

Direct oral anticoagulants in the treatment of venous thromboembolism, with a focus on patients with pulmonary embolism: an evidence-based review

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Abstract: Pulmonary embolism (PE) is a relatively common cardiovascular emergency. PE and deep vein thrombosis (DVT) are considered expressions of the same disease, termed as venous thromboembolism (VTE). In the present review, we describe and meta-analyze the efficacy and safety data available with the direct oral anticoagulants (DOAC; dabigatran, rivaroxaban, apixaban, edoxaban) in clinical trials testing these new compounds in the acute/long-term and extended therapy of VTE, providing subgroup analyses in patients with index PE. We analyzed ten studies in 35,019 randomized patients. A total of 14,364 patients (41%) had index PE. In the acute/long-term treatment of VTE, the DOAC showed comparable efficacy in preventing recurrent VTE to standard treatment in patients with index PE (risk ratio [RR]: 0.88; 95% confidence interval [CI]: 0.70–1.11) and index DVT (RR: 0.93; 95% CI: 0.75–1.16) (*P* for subgroup differences =0.76). VTE recurrence depending on PE anatomical extension and presence/absence of right ventricular dysfunction was only reported in two trials, with results being consistent with those obtained in the overall study populations. In the single trial comparing extended therapy of VTE with DOAC versus warfarin, the point estimate for recurrent VTE tended to disfavor the DOAC in patients with index PE (RR: 2.05; 95% CI: 0.83–5.03) and in patients with index DVT (RR: 1.11; 95% CI: 0.49–2.50) (*P* for subgroup differences =0.32). In trials that compared DOAC versus placebo for extended therapy, the reduction in recurrent VTE was consistent in patients with PE (RR: 0.15; 95% CI: 0.01–1.82) and in patients with DVT (RR: 0.25; 95% CI: 0.10–0.61) (*P* for subgroup differences =0.71). The DOAC were associated with a consistently lower risk of clinically relevant bleeding (CRB) than standard treatment of acute VTE and higher risk of CRB than placebo for extended therapy of VTE regardless of index event. In summary, the DOAC were as effective as, and safer than, standard treatment of (hemodynamically stable) PE. Their efficacy in preventing recurrent VTE seemed consistent regardless of anatomical extension of PE (extensive, intermediate, or limit) or presence/absence of right ventricular dysfunction although the data are limited. For extended therapy, the DOAC were more effective than placebo in preventing recurrent VTE but were associated with an increase in CRB regardless of index event.

Keywords: anticoagulant, pulmonary embolism, dabigatran, apixaban, rivaroxaban, edoxaban

Introduction

Pulmonary embolism (PE) is a relatively common cardiovascular emergency. PE occurs when clots break off from deep vein walls (deep vein thrombosis [DVT]), usually from the lower limbs, and travel through the right side of the heart to the pulmonary

arteries occluding the pulmonary arterial bed. The broader term venous thromboembolism (VTE) refers to DVT, PE, or a combination of both, and has a reported annual incidence of 1–2 cases per 1,000 inhabitants in Western countries.¹ PE and DVT are considered as expressions of the same disease, as in different studies, about 70% of patients with documented symptomatic PE had DVT,² and patients presenting with documented DVT have been shown to have silent PE or perfusion defects on ventilation/perfusion lung scan in 30%–70% of cases.^{3,4}

PE can be broadly classified as either high-risk PE (hemodynamically unstable: presence of shock or hypotension, defined as a systolic blood pressure <90 mmHg or a pressure drop of ≥ 40 mmHg for 15 minutes if not caused by new-onset arrhythmia, hypovolemia, or sepsis; early mortality risk >15%) or non-high-risk PE (hemodynamically stable; early mortality risk <15%).⁵ Non-high-risk PE can be further stratified according to the presence of markers of right ventricular dysfunction (RVD) and/or myocardial injury into intermediate- and low-risk PE. Intermediate-risk PE (early mortality risk $\approx 3\%$ –15%) is diagnosed if at least one of the RVD markers: 1) right ventricular (RV) dilatation, hypokinesis, or pressure overload on echocardiography; 2) RV dilatation on spiral computed tomography; 3) brain natriuretic peptide (BNP) or N-terminal (NT)-pro-BNP elevation; 4) elevated right heart pressure at right heart catheterization; or one myocardial injury marker, cardiac troponin T or I, is positive.⁵ Low-risk PE is diagnosed when all checked RVD and myocardial injury markers are found negative (early mortality risk <1%). Some clinical scores, such as the simplified PE severity index, may also be useful to identify low-risk PE patients who are potential candidates for outpatient treatment.⁶ Patients presenting with hemodynamic instability (high-risk PE) are usually treated with either thrombolytic therapy or pulmonary embolectomy followed by anticoagulant therapy, while most hemodynamically stable patients (non-high risk PE) can be treated with anticoagulation alone.

The basic anticoagulant treatment strategy is similar for patients with PE or DVT, and generally includes a parenteral anticoagulant (eg, low-molecular-weight heparin (LMWH), unfractionated heparin, or fondaparinux) for at least 5 days and until the international normalized ratio (INR) is 2.0 or above for at least 24 hours (initial therapy), overlapping with and followed by an oral vitamin K antagonist (VKA) (dose adjusted to keep an INR between 2.0 and 3.0) for at least 3 months (long-term therapy).⁷ At this point, the decision to continue with anticoagulant treatment depends on the

balance between the risk of VTE recurrences if anticoagulation is withdrawn and the risk of bleeding if it is continued. Patients with ongoing risk factors and patients with unprovoked VTE are often prescribed extended therapy, provided that the bleeding risk is not excessive.⁷

Despite LMWH or fondaparinux being effective and safe, they still require daily parenteral subcutaneous administration. In addition, they are mainly cleared through the kidneys, and their use in patients with severe renal insufficiency may be problematic. On the other hand, the narrow therapeutic window and variability in response of VKA implies that frequent anticoagulant monitoring (using the prothrombin time and its reporting as the INR) is necessary to avoid a subtherapeutic anticoagulation associated with an increased risk of thrombosis or an excessive anticoagulation that increases the risk of bleeding. Such monitoring is inconvenient for patients and medical staff, and costly for health care payers.

