]	0.97	2.10[q]	1.08
			Rivaroxaban	5411		3.02[q]	(0.78–1.19)[q]	2.27[q]	(0.84–1.39)[r]
Larsen *et al.* [45]	RWE – retrospective analysis of Danish healthcare registries	Patients with unprovoked VTE starting treatment within 7 days of discharge (entire cohort)	Warfarin	3253	NR	13.2[n]	0.70	2.0[n]	1.18
			Rivaroxaban	1751		9.8[n]	(0.55–0.88)[r]	2.4[n]	(0.68–2.02)[s]
		(PSM cohort)	Warfarin	2945	NR	13.1[n]	0.69	2.0[n]	1.18
			Rivaroxaban	1734		9.9[n]	(0.55–0.87)	2.4[n]	(0.69–2.04)
Coleman *et al.* [46]	RWE – retrospective analysis of US healthcare claims database	Frail patients with VTE starting treatment within 30 days of index VTE (PSA cohort)	Warfarin	5504	5 months[b]	1.7	0.65	1.7	0.88
			Rivaroxaban	1365		1.3	(0.44–0.97)	1.6	(0.61–1.27)
Coleman *et al.* [47]	RWE – retrospective analysis of US healthcare claims database	Patients with unprovoked VTE starting treatment within 30 days of index VTE (PSA cohort)	Warfarin	26 364	5 months[e]	4.3[t]	0.60	1.2	0.80
			Rivaroxaban	10 489		2.6[t]	(0.54–0.67)	0.9	(0.66–0.98)
Coleman *et al.* [48]	RWE – retrospective analysis of US healthcare claims database	Patients with provoked VTE starting treatment within 30 days of index VTE (PSA cohort)	Warfarin	13 164	91 days[e]	3.66[t]	0.71	1.62[t]	0.68
			Rivaroxaban	4454		2.56[t]	(0.60–0.84)	1.07[t]	(0.53–0.88)
Khorana *et al.* [49]	RWE – retrospective analysis of US healthcare claims database	Patients newly diagnosed with cancer and VTE starting treatment within 7 days of index VTE (PSA cohort)	LMWH	4313	3.2 months[b]	11.7[t]	0.83	4.9[t]	0.91
			Rivaroxaban	3370	5.3 months[b]	8.7[t]	(0.73–0.96)	4.4[t]	(0.71–1.17)
			Warfarin	4774	5.6 months[b]	8.8[t]	0.95	3.8[t]	1.08
			Rivaroxaban	3370	5.9 months[b]	8.2[t]	(0.83–1.09)	4.2[t]	(0.86–1.37)
Streiff *et al.* [50]	RWE – retrospective analysis of US healthcare claims database	Patients newly diagnosed with cancer and VTE starting treatment within 7 days of index VTE (PSA cohort)	LMWH	682	1.0 months[e]	17.6	0.72	4.1	1.03
			Rivaroxaban	685	3.0 months[e]	13.1	(0.52–0.95)	6.7	(0.64–1.65)
			Warfarin	876	3.5 months[e]	17.9	0.74	7.5	1.01
			Rivaroxaban	892	3.0 months[e]	13.3	(0.56–0.96)	7.0	(0.71–1.43)
Kohn *et al.* [51]	RWE – retrospective analysis of US healthcare claims database	Patients with active cancer and VTE starting treatment within 30 days of index VTE	Rivaroxaban	949	114 days[u]	4.0	–	2.7	–

Table 1 (*continued*)

Study name	Type of study	Patient population	Treatment	*N*	Treatment duration	Recurrent VTE %	Recurrent VTE HR (95% CI) or *P* value	Major bleeding[a] %	Major bleeding[a] HR (95% CI) or *P* value
Rivaroxaban for the extended treatment of VTE									
EINSTEIN EXT [9]	Phase III RCT	Patients with VTE who had completed 6–12 months of OAC therapy and were at clinical equipoise regarding need for continued anticoagulation	Placebo	594	189.5 days[b] [55]	7.1	0.18	0	$P=0.11$
			Rivaroxaban 20 mg od	602	189.5 days[b] [55]	1.3	(0.09–0.39)	0.7	
EINSTEIN CHOICE [11]	Phase III RCT	Patients with VTE who had completed 6–12 months of OAC therapy and were at clinical equipoise regarding need for continued anticoagulation	ASA 100 mg od	1131	350 days[e]	4.4	0.26	0.3	1.64
			Rivaroxaban 10 mg od	1127	353 days[e]	1.2	(0.14–0.47)	0.4	(0.39–6.84)
			ASA 100 mg od	1131	350 days[e]	4.4	0.34	0.3	2.01
			Rivaroxaban 20 mg od	1107	349 days[e]	1.5	(0.20–0.59)	0.5	(0.50–8.04)
Khorana *et al.* [52]	RWE – retrospective analysis of US healthcare claims database	Patients with VTE treated with rivaroxaban stopping treatment at 3/6 months postindex VTE or continuing treatment beyond 3/6 months	Stopped treated at 3 months	1536	107 days[e]	3.01[v]	$P=0.017$	1.44[v]	$P=0.813$
			Continued treatment >3 months	5933	199 days[e]	1.97[v]		1.44[v]	
			Stopped treatment at 6 months	1127	197 days[e]	3.70[w]	$P=0.024$	1.32[w]	$P=0.794$
			Continued treatment >6 months	2676	297 days[e]	1.72[w]		1.53[w]	
Berger *et al.* [53]	RWE – retrospective analysis of US healthcare claims database	Patients with unprovoked VTE treated with rivaroxaban stopping treatment at 3 months postindex VTE or continuing treatment beyond 3 months (PSA cohort)	Stopped treated at 3 months	1051	107 days[e]	2.60[v]	$P=0.023$	1.13[v]	$P=0.780$
			Continued treatment >3 months	3763	200 days[e]	1.45[v]		1.06[v]	

