Novel Anticoagulant Treatment for Pulmonary Embolism with Direct Oral Anticoagulants Phase 3 Trials and Clinical Practice

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Abstract

Anticoagulant therapy is the cornerstone of therapeutic management in acute venous thromboembolism (VTE), consisting of pulmonary embolism and deep vein thrombosis. Direct oral anticoagulants (DOACs) have become the standard of care because of their good safety profile and ease of use in clinical practice. Indeed, phase 3 randomized trials (AMPLIFY, EINSTEIN, RECOVER, and HOKUSAI studies) showed that DOACs provided a similar efficacy and a better safety than conventional treatment with parenteral heparin with overlapping loading dose of vitamin K antagonists in acute VTE therapeutic management. The results of published data from real-world registries confirm the safety and efficacy of DOACs demonstrated in the phase 3 trials.

Keywords
- venous thromboembolism
- DOAC
- pulmonary embolism
- deep venous thrombosis
- anticoagulant
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to discuss the role of anticoagulants in the interventional radiology population, as well as differentiate between the most commonly used agents in these drug classes.

Anticoagulation is the cornerstone of acute venous thromboembolism (VTE) treatment including pulmonary embolism (PE) and deep venous thrombosis (DVT).[1,2] The goal of anticoagulation is to prevent thrombus extension and development of new thrombi. Conventional treatment consists of parenteral treatment, usually low-molecular-weight heparin (LMWH), for at least 5 days.[1] Vitamin K antagonists (VKAs) are started parallel to the parenteral treatment which is continued until the international normalized ratio (INR) has reached a therapeutic range (between 2.0 and 3.0) on 2 consecutive days (Class I, Level B recommendation).[1] The widespread introduction of direct oral anticoagulants (DOACs) in stable VTE patients has revolutionized their management. The latest guidelines recommend DOACs as the preferred standard anticoagulation.[2] Indeed, DOACs have several advantages: no requirement for routine monitoring, minimal food and drug interaction, and fixed dose administration. Four DOACs are available for VTE treatment—rivaroxaban, apixaban and edoxaban (direct factor Xa inhibitors),

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and dabigatran (direct thrombin [factor II] inhibitor). Efficacy and safety of DOACS in acute PE have been studied in several large phase 3 randomized trial programs: RE-COVER,[3] HOKUSAI,[4] AMPLIFY,[5] and EINSTEIN.[6,7] Moreover, DOACs have been studied for the long-term management of acute VTE as well: RE-SONATE,[8] RE-MEDY,[8] EINSTEIN EXTENSION,[6] EINSTEIN CHOICE,[9] AMPLIFY EXTENSION,[10] and HOKUSAI EXTENSION.[11]

In this clinical review, we aim (1) to summarize the results of the phase 3 trials assessing DOACs in VTE and (2) to describe the results of real-world registries assessing the safety and efficacy of DOACs.

Phase 3 Trials of Acute VTE: Efficacy and Safety

The efficacy and safety of DOACs have been compared with VKA in 27,096 patients with VTE, of whom 11,612 were diagnosed with acute PE, in four clinical trial programs.[3–7,12] The results of these studies assessing DOACs in PE are summarized in ►**Table 1**. The primary efficacy endpoint of these trials was recurrent VTE or VTE-related death. The primary safety outcome was the composite of major and clinically relevant non-major (CRNM) bleeding according to the International Society on Thrombosis Haemostasis (ISTH) criteria.[13]