In recent years, several direct oral anticoagulants (DOAC) have been developed for the treatment of VTE, among other indications.⁸ DOAC directly inhibit either thrombin or activated factor X (FXa).⁹ Among them, the oral direct thrombin inhibitor dabigatran etexilate (Pradaxa[®], Boehringer Ingelheim, Ingelheim, Germany)¹⁰ and the oral direct FXa inhibitors rivaroxaban (Xarelto[®], Bayer AG, Leverkusen, Germany)¹¹ and apixaban (Eliquis[®], Bristol-Myers Squibb, New York, NY, USA)¹² are currently approved in the European Union, North America, and other regions in several indications related to anticoagulation, including the treatment of VTE, while the oral direct FXa inhibitor edoxaban (Lixiana[®], Daiichi-Sankyo, Tokyo, Japan)¹³ is approved in Japan for thromboprophylaxis after major orthopedic surgery and is currently under regulatory review in the European Union and other regions for the treatment of VTE and for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Their pharmacology is well characterized (Table 1).^{14–30} They are given orally in fixed doses once or twice daily, and they lack validated and available antidotes.^{10–13}

In this review, we describe and meta-analyze the efficacy and safety data available with the DOAC in clinical trials testing these new compounds in VTE, with a focus on patients with index PE, and we discuss their potential advantages and drawbacks over existing therapies in patients with VTE.

Methods

Bibliographic search

A search in Medline database (up to 1 June 2014) and clinical trial registries (ie, clinicaltrials.gov) was conducted using the

Table 1 Pharmacological characteristics of the old and new anticoagulants used for treatment of VTE

Agent	Parenteral anticoagulants			Oral anticoagulants				
	Heparin sodium	LMWH [†]	Fondaparinux	Vitamin K antagonists [#]	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Source	Pig intestinal mucosa	Pig intestinal mucosa	Synthetic	Synthetic	Synthetic	Synthetic	Synthetic	Synthetic
Molecular weight (Da)	12,000–15,000	3,600–6,500	1,728	≈1,000	628	436	460	548
Target	FXa=FlIIa (1:1 ratio)	FXa > FlIIa (2:1 to 9:1 ratio)	FXa only	FlI, VII, IX, X	Thrombin	FXa	FXa	FXa
Type of inhibition	Indirect (bind to AT)	Indirect (bind to AT)	Indirect (bind to AT)	Indirect [‡]	Direct	Direct	Direct	Direct
Prodrug	No	No	No	No	Yes (as etexilate)	No	No	No
Bioavailability (%)	100 (IV), 60% (SC)	90–98 (SC)	≈100 (SC)	>60	6	80–100	50	62
T _{max}	Few min (IV), 4–6 h (SC)	2–3 h	30–60 min	1–3 h	0.5–2 h	2–4 h	3–4 h	1.5 h
Protein binding (%)	High	Low	Low	≈99	35	92–95	87	40–60
Half life	0.5–1 h	3–6 h	17–21 h	8–11 h (acenocoumarol); 36–42 h (warfarin)	14–17 h	7–12 h	12 h	6–11 h
Metabolism	Depolymerization	Desulphation, depolymerization (<10%)	Negligible	CYP2C9/19 (acenocoumarol); CYP2C9/1A2/3A4 (warfarin)	Glucuronidation (<10%)	CYP3A4 > CYP2J2	CYP3A4/5 > CYP21A2, SC8, 2C9/19, 2J2	Hydrolysis > CYP3A4/5
Renal excretion (% of administered dose)	Medium	High	64–77 (unchanged)	92	5 (4 unchanged)	66 (33 unchanged)	27 (22 unchanged)	35 (24 unchanged)
Renal excretion (% of absorbed dose)	Medium	High	64–77 (unchanged)	92	85 (80 unchanged)	73 (37 unchanged)	54 (44 unchanged)	56 (39 unchanged)
Biliary–fecal excretion (% of administered dose)	Medium	Low	Negligible	8	95	34	56	62
Antidote	Protamine	Protamine (partial neutralization)	None	Vitamin K	None	None	None	None
Monitoring test	aPTT (1.5–2.5 times the control value) and/or ACT (≈250–500 secs)	Not required routinely Anti-Xa assay	Not required routinely Anti-Xa assay	INR	Not required routinely. Diluted thrombin time	Not required routinely. Anti-Xa assay	Not required routinely. Anti-Xa assay	NA
Year of first marketing authorization (region)	1939 (EU, US)	1985 (EU)	2000 (US)	1941 (US)	2008 (EU)	2008 (EU)	2011 (EU)	2011 (Japan)

Notes: †Dalteparin (first approved LMWH in 1985), ardeparin, bemparin, certoparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin. ††Dicumarol (first approved VKA in 1941; no longer available), warfarin, acenocoumarol, phenprocoumon. ‡Inhibition of vitamin K epoxide-reductase.

Abbreviations: ACT, activated coagulation time; anti-Xa, anti-activated Factor X activity; aPTT, activated partial thromboplastin time; AT, antithrombin; CYP, cytochrome P450; EU, European Union; h, hours; F, Factor; FlIIa, activated Factor II; FXa, activated Factor X; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; min, minutes; NA, data not available; SC, subcutaneous; secs, seconds; T_{max}, time to maximum concentration; US, United States; VKA, vitamin K antagonist; VTE, venous thromboembolism.

terms: “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, and “pulmonary embolism”. We also searched regulatory agencies’ websites (European Medicines Agency, US Food and Drug Administration) and relevant conference proceedings related to anticoagulant therapy.

Study selection criteria

We included randomized controlled trials comparing a DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) with the standard treatment for acute VTE or with warfarin or placebo for extended treatment of VTE.