ASA, acetylsalicylic acid; CI, confidence interval; CrCl, creatinine clearance; DOD, US Department of Defense; DVT, deep vein thrombosis; EMR, electronic medical record; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; NIS, noninterventional study; NR, not reported; OAC, oral anticoagulant; od, once daily; PE, pulmonary embolism; PSA, propensity score adjusted; PSM, propensity score matched; PSS, propensity score stratified; RCT, randomized controlled trial; RWE, real-world evidence; VKA, vitamin K antagonist; VTE, venous thromboembolism. [a] Major bleeding definitions are not consistent between studies [major bleeding was defined according to the ISTH criteria in the EINSTEIN studies, select-d, XALIA and XALIA-LEA, REMOTEV, SWIVTER, Dresden NOAC Registry, Mayo clinic thrombophilia database and the study by Mantha *et al.*; major bleeding was identified from healthcare databases using the Cunningham algorithm in Peacock *et al.*, Coleman *et al.*, Khorana *et al.*, Streiff *et al.* and Kohn *et al.*; in Sindet-Pederson *et al.*, major bleeding was defined as an in-patient hospital admission with gastrointestinal, intracranial, urinary tract, respiratory, vitreous, retroperitoneal, intraspinal or pericardial bleeding, or anaemia caused by recent haemorrhage; in Larsen *et al.*, bleeding events included intracranial bleeding (including traumatic intracranial bleeding), gastrointestinal bleeding and major clinically relevant bleedings in various anatomical positions]. In addition, the *N* numbers used for some safety analyses may have differed from the total number of patients randomized (e.g. due to patients not receiving study medication or switching treatment groups after randomization). [b] Mean treatment duration. [c] Fragile patients were those with at least one of the following criteria: age more than 75 years, CrCl less than 50 ml/min or body weight of 50 kg or less. [d] Active cancer at baseline or diagnosed during the study. [e] Median treatment duration. [f] Cumulative event rate at 6 months. [g] Protocol amended during the study, following the approval of rivaroxaban for the treatment of PE, to allow enrolment of patients presenting with DVT and concomitant PE (but not patients with isolated PE). [h] Standard anticoagulation included parenteral anticoagulant only and parenteral anticoagulant overlapping with and followed by a VKA. [i] Early switchers were patients who received parenteral anticoagulants for at least 2–14 days and/or a VKA for 1–14 days before switching to rivaroxaban. [j] Annualized event rates. [k] Adjusted HR from Cox regression (adjusted for cancer and stratified by index VTE type). [l] 90-day cumulative incidence. [m] Recurrent DVT. [n] Events per 100 patient-years. [o] Recurrent PE. [p] Average follow-up duration. [q] Standardized absolute risk at 6 months' follow-up. [r] Adjusted HR from Cox regression (adjusted for baseline comorbidities and concomitant medications used in the propensity model). [s] Adjusted HR from Cox regression (adjusted based on risk factors for VTE and bleeding, including age, comorbidities and concomitant medications). [t] At 6 months' follow-up. [u] Median time between first and last rivaroxaban prescriptions. [v] At 15 months postindex VTE (excluding events occurring in the first 3 months of treatment). [w] At 18 months postindex VTE (excluding events occurring in the first 3 months of treatment).

respectively; hazard ratio 1.83, 95% CI 0.68–4.96). There was one fatal bleeding event in each arm, and overall survival at 6 months was 75 and 70% in the rivaroxaban and dalteparin groups, respectively [19]. Two other ongoing CALLISTO studies (CONKO-011 and CASTA-DIVA) will provide additional data on the relative efficacy and safety of rivaroxaban compared with LMWH for the treatment of cancer-associated thrombosis [30,58].

EINSTEIN DVT and EINSTEIN PE data in context: how do real-world data compare?

Given that randomized controlled trials have strict eligibility criteria and relatively constrained methodologies, the applicability of their results may be limited for routine clinical practice. Real-world evidence can provide insights into whether a drug works as expected in unselected patients treated in routine clinical practice. A comprehensive review of all the available real-world evidence on the use of rivaroxaban for the treatment of VTE is beyond the scope of the article, but key findings from the main studies published to date are discussed in brief below and summarized in Table 1.