In the double-blind, noninferiority RE-COVER I (efficacy and safety of dabigatran compared with warfarin for 6 months treatment of acute symptomatic venous thromboembolism) study, dabigatran after a mean parenteral anticoagulation duration of 10 days was compared with VKA in 2,539 patients with VTE.[12] Both study arms were equally efficacious for the incidence of recurrent VTE or VTE-related death (2.4 vs. 2.1%, hazard ratio [HR]: 1.10, 95% confidence interval [CI]: 0.65–1.84). Major bleeding incidences were similar (1.6 vs. 1.9%, HR: 0.82, 95% CI: 0.45–1.48) between the study arms, whereas the combined safety criteria including major or CRNM bleeding was significantly reduced in the dabigatran arm (5.6 vs. 8.8%, HR: 0.63, 95% CI: 0.47–0.84). RECOVER II[3] study design was essentially identical to RECOVER I[12] study design. RECOVER II[3] study including 2,589 patients with acute VTE confirmed the results of RECOVER I study[12] with noninferiority of dabigatran to warfarin in the prevention of recurrent VTE and with superiority of dabigatran for CRNM and for any bleeding. In the pooled analysis of these two studies, HRs for recurrent VTE, major bleeding, and any bleeding for dabigatran versus warfarin were 1.09 (95% CI: 0.76–1.57), 0.73 (95% CI: 0.48–1.11), and 0.70 (95% CI: 0.61–0.79), respectively.

In the open-label and noninferiority EINSTEIN studies, rivaroxaban was compared with conventional treatment by heparin and warfarin in 8,281 patients with VTE, including 4,855 patients with acute PE.[6,7] The incidence of recurrent VTE in EINSTEIN PE study was noninferior in rivaroxaban arm compared with enoxaparin/VKA arm (2.1 vs. 1.8%, HR: 1.12, 95% CI: 0.75–1.68).[7] The rate of major bleeding was significantly lower in rivaroxaban group compared with warfarin group (HR: 0.49, 95% CI: 0.31–0.79), whereas the incidence of clinical relevant bleeding was similar in both treatment arms (10.3 vs. 11.4%, HR: 0.90, 95% CI: 0.76–1.07).

A total of 5,395 patients with VTE were included in the AMPLIFY study of whom 1,836 had PE. Apixaban was found to be noninferior to standard anticoagulation therapy for the incidence of VTE or VTE-related deaths (2.3 vs. 2.7%, HR: 0.84, 95% CI: 0.60–1.18) and was associated with a significant reduction of the incidence of major bleeding (0.6 vs. 1.8%, RR = 0.31, 95% CI: 0.17–0.55; $p < 0.001$).[5]

In the double-blind Hokusai-VTE study, standard anticoagulation therapy was compared with edoxaban after a short course of heparin in 8,292 patients with VTE, of whom 3,319 were diagnosed with acute PE.[4] The incidence of recurrent VTE or VTE-related deaths following 12 months of treatment was similar in both arms (3.5 vs. 3.2%, HR: 0.89, 95% CI: 0.70–1.13) and the incidence of clinically relevant bleeding events was significantly lower in the edoxaban group with 8.5 versus 10.3%, respectively (HR = 0.81, 95% CI: 0.71–0.94). The rates of major bleeding in both arms were similar (1.4 vs. 1.6%, HR: 0.84, 95% CI: 0.59–1.21).

A meta-analysis pooling the data of these phase 3 trials comparing DOACs with VKAs showed that relative risks (RRs) for recurrent VTE, fatal PE, and overall mortality for DOACs versus VKAs were 0.88 (95% CI: 0.74–1.05, $p = 0.46$), 1.02 (95% CI: 0.39–5.96, $p = 0.71$), and 0.97 (95% CI: 0.83–1.14, $p = 0.50$), respectively.[14] Moreover, all combined RRs of bleeding were significantly lower for patients treated with DOACs, which is especially relevant for nonintracranial bleeding (RR: 0.39, 95% CI: 0.16–0.94) and fatal bleeding (RR: 0.36, 95% CI: 0.15–0.87). These results confirm that DOACs present lower risk of major bleeding compared with VKAs and that DOACs and VKAs have a similar efficacy in the treatment of acute PE.

Patients with right ventricular dysfunction were mostly excluded from the DOACs clinical trial programs. Only the HOKUSAI study involved a predefined subgroup analysis in PE patients with signs of right ventricular dysfunction defined as a concentration of NT-proBNP of 500 pg/mL or higher or CT evidence of right ventricular dilatation.[15] The rates of recurrent VTE in the edoxaban-treated group and in the warfarin-treated group were 2.6 and 4.6% (RR: 0.57, 95% CI: 0.27–1.17; $p = 0.033$), respectively. The rates of major bleeding and the duration of heparin treatment were similar in the edoxaban and warfarin groups (2.7 vs. 2.6%). Based on these results, there is no reason to question the safety and efficacy of DOACs in patients with stable PE.