Data extraction and quality assessment

We collected outcome data on the overall trial populations as well as by index event at baseline: index PE (with or without concomitant DVT) or index DVT (without PE). Primary efficacy outcome was recurrent symptomatic VTE (ie, the composite of recurrent DVT, recurrent non-fatal PE, and VTE-related death) and primary safety outcome was clinically relevant bleeding (CRB) (ie, the composite of major and clinically relevant non-major bleeding). We also extracted data on clinical trials design (eg, superiority, non-inferiority, duration of treatment and follow-up, inclusion and exclusion criteria, and outcomes definitions), treatment characteristics (eg, dosage used in the experimental and control groups), and patients’ characteristics (age and sex; percentage of patients evaluable for efficacy and safety). Study quality was assessed using the Cochrane Collaboration’s tool for assessing risk of bias in randomized studies.³¹

Data synthesis and analysis

We carried out direct comparisons between the DOAC and standard treatment (initial/long-term therapy), placebo or warfarin (extended therapy) on an intention-to-treat basis.³² We included the randomized population in the overall analysis. Clinical outcomes were analyzed in subgroups of patients with index PE versus those with index DVT when disaggregated data were available. Subgroup analyses by index event (PE or DVT) were conducted in the assessable population for efficacy and safety, as reported in the original publications. A random effects meta-analysis was carried out by conventional methods, as described by DerSimonian and Laird.³³ Heterogeneity was assessed using the Cochran Q test³⁴ and the Higgins I^2 test.³⁵ A Cochran’s Q $P < 0.05$ and $I^2 > 50\%$ were considered to show significant heterogeneity. Calculations were performed using RevMan software, version 5.2 (The Nordic Cochrane Centre, Copenhagen,

Denmark) and StatsDirect software, version 2.8.0 (StatsDirect Ltd, Cheshire, UK).

Results

Characteristics of studies and patients

Table 2 shows the characteristics of the studies and patients. We included ten studies in 35,019 randomized patients. A total of 14,364 patients (41.0%) had index PE.

The six studies in the initial/long-term therapy of VTE^{36–41} included 27,127 randomized patients (Table 2). Of them, 11,613 patients (42%) had index PE. The four studies in the extended therapy of VTE^{38,42,43} comprised 7,892 randomized patients (Table 2). Of them, 2,751 patients (35%) had index PE. Mean age of patients was 55–58 years across trials and 55%–61% were males (Table 2). Ethnic group distribution was reported in seven trials.^{36–39,42} Across studies, the majority of patients included were Caucasians (70%–95%), followed by Asians (2%–21%) and Blacks or African Americans (1%–4%). Extensive PE was present in 24%–46% of patients with index PE (data only available from Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism [EINSTEIN PE], Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism [AMPLIFY] and Comparative Investigation of Low Molecular Weight [LMW] Heparin/Edoxaban Tosylate [DU176b] Versus [LMW] Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots [HOKUSAI-VTE]) (Table 2).

In the initial/long-term therapy of VTE, a single drug approach was used in rivaroxaban and apixaban trials, while heparin lead-in was used in dabigatran and edoxaban trials. Treatment durations ranged between 3 months and 12 months in clinical trials in the acute/long-term therapy of VTE and between 6 months and 18 months in the extended therapy of VTE (Table 2). All studies in the acute/long-term therapy of VTE and Secondary Prevention of Venous Thrombo Embolism (VTE) (RE-MEDY)⁴² study in extended therapy of VTE used a non-inferiority approach, while placebo-controlled studies in extended therapy of VTE were superiority trials (Table 2). In placebo-controlled trials, patients were recruited if there was clinical equipoise about the continuation or cessation of anticoagulant therapy. All studies but two (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis [EINSTEIN DVT] and PE) were double blinded (Table 2). Methods for assessment of recurrent VTE were consistent across studies.^{36–43} DVT diagnosis was established by compression ultrasonography or venography of leg veins, while non-fatal PE was diagnosed

Table 2 Clinical trials with DOAC in the treatment of VTE

Study (DOAC)	N (patients)	Age (yrs)	Male sex (%)	Index PE, n (%)	Anatomical extent of PE (%) [*]	Design	Experimental treatment	Control treatment	Planned duration	TTR (%)	Risk of bias
Acute treatment											
RE-COVER I (Dabigatran)	2,564	55	58	786 (31)	NR	DBRCNI	Heparin \geq 5 days followed by DAB 150 mg BID	Heparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	60	Low
RE-COVER II (Dabigatran)	2,589	55	61	816 (32)	NR	DBRCNI	Heparin \geq 5 days followed by DAB 150 mg BID	Heparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	57	Low
EINSTEIN DVT (Rivaroxaban)	3,449	56	57	23 (1)	NA	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3, 6, or 12 months [‡]	57.7	Unclear
EINSTEIN PE (Rivaroxaban)	4,833	58	53	4,833 (100)	Extensive: 24; intermediate: 58; limited: 13; missing: 5	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3, 6, or 12 months [‡]	62.7	Unclear
AMPLIFY (Apixaban)	5,400	57	59	1,836 (35)	Extensive: 37; intermediate: 43; limited: 9; missing: 11	DBRCNI	API 10 mg BID 7 days, followed by API 5 mg BID	Enoxaparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	61	Low
HOKUSAI-VTE (Edoxaban)	8,292	56	57	3,319 (40)	Extensive: 46; intermediate: 41; limited: 7; missing: 6	DBRCNI	Heparin \geq 5 days followed by EDO 60 mg OD [#]	Heparin \geq 5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3 to 12 months [‡]	63.5	Low
Extended treatment											
RE-MEDY (Dabigatran)	2,866	55	61	994 (35)	NR	DBRCNI	DAB 150 mg BID	Warfarin dose-adjusted (INR: 2.0–3.0)	18 months [§]	65	Low
RE-SONATE (Dabigatran)	1,343	56	55	443 (33)	NR	DBRCS	DAB 150 mg BID	Placebo	6 months [§]	NA	Low
EINSTEIN-EXTENSION (Rivaroxaban)	1,197	58	58	454 (38)	NR	DBRCS	RIV 20 mg OD	Placebo	6 or 12 months [§]	NA	Low
AMPLIFY-EXT (Apixaban)	2,486	57	57	34	NR	DBRCS	API 2.5 mg and 5 mg BID	Placebo	12 months [§]	NA	Low

Notes: Extensive: clots in \geq 2 lobes and $>$ 25% of entire pulmonary vasculature (EINSTEIN-PE and HOKUSAI-VTE) or involving \geq 50% or more of the vasculature for each lobe (AMPLIFY); intermediate: limited: clots in \leq 25% of vasculature of a single lobe. [#]Edoxaban 30 mg OD was administered to patients who had a CrCl of 30 to 50 mL/min or a body weight \leq 60 kg, or who were receiving concomitant potent P-glycoprotein inhibitors. [‡]Physician's criteria. [§]Patients had received at least 3 months of anticoagulant therapy before inclusion (RE-MEDY: 3–12 months; RE-SONATE: 6–18 months; EINSTEIN-EXTENSION and AMPLIFY-EXT: 6–12 months).