To date, the XALIA study is the largest prospective real-world study on the use of a DOAC for the treatment of VTE. XALIA was a multicentre, prospective, noninterventional study of patients with DVT treated with rivaroxaban or standard anticoagulation therapy (heparin/fondaparinux only or overlapping with and followed by a VKA) in routine clinical practice. XALIA enrolled 5142 patients in Europe, Canada and Israel – treatment decisions were entirely at the discretion of the attending physician. Patients in the rivaroxaban cohort had a lower baseline risk profile than those receiving standard anticoagulation, reflective of the noninterventional study design, so propensity score-adjusted outcomes were determined to account for the differences in baseline characteristics between cohorts. After propensity score adjustment, the incidences of major bleeding, recurrent VTE and all-cause mortality were similar between rivaroxaban and standard anticoagulation cohorts and consistent with the results of EINSTEIN DVT, confirming rivaroxaban to be a safe and effective alternative to standard anticoagulation therapy for the treatment of VTE [32]. Similar results have been reported in the XALIA-LEA study (a companion study to XALIA, which enrolled 1987 patients with DVT and/or PE from Latin America, Eastern Europe, Middle East, Africa and Asia) [34], and from the small, prospective REMOTEV registry ($n = 445$) [36], a retrospective analysis of the prospective SWIVTER registry ($n = 2062$) [44], two retrospective analyses of Danish healthcare registries ($n = 5004$ and $n = 12\,318$) [43,45] and a large ($n = 45\,853$) retrospective US claims database analysis (Table 1) [31].

Because only a small subgroup of patients had cancer in the EINSTEIN DVT and EINSTEIN PE studies, real-world evidence can provide important insights into the use of rivaroxaban in this under-represented, but important, patient group. Data from prospective real-world studies (including XALIA and two small, single-centre studies) showed low rates of recurrent VTE and major bleeding in patients with active cancer and VTE treated with rivaroxaban in routine clinical practice [38–40]. Both XALIA ($n = 587$ patients with cancer-associated thrombosis) and the Mayo thrombophilia clinic NOAC registry ($n = 256$ patients with cancer-associated thrombosis) reported outcomes in patients treated with rivaroxaban or LMWH, and the incidences of recurrent VTE and major bleeding were broadly similar between treatments. However, in both studies, mortality was markedly increased in LMWH-treated patients, indicating that rivaroxaban was most likely administered to patients with a better prognosis [38,39,59]. Retrospective data from the US indicated that rivaroxaban is prescribed about as often as LMWH in patients with cancer-associated thrombosis, and that treatment persistence is higher in patients treated with rivaroxaban [49]. In the largest propensity-weighted retrospective US claims database analysis in patients with cancer-associated thrombosis treated with LMWH ($n = 4313$) or rivaroxaban ($n = 3370$) available to date, mean treatment duration was significantly shorter in patients treated with LMWH versus rivaroxaban (3.2 versus 5.3 months). In addition, compared with LMWH, rivaroxaban was associated with significantly lower rates of recurrent VTE (11.9 versus 14.7% at 12 months; hazard ratio 0.83; 95% CI 0.73–0.96; $P = 0.01$) and similar rates of major bleeding (the latter of which was identified using the Cunningham algorithm) [60]. COSIMO, an ongoing noninterventional, observational study that is part of the CALLISTO programme, will provide data on patient-reported outcomes and treatment satisfaction in patients with cancer-associated thrombosis switching to rivaroxaban therapy after at least 4 weeks' treatment with standard anticoagulation (LMWH/VKA) [61].

Rivaroxaban for the extended treatment of venous thromboembolism in adult patients

Based on the results of EINSTEIN EXT and EINSTEIN CHOICE, two doses of rivaroxaban (10 mg od and 20 mg od) have been approved for the extended secondary prevention of VTE in patients who have completed at least 6 months' anticoagulation therapy [12]. The approval (October 2017) of the rivaroxaban 10 mg od dose in this indication is based on the results of the EINSTEIN CHOICE study, which compared two doses of rivaroxaban (10 mg od and 20 mg od) with acetylsalicylic acid [ASA (aspirin)] for the extended treatment of VTE [11]. In the updated product label, the recommended dose of rivaroxaban for the extended secondary prevention of VTE is rivaroxaban 10 mg od. However, the rivaroxaban 20 mg od dose should be considered in those patients at high risk of recurrent VTE, such as those with complicated comorbidities

(and in those who experience a recurrent VTE while receiving the rivaroxaban 10 mg od regimen).

Overview of the EINSTEIN EXT and EINSTEIN CHOICE studies

EINSTEIN EXT and EINSTEIN CHOICE were both randomized, double-blind trials investigating the use of rivaroxaban for the extended secondary prevention of recurrent VTE in patients who had completed an initial 6–12 months of anticoagulant therapy and were at equipoise regarding the need for continued anticoagulation therapy [9,11]. Thus, patients were eligible for either study if it was unclear whether they should continue or stop anticoagulant treatment; patients were ineligible if they required extended anticoagulant therapy at therapeutic doses. In EINSTEIN EXT, patients received treatment for an additional 6 or 12 months, and in EINSTEIN CHOICE the study drugs were given for up to 12 months. The key differences between the two trials were that EINSTEIN EXT compared one dose of rivaroxaban (20 mg od) with placebo [9] and EINSTEIN CHOICE compared two doses of rivaroxaban (10 mg od and 20 mg od) with an active comparator, ASA [11]. The rationale for testing rivaroxaban 10 mg od and using an active comparator in the EINSTEIN CHOICE study was two-fold. First, because of concerns about bleeding associated with long-term use of anticoagulants at doses approved for the initial treatment of VTE, ASA and lower doses of anticoagulants are often used for extended secondary prevention of recurrent VTE (and some physicians elect to stop anticoagulation treatment to avoid the risk of bleeding) [11]. For example, the approved dose of apixaban for the extended secondary prevention of VTE after at least 6 months' therapy is 2.5 mg bid, whereas the approved dosing regimen for the initial treatment of VTE is 10 mg bid for 7 days followed by 5 mg bid [13]. Second, in the RECORD1–4 studies, rivaroxaban 10 mg od was shown to be safe and efficacious for the prevention of VTE after major orthopaedic surgery [55]. One aim of EINSTEIN CHOICE was to investigate whether physicians are justified in using lower rivaroxaban doses or switching to ASA to ameliorate bleeding risk rather than continuing to use rivaroxaban 20 mg od for extended treatment.

Both EINSTEIN EXT and EINSTEIN CHOICE demonstrated that rivaroxaban was a safe and effective treatment option for extended secondary prevention of VTE. In EINSTEIN EXT, rivaroxaban 20 mg od was superior to placebo for the prevention of recurrent VTE, without significantly increasing the rate of major bleeding, although, as expected in a placebo-controlled study (Table 1), clinically significant bleeding was significantly higher with rivaroxaban [9]. In EINSTEIN CHOICE, both doses of rivaroxaban (10 mg od and 20 mg od) were shown to be superior to ASA for the prevention of recurrent VTE, with similar incidences of major bleeding and nonmajor clinically significant bleeding – the number of patients who needed to be treated with rivaroxaban 10 mg od or rivaroxaban 20 mg od, instead of ASA, to prevent one recurrent VTE without increasing the risk of bleeding were 30 and 33, respectively. The EINSTEIN CHOICE study did not aim to compare both rivaroxaban doses with each other; it was powered to test for superiority of each dose versus ASA [11]. Within each trial, the relative efficacy and safety of rivaroxaban versus placebo or ASA was consistent across multiple patient subgroups, including in elderly patients and patients with renal impairment [9,11].

EINSTEIN EXT and EINSTEIN CHOICE included patients with provoked as well as unprovoked VTE [9,11]. However, VTE treatment guidelines generally recommend 3 months' treatment over treatment for longer time periods in patients with provoked VTE [16]. In a benefit–risk analysis of EINSTEIN EXT, extended treatment with rivaroxaban resulted in a clinically important benefit – including for patients with all types of provoked VTE and patients with unprovoked VTE [62]. The number of patients who needed to be treated with rivaroxaban instead of placebo to avoid one recurrent VTE were 14 and 16 for patients with provoked and unprovoked VTE, respectively. Conversely, 75 and 219 patients with provoked and unprovoked VTE, respectively, would have to be treated with rivaroxaban instead of placebo to cause one major bleeding event [62]. Similarly, in EINSTEIN CHOICE, both doses of rivaroxaban reduced the risk of recurrent VTE by approximately 70% (compared with ASA) in patients with provoked VTE and in patients with unprovoked VTE [11]. Together, these results suggest that many patients with provoked VTE, as well as those with unprovoked VTE, may benefit from extended treatment with rivaroxaban.

A recent analysis of the EINSTEIN EXT and EINSTEIN CHOICE studies has provided insights into identifying which patient groups stand to benefit most from extended rivaroxaban treatment based on baseline risk factor profiles [52]. The index venous thromboembolic events were classified into five categories:

(1) Provoked by major persistent risk factors (e.g. active cancer).
(2) Provoked by minor persistent risk factors (e.g. lower extremity paralysis or paresis, inflammatory bowel disease, congestive heart failure, BMI $> 30\,kg/m^2$, CrCl < 50 ml/min, family history of VTE or known thrombophilia).
(3) Provoked by minor transient risk factors (e.g. immobilization, travel >8 h, pregnancy, puerperium or use of hormone therapy, or lower limb trauma with transient impairment of mobility).
(4) Provoked by major transient risk factors (e.g. major surgery or trauma, or caesarean section).

(5) Unprovoked VTE (patients without any risk factors for VTE).

Across both studies, the risks of recurrent VTE were highest in patients with unprovoked VTE (6.9% with placebo or ASA). However, the risks of recurrent VTE were also substantial in patients with VTE provoked by both major or minor persistent risk factors and minor transient risk factors (4.5–6.9% with placebo or ASA); no recurrent venous thromboembolic events were observed in patients with VTE provoked by major transient risk factors. Regardless of risk factor profile, rivaroxaban substantially reduced the risk of VTE compared with ASA or placebo [52]. These findings support current guideline recommendations for extended treatment in patients with unprovoked VTE and major persistent risk factors (i.e. cancer), as well as recommendations for 3 months' treatment in patients with VTE provoked by surgery. However, they also suggest that patients with VTE provoked by minor persistent or transient risk factors will benefit from extended anticoagulation therapy [16,52].

EINSTEIN EXT and EINSTEIN CHOICE data in context: how do real-world data compare?

A recent propensity-weighted retrospective US healthcare claims database analysis provided data on the use of rivaroxaban for extended treatment of VTE in routine clinical practice [63]. The analysis included adult patients who initiated rivaroxaban therapy within 7 days of their index VTE and were treated with rivaroxaban for at least 3 or 6 months. Outcomes were then compared between patients who stopped rivaroxaban treatment at 3 or 6 months and those who continued treatment. Rates of VTE recurrence at 15–18 months postindex VTE were significantly lower in patients who continued treatment (beyond 3 or 6 months) compared with those who stopped treatment (at 3 or 6 months); major bleeding rates were similar between patients who stopped and those who continued therapy (Table 1) [63]. These data support the results of EINSTEIN EXT and EINSTEIN CHOICE and suggest that the efficacy benefits of extended treatment with rivaroxaban are maintained in routine clinical practice.