Abbreviations: AMPLIFY, Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism; AMPLIFY-EXT, Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein; API, apixaban; BID, twice-daily; CrCl, creatinine chloride; DAB, dabigatran; DBRCNI, double-blind randomized controlled non-inferiority trial; DBRCS, double-blind randomized controlled superiority trial; DOAC, direct oral anticoagulant; EDO, edoxaban; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in The Long-Term Prevention Of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; INR, International Normalized Ratio; N, total patients in the trial; n, number of patients in the trial that have index PE; NA, not applicable; NR, not reported; OD, once-daily; OLRNCI, open-label randomized controlled non-inferiority trial; PE, pulmonary embolism; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etexilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE; RIV, rivaroxaban; TTR, time within therapeutic range; VKA, vitamin K antagonist (warfarin or acenocoumarol); VTE, venous thromboembolism; yrs, years.

by ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries. Diagnosis of fatal PE was based on objective testing, autopsy, or death that could not be attributed to a documented cause and for which PE could not be ruled out. CRB definition was based on that used by the van Gogh trialists⁴⁴ in studies with rivaroxaban, apixaban, and edoxaban, but all dabigatran studies used a different definition.³⁶ Time in therapeutic range (TTR) ranged between 57% and 65% across studies that included warfarin as control treatment (Table 2).^{36–42}

Risk of bias was assessed as “low” in the eight double-blinded studies and “uncertain” in the two open-label studies, EINSTEIN DVT and PE (Table 2).

Recurrent VTE

Initial and long-term treatment of VTE

In the overall populations, the DOAC were as effective as standard therapy (risk ratio [RR]: 0.91; 95% confidence interval [CI]: 0.79–1.06), with no evidence of heterogeneity (Figure 1). A total of 11,589 patients (DOAC: 5,794; standard therapy: 5,795) with index PE and 15,434 patients (DOAC: 7,718; standard therapy: 7,716) with index DVT

were assessable for recurrent VTE (Figure 2A). The DOAC showed comparable efficacy in preventing recurrent VTE to standard treatment in patients with index PE (RR: 0.88; 95% CI: 0.70–1.11) and index DVT (RR: 0.93; 95% CI: 0.75–1.16) (*P* for subgroup differences =0.76) (Figure 2A).

VTE recurrence depending on PE anatomical extension and presence/absence of RVD was only reported in two trials.^{39,41} In EINSTEIN PE, the rates of recurrent VTE in the rivaroxaban versus standard-therapy group were 1.7% (10 of 597) versus 1.4% (8 of 576) among patients with anatomically extensive PE at baseline, respectively; 2.5% (35 of 1,392) versus 2.2% (31 of 1424) in intermediate PE, respectively; and 1.6% (5 of 309 patients) versus 1.3% (4 of 299) in limited PE at baseline, respectively.³⁹ In HOKUSAI-VTE, 28% (n=938) of patients with PE (n=3,319) had RVD (NT-pro-BNP level \geq 500 pg/mL). The rate of recurrent VTE in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (HR: 0.52; 95% CI: 0.28–0.98).⁴¹ Similar results were observed among patients with RVD assessed by the presence of RV dilatation on computed tomography (HR: 0.42; 95% CI: 0.15–1.20).⁴¹

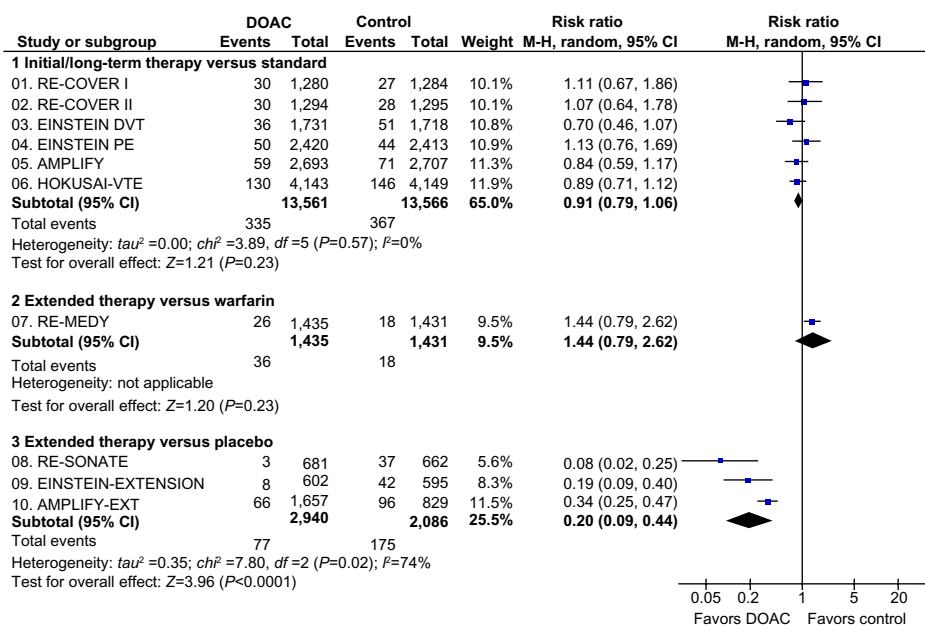


Figure 1 Recurrent VTE in clinical trials with DOAC in the treatment of VTE.

Abbreviations: AMPLIFY, Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism; AMPLIFY-EXT, Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein; CI, confidence interval; *df*, degrees of freedom; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-Term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; M-H, Mantel–Haenszel; PE, pulmonary embolism; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etxilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long Term Prevention of Recurrent Symptomatic VTE; VTE, venous thromboembolism.

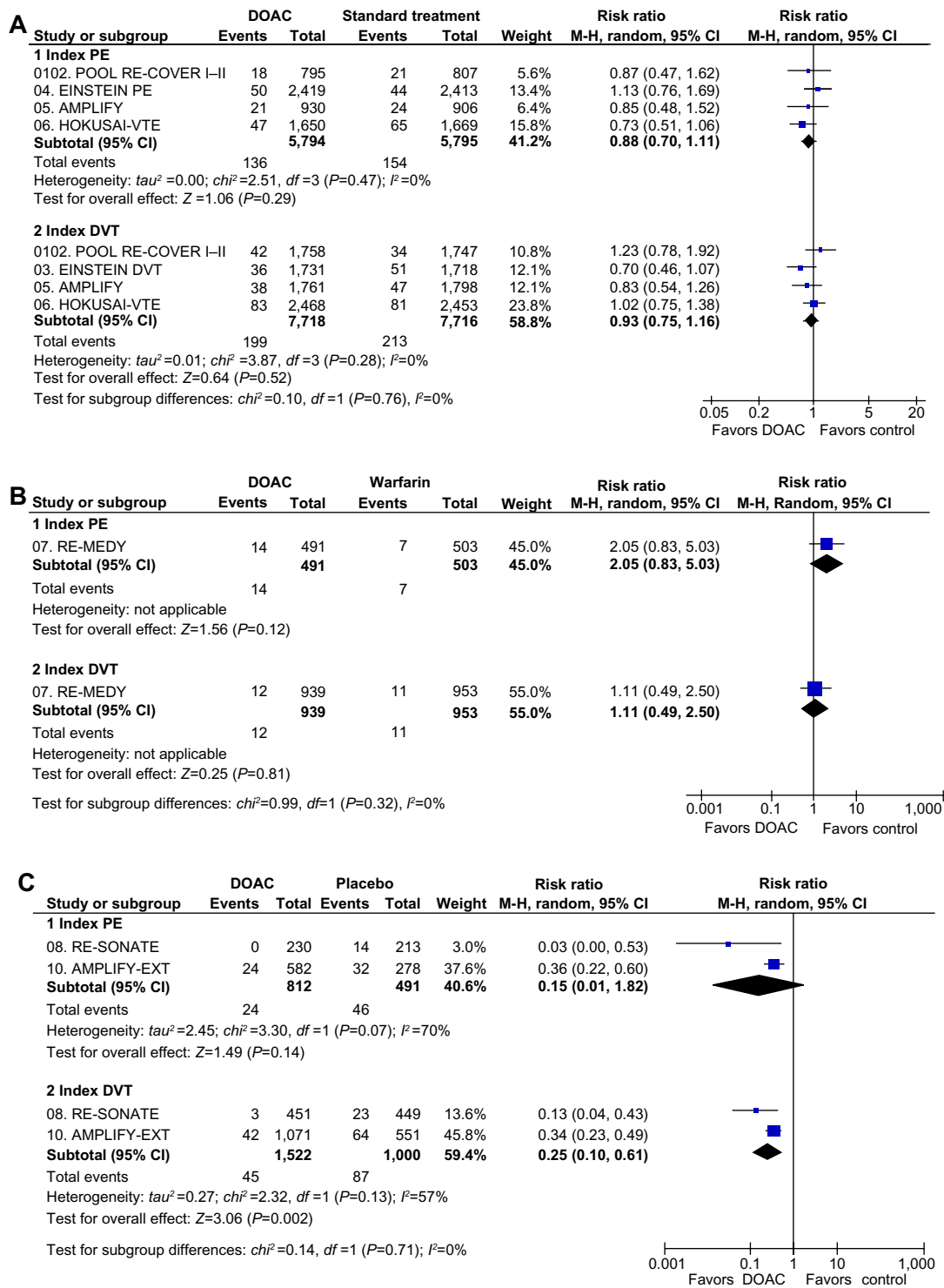


Figure 2 Subgroup analysis of recurrent VTE depending on index event (PE or DVT) in clinical trials with DOAC in the treatment of VTE.

Notes: (A) Initial/long-term therapy versus standard treatment. (B) Extended therapy versus warfarin. (C) Extended therapy versus placebo.

Abbreviations: AMPLIFY, Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism; AMPLIFY-EXT, Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein; CI, confidence interval; df , degrees of freedom; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-Term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DUI176b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; M-H, Mantel-Haenszel; PE, pulmonary embolism; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etxilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long Term Prevention of Recurrent Symptomatic VTE; VTE, venous thromboembolism.

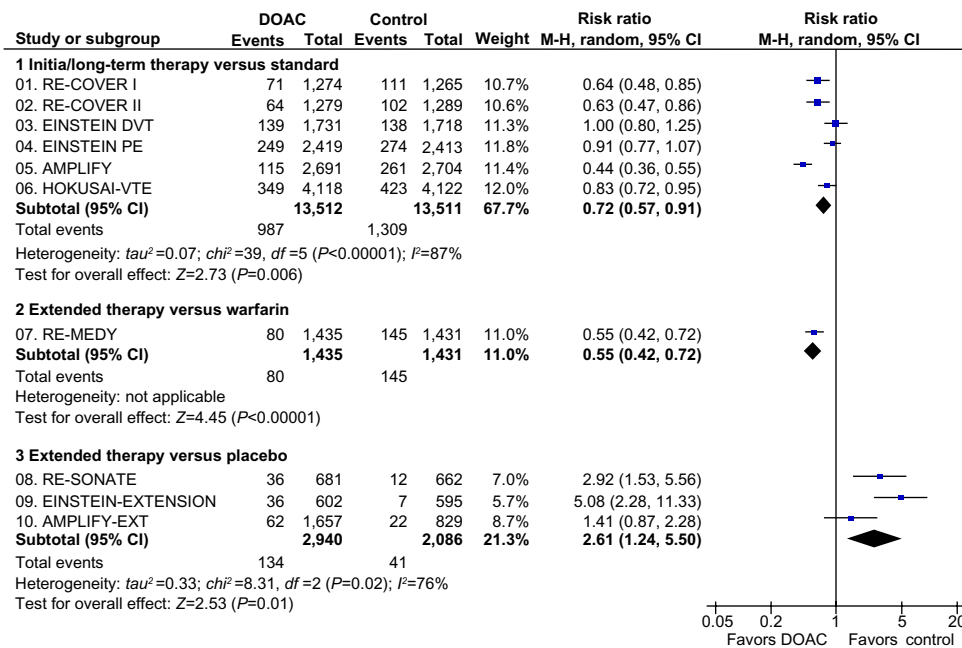


Figure 3 Major and clinically relevant nonmajor bleeding in clinical trials with DOAC in the treatment of VTE.

Abbreviations: AMPLIFY, Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism; AMPLIFY-EXT, Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein; CI, confidence interval; df , degrees of freedom; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN-EXTENSION, Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-Term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; M-H, Mantel-Haenszel; PE, pulmonary embolism; RE-COVER I, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy and Safety of Oral Dabigatran Etxelilate versus Warfarin for 6 Month Treatment for Acute Symptomatic Venous Thromboembolism (VTE); RE-MEDY, Secondary Prevention of Venous Thrombo Embolism (VTE); RE-SONATE, Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxelilate in the Long Term Prevention of Recurrent Symptomatic VTE; VTE, venous thromboembolism.