Practical guidance on rivaroxaban dose selection for extended treatment of venous thromboembolism

As a result of the findings from EINSTEIN CHOICE, two doses of rivaroxaban (20 mg od and 10 mg od), are now approved for the extended secondary prevention of VTE in patients who have completed at least 6 months' therapy [12]. The rivaroxaban 20 mg od dose is expected to remain the preferred option for patients at high risk of recurrent VTE, such as those with active cancer, a second unprovoked VTE or high-risk thrombophilia. The rivaroxaban 10 mg od dose will be suitable for a broad range of patients, such as those with a first VTE provoked by a minor risk factor. Lifestyle-specific considerations may also influence dose selection – for example, the rivaroxaban 10 mg od dose may be preferred in patients participating in sports or activities where injuries might occur (e.g. contact sports, cycling or horse riding) or in patients who may be at risk of bleeding because of work-related accidents (e.g. manual labourers). The approach could be combined with a further preference for evening dosing to avoid anticoagulant drug concentration peaks at or around the time of the activity in question. It should be noted that there are no data available to support dose reduction based on lifestyle-specific considerations. If a patient experiences a recurrent VTE while receiving rivaroxaban 10 mg od, dose re-escalation is permitted within the label.

Recent evidence (from the EINSTEIN DVT and EINSTEIN PE studies, together with real-world data) indicate that women of child-bearing age receiving rivaroxaban are at an increased risk of heavy menstrual bleeding. As such, a management strategy sometimes employed in routine clinical practice is temporary rivaroxaban dose reduction [64–68]. Because of this adjustment, a subanalysis of the EINSTEIN CHOICE study compared menstrual bleeding patterns in 353 women receiving rivaroxaban 20 mg od, rivaroxaban 10 mg od or ASA. Women treated with rivaroxaban 20 mg od reported an increase in menstrual flow length and intensity compared with those treated with rivaroxaban 10 mg or ASA, suggesting that heavy menstrual bleeding in rivaroxaban-treated women may be dose-dependent [69].

Rivaroxaban for the treatment of venous thromboembolism in paediatric patients

In addition to the studies in adult patients, the ongoing EINSTEIN Junior programme is investigating the potential of rivaroxaban in the paediatric patient population. EINSTEIN Junior consists of one completed phase I pharmacokinetics/pharmacodynamics (PK/PD) trial, two completed phase II trials and an ongoing phase III trial [21–24].

The phase II trials were 30-day, single-arm trials investigating the safety, efficacy and PK/PD profiles of body weight-adjusted regimens of rivaroxaban in children with VTE aged 6 months–18 years who had completed at least 2 months of anticoagulation therapy [70,71]. One study included patients aged 5 months–12 years ($n = 59$) who were treated with rivaroxaban suspension (1 mg/ml) in a rivaroxaban 10 mg od equivalent dose using a bid regimen [70]. The other study included patients aged 6–18 years ($n = 24$), who were treated with body weight-adjusted od rivaroxaban tablets at a rivaroxaban 20 mg od equivalent dose [71]. No major bleeding (defined using the ISTH criteria as for the adult studies in the EINSTEIN programme [72]) or recurrent venous thromboembolic events occurred in either study, and repeat imaging showed improvement or normalization of clot burden in more than 90% of patients. In general, the PK/PD

profiles in both studies were similar to the reference adult population treated with rivaroxaban 20 mg od [70,71]. However, children weighing less than 30 kg receiving the tablet formulation tended to have minimum plasma drug concentrations at the lower end of the spectrum of values observed in adults and may require a bid rivaroxaban regimen [71].

Based on the results of these phase II trials, the ongoing phase III EINSTEIN Junior trial is assessing the efficacy and safety of several rivaroxaban regimens for the treatment of VTE in children [21]. This is a multicentre, open-label, randomized, active-controlled study comparing the efficacy and safety of rivaroxaban 20-mg-equivalent dose regimens with standard of care (LMWH, fondaparinux or VKA) in children with acute VTE aged 0–18 years; it is anticipated that approximately 170 patients will be enrolled. Children are eligible if they have confirmed VTE and receive initial treatment with therapeutic doses of unfractionated heparin, LMWH or fondaparinux and required treatment for at least 90 days; children with catheter-related thrombosis, aged less than 2 years who require treatment for at least 30 days are also eligible. Additional eligibility criteria for children aged less than 6 months include full-term birth ($\geq$37 weeks' gestational age), body weight at least 2.6 kg and oral/nasogastric/gastric feeding for at least 10 days. The rivaroxaban 20-mg-equivalent regimens being tested include tablets dosed od or bid, and an oral suspension dosed od, bid or three-times daily [21]. Frequency of rivaroxaban dosing is determined by body weight: children less than 12 kg, 12–30 kg and at least 30 kg will be dosed three-times daily, bid and od, respectively. The primary efficacy outcome is symptomatic recurrent VTE and the primary safety outcome is overt major and clinically relevant nonmajor bleeding [21].