Extended therapy of VTE

During extended therapy of VTE, the DOAC were as effective as warfarin (RR: 1.44; 95% CI: 0.79–2.62) and more effective than placebo (RR: 0.20; 95% CI: 0.09–0.44) in preventing recurrent VTE. However, there was statistical heterogeneity among placebo-controlled studies ($P=0.02$), mainly due to a greater effect size in reduction of recurrent VTE in RE-SONATE than in the other studies (Figure 1).

A total of 2,297 patients (DOAC: 1,303; warfarin: 503; placebo: 491) with index PE and 4,414 patients (DOAC: 2,461; warfarin: 953; placebo: 1,000) with index DVT were assessable for recurrent VTE (Figure 2B and C). In the single trial that compared a DOAC with warfarin for extended therapy of VTE (RE-MEDY), the point estimate for recurrent VTE tended to favor warfarin without significant differences between patients with index PE (RR: 2.05; 95% CI: 0.83–5.03) or index DVT (RR: 1.11; 95% CI: 0.49–2.50) (P for subgroup differences =0.32) (Figure 2B). In trials that compared the DOAC and placebo for extended therapy, the effect on recurrent VTE was also consistent in patients with PE (RR: 0.15; 95% CI: 0.01–1.82) and in patients with DVT (RR:

0.25; 95% CI: 0.10–0.61) (P for subgroup differences =0.71) (Figure 2C).

Clinically relevant bleeding

Initial and long-term treatment of VTE

The DOAC were associated with a lower risk of CRB than standard treatment in the overall population (RR: 0.72; 95% CI: 0.57–0.91), but there was evidence of statistical heterogeneity across studies ($P<0.00001$), mainly at the expense of a greater effect size in reduction of CRB in the studies with dabigatran and apixaban than in studies with rivaroxaban and edoxaban (Figure 3).

The risk of CRB versus standard treatment was consistent in patients with index PE (RR: 0.90; 95% CI: 0.80–1.02) and index DVT (RR: 0.87; 95% CI: 0.67–1.12) (P for subgroup differences =0.80) (Figure 4A).

Extended therapy of VTE

The DOAC were associated with a lower risk of CRB than warfarin (RR: 0.55; 95% CI: 0.42–0.72) and a higher risk of CRB than placebo (RR: 2.61; 95% CI: 1.24–5.50). However,

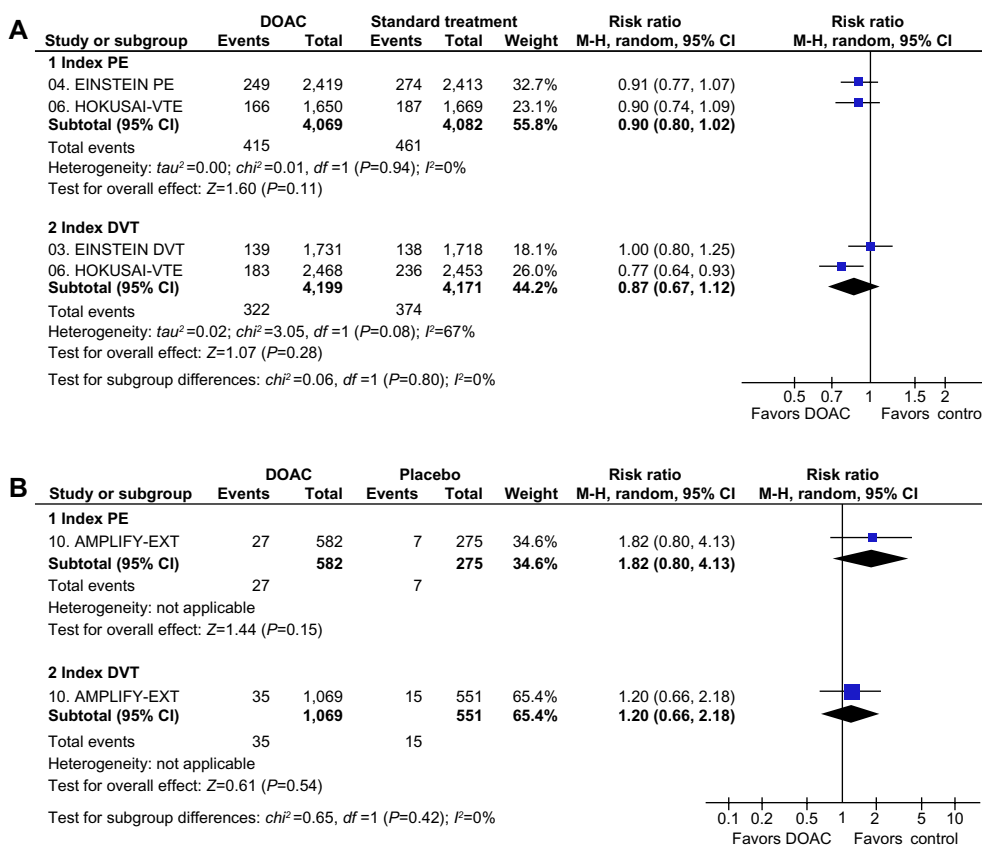


Figure 4 Subgroup analysis of major and clinically relevant nonmajor bleeding events depending on index event (PE or DVT) in clinical trials with DOAC in the treatment of VTE.

Notes: (A) Initial/long-term therapy versus standard treatment. (B) Extended therapy versus placebo.

Abbreviations: AMPLIFY-EXT, Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein; CI, confidence interval; *df*, degrees of freedom; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DUI76b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; M-H, Mantel-Haenszel; PE, pulmonary embolism; VTE, venous thromboembolism.

there was evidence of statistical heterogeneity among placebo-controlled studies ($P=0.02$), mainly at expenses of a higher increase in bleeding in dabigatran and rivaroxaban studies than in the AMPLIFY-EXT study with apixaban (Figure 3).

Disaggregated safety data of extended therapy in patients with PE or DVT were only available from AMPLIFY-EXT.⁴³ In that trial, the trend toward increase in risk of CRB with apixaban versus placebo was consistent in patients with index PE (RR: 1.82; 95% CI: 0.80–4.13) and index DVT (RR: 1.20; 95% CI: 0.66–2.18) (P for subgroup differences = 0.42) (Figure 4B). No disaggregated data of CRB depending on index VTE were reported in the remaining three studies in the extended therapy.^{38,42}

Clinical outcomes in anticoagulated patients with index PE versus index DVT

Recurrent VTE and mortality risk were similar in both clinical presentations (index PE and index DVT).

However, patients with index PE had more CRB complications than patients with index DVT during the initial/long-term anticoagulation therapy (RR: 1.29; 95% CI: 1.18–1.42) (Table 3). Patients with index PE had similar clinical outcomes than patients with DVT during extended anticoagulation therapy (Table 3).

Discussion

Overall, the DOAC seem associated with similar efficacy and lower bleeding risk than standard therapy following acute VTE. Our analysis shows that the efficacy and safety of the DOAC are consistent regardless of the clinical presentation of acute VTE as hemodynamically stable PE or DVT. The analysis is based on six clinical trials in the initial/long-term therapy of VTE (range: 3–12 months of treatment).^{36–41} These studies included a total of 11,589 randomized patients with index PE and 15,434 randomized patients with index DVT. Across trials, 24%–46% of patients with index PE had

Table 3 Pooled risks of recurrent VTE, CRB, and mortality by index event in patients receiving anticoagulant therapy (DOAC or heparin/warfarin)*

Clinical setting	Outcome			
	Index PE, % (n/N)	Index DVT, % (n/N)	% Absolute risk difference (95% CI)	Relative risk difference (95% CI)
Initial/long-term therapy ³⁶⁻⁴¹				
Recurrent VTE	2.5% (290/11589)	2.7% (412/15434)	-0.2 (-0.6 to 0.2)	0.94 (0.81 to 1.09)
CRB	10.7% (876/8151)	8.3% (696/8370)	2.4 (1.5 to 3.3)[‡]	1.29 (1.18 to 1.42)[#]
All-cause mortality [‡]	2.2% (108/4833)	2.5% (87/3449)	-0.3 (-1.04 to 3.7)	0.89 (0.67 to 1.17)
Extended therapy ^{38,42,43}				
Recurrent VTE	3.0% (24/812)	3.0% (45/1522)	0.0 (-1.4 to 1.6)	1.00 (0.62 to 1.62)
Clinically relevant bleeding	4.6% (27/582)	3.3% (35/1069)	1.4 (-0.5 to 3.6)	1.42 (0.87 to 2.31)

Notes: Based on total events and patients with PE or DVT included in clinical trials in the initial/long-term and extended therapy of VTE. * $P < 0.05$; [‡]Data only available from EINSTEIN PE and EINSTEIN DVT. Data shown in bold font signifies statistical significance, $P < 0.05$.

Abbreviations: CI, confidence interval; CRB, clinically relevant bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EINSTEIN DVT, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; EINSTEIN PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; N, total patients in the trial; n, number of events; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 4 Summary of prescribing information of the DOAC in the treatment of VTE

Characteristic	Dabigatran etexilate (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)*
Dosing				
Initial therapy	LMWH or fondaparinux for at least 5 days	Rivaroxaban 15 mg BID for 21 days (3 weeks)	Apixaban 10 mg BID for 7 days (1 week)	LMWH or fondaparinux for at least 5 days
Long-term therapy	Dabigatran 150 mg BID	Rivaroxaban 20 mg OD (15 mg OD in patients with CrCl 15–50 judged to be at high risk of bleeding) from day 22 onward	Apixaban 5 mg BID from day 8 onward	Edoxaban 60 mg OD (30 mg in patients with a CrCl 30–50 mL/min, a body weight ≤ 60 kg or concomitant treatment with potent Pg-p inhibitors)
Extended therapy [#]	Same posology as long-term therapy	Same posology as long-term therapy	Dose reduction to 2.5 mg BID is recommended following completion of at least 6 months of anticoagulation	Same as long-term therapy but no clinical experience is available beyond 12 months [‡]
Intake with food	Not necessary	Mandatory (39% decrease in absorption when administered without food)	Not necessary	Not necessary
Absorption with proton pump inhibitors	30% decrease (no dose-adjustment necessary)	Not significantly altered	Not significantly altered	Not significantly altered
Relevant pharmacokinetic interactions	– Potent Pg-p inhibitors (contraindicated), – Potent Pg-p inducers (not recommended)	– Potent inhibitors of both P-gp and CYP3A4 (not recommended), – Potent inducers of both P-gp and CYP3A4 (use with caution)	– Potent inhibitors or inducers of both P-gp and CYP3A4 (use with caution)	– Potent Pg-p inhibitors (dose reduction) (see long-term therapy) – Potent Pg-p inducers (no specific recommendations available)
Relevant pharmacodynamic interactions	Drugs that alter hemostasis [¶]	Drugs that alter hemostasis [¶]	Drugs that alter hemostasis [¶]	Drugs that alter hemostasis [¶]
Use in renal insufficiency	Contraindicated in severe renal insufficiency (CrCl < 30 mL/min)	Not recommended if CrCl < 15 mL/min Dose-adjustment in some cases (see long-term therapy above)	Not recommended if CrCl < 15 mL/min	Dose adjustment in some cases (see long-term therapy above). No data available in severe renal insufficiency)

Notes: *Not approved yet (as of August 2014) in the European Union and other regions for the treatment of VTE. [#]In selected patients at high risk of recurrence, according to clinical practice guidelines. [‡]Maximum treatment duration tested in HOKUSAI-VTE was 12 months. No experience beyond this period is available and no specific extended treatment studies with edoxaban have been conducted). [¶]Includes other anticoagulants (use contraindicated unless switching therapy), fibrinolytics, and antiplatelet drugs (use with caution unless formal contraindication). Grade 1–2, strong–weak evidence; Grade A–B–C, high–moderate–low quality of data.