Conclusion

Once completed, the EINSTEIN clinical development programme, evaluating the use of rivaroxaban for the treatment of VTE, will have included over 13 100 patients – 12 842 adults in four completed studies and 309 children in the ongoing paediatric studies. A further 1756 patients with VTE and cancer are being evaluated in the ongoing CALLISTO programme. The completed EINSTEIN DVT and EINSTEIN PE studies in adult patients demonstrated that rivaroxaban is a safe and effective alternative to standard anticoagulation for the treatment of VTE in a broad range of patients, and these findings are supported by increasing amounts of real-world data from patients treated with rivaroxaban in routine clinical practice. In the extended treatment trials, EINSTEIN EXT and EINSTEIN CHOICE, rivaroxaban was more effective than placebo and ASA, respectively, for prevention of recurrent VTE. Physicians are now able to choose between two doses of rivaroxaban for the extended prevention of recurrent VTE, based on a patient's risk of recurrence, bleeding and personal preferences. Ongoing studies, including those that are part of the EINSTEIN Junior and CALLISTO programmes, are expected to provide valuable insights into the use of rivaroxaban for the treatment of VTE in children and patients with cancer who were ineligible or under-represented in many other trials completed to date.

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Conflicts of interest

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References

1 Sindet-Pedersen C, Pallisgaard JL, Staerk L, Berger JS, Lamberts M, Torp-Pedersen C, *et al.* Temporal trends in initiation of VKA, rivaroxaban, apixaban and dabigatran for the treatment of venous thromboembolism – a Danish nationwide cohort study. *Sci Rep* 2017; **7**:3347.

2 Haas S, Turpie AGG, Weitz JI, Ageno W, Angchaisuksiri P, Bounameaux H, *et al.* Anticoagulation treatment patterns of venous thromboembolism in GARFIELD-VTE. International Society on Thrombosis and Haemostasis 2017 Congress. Berlin, Germany, 8–13 July 2017, Poster PB 460. Available at: http://vte.garfieldregistry.org/wp-content/uploads/2017/06/Garfield-VTE-Posters-1200-x-900-TREATMENT-PATTERNS-Proof-6.pdf. [Accessed 3 December 2018].

3 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.* Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369**:799–808.

4 Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.* Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013; **368**:699–708.

5 Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, *et al.* Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361**:2342–2352.

6 Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, *et al.* Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013; **368**:709–718.

7 Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, *et al.* Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014; **129**:764–772.

8 The Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369**:1406–1415.

9 The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**:2499–2510.

10 The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**:1287–1297.

11 Weitz JI, Lensing AWA, Prins M, Bauersachs R, Beyer-Westendorf J, Brighton TA, *et al.* Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med* 2017; **376**:1211–1222.

12 Bayer AG. *Xarelto® (rivaroxaban) summary of product characteristics.* Europe Medicines Agency; 2018; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf. [Accessed 9 January 2019].

13 Bristol-Myers Squibb; Pfizer. *Eliquis® (apixaban) summary of product characteristics.* Europe Medicines Agency; 2018; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. [Accessed 9 January 2019].

14 Boehringer Ingelheim International GmbH. *Pradaxa® (dabigatran etexilate) summary of product characteristics*. Europe Medicines Agency; 2018; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. [Accessed 9 January 2019].

15 Daiichi Sankyo Europe GmbH. *Lixiana® (edoxaban) summary of product characteristics*. Europe Medicines Agency; 2018; Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf. [Accessed 9 January 2019].

16 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; **149**:315–352.

17 Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016; **41**:92–128.

18 Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, *et al.* Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018; **378**:615–624.

19 Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, *et al.* Comparison of an oral Factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018; **36**:2017–2023.

20 Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, *et al.* Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost* 2018; **16**:1891–1894.

21 Bayer; Janssen Research & Development LLC. *EINSTEIN junior: oral rivaroxaban in children with venous thrombosis (EINSTEIN Jr)*. 2018; ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02234843. [Accessed 3 December 2018].

22 Bayer. *EINSTEIN Junior phase II: oral rivaroxaban in young children with venous thrombosis (EINSTEINJr)*. 2017; ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT02309411. [Accessed 5 October 2017].

23 Bayer; Janssen Research & Development LLC. *Oral rivaroxaban in children with venous thrombosis (EINSTEINJunior)*. 2017; ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01684423. [Accessed 5 October 2017].

24 Bayer; Janssen Research & Development LLC. *Rivaroxaban pharmacokinetics/pharmacodynamics (PK/PD) study in pediatric subjects*. 2015; ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01145859. [Accessed 5 October 2017].

25 Prins MH, Lensing AWA, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, *et al.* Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; **11**:21.

26 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients. *J Thromb Haemost* 2005; **3**:692–694.

27 Bauersachs RM, Lensing AWA, Prins MH, Kubitza D, Pap ÁF, Decousus H, *et al.* Rivaroxaban versus enoxaparin/vitamin K antagonist therapy in patients with venous thromboembolism and renal impairment. *Thromb J* 2014; **12**:25–32.

28 Prins MH, Lensing AWA, Brighton TA, Lyons RM, Rehm J, Trajanovic M, *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**:e37–e46.

29 Peacock WF, Coleman CI, Diercks DB, Francis S, Kabrhel C, Keay C, *et al.* Emergency department discharge of pulmonary embolus patients. *Acad Emerg Med* 2018; **25**:995–1003.

30 Assistance Publique – Hôpitaux de Paris. *Cancer associated thrombosis, a pilot treatment study using rivaroxaban (CASTA-DIVA)*. 2018; ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02746185. [Accessed 16 October 2018].

31 Coleman CI, Bunz TJ, Turpie AGG. Effectiveness and safety of rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism. *Thromb Haemost* 2017; **117**:1841–1847.

32 Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, *et al.* Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, noninterventional study. *Lancet Haematol* 2016; **3**:e12–e21.

33 Turpie AGG, Mantovani A, Haas S, Kreutz R, Monje D, Schneider J, *et al.* A pooled analysis of the XALIA and XALIA-LEA non-interventional studies of rivaroxaban versus standard anticoagulation in venous thromboembolism. *Blood* 2017; **130**:2386; Abstract 2386.

34 Turpie AGG, Mantovani LG, Haas S, Kreutz R, Monje D, Scheinder J, *et al.* XALIA-LEA, a non-interventional study comparing rivaroxaban with standard anticoagulation for initial and long-term therapy in deep vein thrombosis. *Res Pract Thromb Haemost* 2017; **1**:914; Abstract PB 456.

35 Keller L, Marten S, Hecker J, Sahin K, Tittl L, Beyer-Westendorf J. Venous thromboembolism therapy with rivaroxaban in daily-care patients: Results from the Dresden NOAC registry. *Int J Cardiol* 2018; **257**:276–282.

36 Gaertner S, Cordeanu EM, Nouri S, Faller AM, Frantz AS, Mirea C, *et al.* Rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMOTEV observational study): analysis of 6-month outcomes. *Int J Cardiol* 2017; **226**:103–109.

37 Di Micco P, Trujillo-Santos J, Merah A, Fidalgo A, Vela JR, Mahe I, *et al.* Rivaroxaban for initial therapy in patients with pulmonary embolism. A real-life study. *Res Pract Thromb Haemost* 2017; **1**:914–915; Abstract PB 457.

38 Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, *et al.* Subgroup analysis of patients with cancer in XALIA: a noninterventional study of rivaroxaban versus standard anticoagulation for VTE. *TH Open* 2017; **1**:e33–e42.

39 Mantha S, Laube E, Miao Y, Sarasohn DM, Parameswaran R, Stefanik S, *et al.* Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a prospective cohort study. *J Thromb Thrombolysis* 2017; **43**:166–171.

40 Bott-Kitslaar DM, Saadiq RA, McBane RD, Loprinzi CL, Ashrani AA, Ransone TR, *et al.* Efficacy and safety of rivaroxaban in patients with venous thromboembolism and active malignancy: a single-center registry. *Am J Med* 2016; **129**:615–619.

41 McBane RD, Simmons B, Saadiq R, Wysokinski W, Bott-Kitslaar D, Lenz C, *et al.* Rivaroxaban compared to low molecular weight heparin in treatment of malignancy associated venous thromboembolism. *J Am Coll Cardiol* 2016; **67**:2257; Abstract 1243M-05.

42 Peacock WF, Tamayo S, Patel MR, Sicignano N, Hopf K, Yuan Z. Major bleeding in patients taking rivaroxaban for VTE treatment. *Chest* 2016; **150**:286A; Abstract 286A.

43 Larsen TB, Skjoth F, Kjaeldgaard JN, Lip G, Nielsen PB, Sogaard M. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. *Lancet Haematol* 2017; **4**:e237–e244.

44 Kucher N, Aujesky D, Beer JH, Mazzolai L, Baldi T, Banyai M, *et al.* Rivaroxaban for the treatment of venous thromboembolism. The SWIss Venous ThromboEmbolism Registry (SWIVTER). *Thromb Haemost* 2016; **116**:472–479.

45 Sindet-Pedersen C, Langtved Pallisgaard J, Staerk L, Gerds TA, Fosbol EL, Torp-Pedersen C, *et al.* Comparative safety and effectiveness of rivaroxaban versus VKAs in patients with venous thromboembolism. A Danish nationwide registry-based study. *Thromb Haemost* 2017; **117**:1182–1191.

46 Coleman CI, Turpie AGG, Bunz TJ, Beyer-Westendorf J. Effectiveness and safety of rivaroxaban versus warfarin in frail patients with venous thromboembolism. *Am J Med* 2018; **131**:; 933–938 e931.

47 Coleman CI, Peacock WF, Bunz TJ, Beyer-Westendorf J. Effectiveness and safety of rivaroxaban versus warfarin in patients with unprovoked venous thromboembolism: A propensity-score weighted administrative claims cohort study. *Thromb Res* 2018; **168**:31–36.

48 Coleman CI, Turpie AGG, Bunz TJ, Beyer-Westendorf J. Effectiveness and safety of rivaroxaban versus warfarin in patients with provoked venous thromboembolism. *J Thromb Thrombolysis* 2018; **46**:339–345.

49 Khorana AA, McCrae KR, Milentijevic D, Fortier J, Nelson WW, Laliberte F, *et al.* Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. *Res Pract Thromb Haemost* 2017; **1**:14–22.

50 Streiff MB, Milentijevic D, McCrae K, Yannicelli D, Fortier J, Nelson WW, *et al.* Effectiveness and safety of anticoagulants for the treatment of venous thromboembolism in patients with cancer. *Am J Hematol* 2018; **93**:664–671.

51 Kohn CG, Lyman GH, Beyer-Westendorf J, Spyropoulos AC, Bunz TJ, Baker W.L., *et al.* Effectiveness and safety of rivaroxaban in patients with cancer-associated venous thrombosis. *J Natl Compr Canc Netw* 2018; **16**:491–497.