Abbreviations: BID, twice-daily; BP, blood pressure; CrCl, creatine chloride; DOAC, direct oral anticoagulant; HOKUSAI-VTE, Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DUI76b) Versus (LMW) Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots; LMWH, low-molecular-weight heparin; min, minute; OD, once-daily; Pg-p, P-glycoprotein; VTE, venous thromboembolism.

anatomically extensive PE,^{39–41} and 28% of patients with index PE had RVD.⁴¹ Available data in these subgroups, although scarce, suggest that the effect in patients with index PE is consistent regardless of anatomical extension of PE,³⁴ or presence/absence of RVD.⁴¹

In the extended therapy, we found a reduction in recurrent VTE with the DOAC in comparison with placebo, which was also consistent in patients with PE and in patients with DVT. On the contrary, the point estimate for the RR of recurrent VTE disfavored dabigatran versus warfarin in the RE-MEDY trial, particularly in patients with PE. Moreover, the trend toward a poorer efficacy of dabigatran versus warfarin during extended therapy of VTE was further suggested by the numerical increase in acute coronary syndromes (ACS) (13 versus three patients). The TTR in RE-MEDY was 65%, better than in all the remaining studies with the DOAC in the treatment of VTE. These data may suggest that patients with index PE who remain well controlled while on extended therapy with warfarin should not generally be switched to dabigatran, as it could potentially result in an increased risk of thromboembolism. Since the RE-MEDY trial is so far the only study comparing the DOAC and warfarin in extended anticoagulant therapy in patients with VTE, these results must be interpreted with caution and are not necessarily applicable with other DOAC. Moreover, in the RE-SONATE study (extended therapy with dabigatran or placebo), the rates of recurrent VTE and ACS with dabigatran (0.4% and 0.1%, respectively) were much lower than those in the dabigatran arm of the RE-MEDY study (1.8% and 0.9%, respectively). These differences could be explained by an optimal quality of anticoagulation with warfarin in RE-MEDY and by different baseline risk of treatment groups and follow-up duration between trials. Whether dabigatran increases the risk of ACS or the findings are due to a more protective effect of warfarin than of dabigatran against ACS is still unclear.

In extended therapy, dabigatran showed a significantly lower risk of bleeding than warfarin in RE-MEDY,⁴² which is consistent with the lower bleeding tendency of all DOAC versus standard initial/long-term therapy. On the contrary, we found an increase in CRB with the DOAC versus placebo, which was heterogeneous across trials. The heterogeneity found may be due to differences in bleeding definitions across trials or might reflect differences in the bleeding profile of each of the DOAC, as they are different compounds with unique pharmacological characteristics. Head-to-head comparisons between the DOAC are needed to solve this issue.

Important differences are apparent between trials regarding the dosing regime (single-drug approach used in rivaroxaban and apixaban trials versus heparin lead-in used in dabigatran and edoxaban trials) that have implications when prescribing the DOAC in patients with VTE (Table 4). In addition, there are other issues to bear in mind when prescribing the new compounds, like their potential for drug–drug or food–drug interactions and appropriate use in renal insufficiency (Table 4).

A single-drug regimen with rivaroxaban or apixaban may simplify treatment of acute PE, thus allowing for outpatient treatment in low-risk PE⁶ or early discharge in intermediate-risk PE patients and potentially reducing hospital stays. A post hoc analysis of EINSTEIN studies has shown that the proportion of hospitalized patients for PE with a length of stay of 5 days or fewer receiving rivaroxaban was 45% compared with 33% for enoxaparin/VKA.⁴⁵ Reduction in subsequent hospitalizations after initial discharge has been reported with apixaban in the acute/long-term therapy versus standard treatment (AMPLIFY)⁴⁶ and during extended therapy versus placebo (AMPLIFY-EXT).⁴⁷ Limitations of these analyses include their post hoc nature and well-monitored clinical trial setting, in which decisions on admission and discharge could vary from real-world management.

The DOAC may provide an alternative to warfarin for extended therapy of PE, particularly in those patients considered to be at high risk of bleeding. Patients with VTE and cancer are among those patients who have a high risk of both recurrence and bleeding. DOAC have shown promising results in patients with cancer in comparison with warfarin.^{48,49} However, LMWH instead of VKA is the standard of care in VTE associated with cancer.⁵⁰ Further head-to-head comparative trials between the DOAC and LMWH are needed to recommend the use of the DOAC in VTE associated with cancer.

Heparin-induced thrombocytopenia (HIT) is a rare but serious complication of heparin treatment.⁵¹ DOAC may provide an alternative for anticoagulation in patients with VTE and with history of HIT, because they do not interact with PF4 in vitro.^{52–54} A clinical study is underway to investigate rivaroxaban for treatment of patients with current suspected or confirmed HIT (n=200) (Clinicaltrials.gov identifier: NCT01598168).⁵⁵

The lack of validated and currently available antidotes is one of the drawbacks of the DOAC.⁴⁸ Adequate supportive care and temporary removal of all antithrombotic drugs constitute the basis for management of serious bleeding complications.⁵⁶ Prohemostatic agents (unactivated or

activated prothrombin complex concentrate and activated factor VIIa) have been tried for the DOAC with varying success.⁵⁶ Hemodialysis can remove 50%–60% of circulating dabigatran,¹⁰ while administration of activated charcoal may be useful to reduce absorption of rivaroxaban or apixaban if taken <6 hours after overdose or accidental ingestion.^{11,12} Highly specific reversal agents for the direct thrombin and FXa inhibitors are under development and might be available during the next years.⁵⁶

Other drawbacks of the DOAC include their higher costs in comparison with VKA and the uncertainty about the adherence to therapy in day-to-day practice. Since the DOAC have a shorter half-life (<24 hours) than warfarin (36–42 hours), suboptimal adherence may be more dangerous for the DOAC than for warfarin. Furthermore, some DOAC have twice-daily dosing schedules (Table 4), which may be more difficult for some patients with DVT or PE to adhere to than a daily regimen, particularly in the long term.⁵⁷ However, no head-to-head comparisons for checking compliance with once-daily versus twice-daily regimens of DOAC are available, and therefore no firm conclusions can be drawn in this respect.

Conclusion

The DOAC are as effective as, and probably safer than standard treatment of hemodynamically stable PE. The efficacy and safety of the DOAC seem consistent regardless anatomical extension of PE (extensive, intermediate, or limit) or presence/absence of RVD, although the data are limited. For extended therapy, the DOAC are more effective than placebo in preventing recurrent VTE but are associated with an increase in CRB either in patients with PE or DVT.

Disclosure

The contents of this review are solely the responsibility of the authors and do not necessarily represent the official view of their institutions or any other party. No funding/support grant was received for this review. A Gómez-Outes, ML Suárez-Gea, AI Terleira-Fernández, and E Vargas-Castrillón declare no conflicts of interest. R Lecumberri declares personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo, and grants and personal fees from Rovi Pharmaceuticals, outside the submitted work.

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