52 Prins MH, Lensing AWA, Prandoni P, Wells PS, Verhamme P, Beyer-Westendorf J, *et al.* Risk of recurrent venous thromboembolism according to baseline risk factor profiles. *Blood Adv* 2018; **2**:788–796.

53 Berger JS, Seheult R, Laliberte F, Crivera C, Lejeune D, Xiao Y, *et al.* Clinical outcomes of prolonged anticoagulation with rivaroxaban after unprovoked venous thromboembolism. *Res Pract Thromb Haemost* 2018; **2**:58–68.

54 Turpie AGG, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, *et al.* Analysis of patients with deep vein thrombosis switched from standard therapy to rivaroxaban in the non-interventional XALIA study. *Thromb Res* 2017; **155**:23–27.

55 Turpie AGG, Lassen MR, Eriksson BI, Gent M, Berkowitz SD, Misselwitz F, *et al.* Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011; **105**:444–453.

56 Di Nisio M, Vedovati MC, Riera-Mestre A, Prins MH, Mueller K, Cohen AT, *et al.* Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. *Thromb Haemost* 2016; **116**:739–746.

57 Bach M, Bauersachs R. Spotlight on advances in VTE management: CALLISTO and EINSTEIN CHOICE. *Thromb Haemost* 2016; **116**: S24–S32.

58 AIO-Studien-gGmbH. *Rivaroxaban in the treatment of venous thromboembolism (VTE) in cancer patients*. 2018; ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02583191. [Accessed 16 October 2018].

59 Simmons B, Wysokinski W, Saadiq RA, Bott-Kitslaar D, Henkin S, Casanegra A, *et al.* Efficacy and safety of rivaroxaban compared to enoxaparin in treatment of cancer-associated venous thromboembolism. *Eur J Haematol* 2018; [Epub ahead of print].

60 Khorana AA, McCrae K, Milentijevic D, McCormick N, Laliberté F, Crivera C, *et al.* VTE recurrence and safety of anticoagulants among patients with cancer treated for venous thromboembolism. *Blood* 2017; **130**:4631.

61 Cohen AT, Maraveyas A, Beyer-Westendorf J, Lee AYY, Mantovani LG, Bach M, *et al.* COSIMO – patients with active cancer changing to rivaroxaban for the treatment and prevention of recurrent venous thromboembolism: a non-interventional study. *Thromb J* 2018; **16**:21.

62 Wells PS, Prins MH, Levitan B, Beyer-Westendorf J, Brighton TA, Bounameaux H, *et al.* Long-term anticoagulation with rivaroxaban for preventing recurrent VTE: a benefit–risk analysis of EINSTEIN-Extension. *Chest* 2016; **150**:1059–1068.

63 Khorana AA, Vadhan-Raj S, Kuderer NM, Wun T, Liebman H, Soff G, *et al.* Rivaroxaban for preventing venous thromboembolism in high-risk ambulatory patients with cancer: rationale and design of the CASSINI trial. *Thromb Haemost* 2017; **117**:2135–2145.

64 Martinelli I, Lensing AWA, Middeldorp S, Levi M, Beyer-Westendorf J, van Bellen B, *et al.* Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. *Blood* 2016; **127**:1417–1425.

65 Beyer-Westendorf J, Michalski F, Tittl L, Hauswald-Dorschel S, Marten S. Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral antifactor Xa inhibitor therapy: a case series. *Lancet Haematol* 2016; **3**:e480–e488.

66 Bryk AH, Pirog M, Plens K, Undas A. Heavy menstrual bleeding in women treated with rivaroxaban and vitamin K antagonists and the risk of recurrent venous thromboembolism. *Vascul Pharmacol* 2016; **87**:242–247.

67 Ferreira M, Barsam S, Patel JP, Czuprynska J, Roberts LN, Patel RK, *et al.* Heavy menstrual bleeding on rivaroxaban. *Br J Haematol* 2016; **173**:314–315.

68 De Crem N, Peerlinck K, Vanassche T, Vanheule K, Debaveye B, Middeldorp S, *et al.* Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. *Thromb Res* 2015; **136**:749–753.

69 Boonyawat K, Lensing AW, Prins MH, Prandoni P, Weitz JI, Crowther M. Menstrual bleeding patterns in women treated with rivaroxaban: data from the EINSTEIN CHOICE trial. *Res Pract Thromb Haemost* 2017; **1**:963; Abstract PB 1191.

70 Chan A, Kubitza D, Santamaria A, Samochatova E, Martinelli I, Connor P, *et al.* Safety, efficacy and PK/PD of a rivaroxaban suspension in children with VTE. An EINSTEIN Junior phase II evaluation. *Res Pract Thromb Haemost* 2017; **1**:1176; Abstract PB 512.

71 Monagle P, Kubitza D, Kumar R, Holzhauer S, Grangl G, Robertson J, *et al.* Safety, efficacy and PK/PD of rivaroxaban tablets in children with VTE. An EINSTEIN Junior phase II evaluation. *Res Pract Thromb Haemost* 2017; **1**:1175–1176; Abstract PB 511.

72 Lensing AWA, Male C, Young G, Kubitza D, Kenet G, Patricia Massicotte M, *et al.* Rivaroxaban versus standard anticoagulation for acute venous thromboembolism in childhood. Design of the EINSTEIN-Jr phase III study. *Thromb J* 2018; **16**:34.