Importantly, all phase 3 trial programs used comparable exclusion criteria, including patients with cancer-associated VTE, with high risk of bleeding, during pregnancy or breast-feeding, and with renal insufficiency (creatinine clearance below 30 mL/minute). For that reason, DOACs cannot currently be used in these patient categories.

Long-Term Treatment after 3 Months of Initial Anticoagulant Therapy

DOACs have been assessed on long-term secondary prevention after initial management for VTE as well.[6,8–11,16] The results of these studies are summarized in ►**Table 2**.

Rivaroxaban was compared with placebo in 1,196 patients for an additional 6 to 12 months in the EINSTEIN-extension

Table 1 DOACs phase 3 trials on acute VTE treatment

Trial name	HOKUSAI	AMPLIFY	RE-COVER I	RE-COVER II	EINSTEIN DVT	EINSTEIN PE
Design	Double blinded Noninferiority	Double blinded Noninferiority	Double blinded Noninferiority	Double blinded Noninferiority	Open-label Noninferiority	Open-label Noninferiority
Noninferiority Margin for Hazard ratio	1.5	1.8	2.75	2.75	2.0	2.0
Number of patients	8,292	5,395	2,539	2,589	3,449	4,832
Number of PE (±DVT)	3,319	1,836	786	816	23	4,832
Primary efficacy outcome	Recurrent VTE	Recurrent VTE and VTE-related deaths	Recurrent VTE and VTE-related deaths	Recurrent VTE and VTE-related deaths	Recurrent VTE	Recurrent VTE
Safety endpoints	Major or CRNM bleeding	Major or CRNM bleeding	Bleeding events, acute coronary syndromes, results of liver function tests	Bleeding events, acute coronary syndromes	Major or CRNM bleeding	Major or CRNM bleeding
Comparator	LMWH/VKA	LMWH/VKA	Enox/VKA	Enox/VKA	Enox/VKA	Enox/VKA
Duration	< 12 mo	6 mo	6 mo	6 mo	3, 6, 12 mo	3, 6, 12 mo
Design	LMWH pre-treatment Edoxaban 60 mg once daily; Edoxaban 30 mg once daily for patients with CrCl 30 50 mL/min, body weight ≤60 kg; concomitant use of P-gp inhibitors	Apixaban 10 mg twice daily for 7 days; then 5 mg twice daily	LMWH pre-treatment Dabigatran 150 mg twice daily	LMWH pre-treatment Dabigatran 150 mg twice daily	Rivaroxaban 15 mg twice daily for 3 wk; then 20 mg once daily	Rivaroxaban 15 mg twice daily for 3 wk; then 20 mg once daily
Recurrent symptomatic VTE or related death, DOACs vs. VKA (%)	3.2 vs. 3.5[a]	2.3 vs. 2.7[a]	2.4 vs. 2.1[a]	2.3 vs. 2.2[a]	2.1 vs. 3.0[a]	2.1 vs. 1.8[a]
All-cause mortality, DOACs vs. VKA (%)	3.2 vs. 3.1	1.5 vs. 1.9	1.6 vs. 1.7	2.0 vs. 1.9	2.2 vs. 2.9	2.4 vs. 2.1
Major bleeding, DOACs vs. VKA (%)	1.4 vs. 1.6	0.6 vs. 1.8[b]	1.6 vs. 1.9	1.2 vs. 1.7	0.8 vs. 1.2	1.1 vs. 2.2[b]
Major or CRNM bleeding, DOACs vs. VKA (%)	8.5 vs. 10.3[b]	4.3 vs. 9.7[b]	5.6 vs. 8.8[b]	5.3 vs. 8.5[b]	8.1 vs. 8.1	10.3 vs. 11.4

Abbreviations: CRNM, clinically relevant non major; DOACs, direct oral anticoagulants; DVT, deep venous thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]Noninferior.
[b]Statistically significant difference.

study, and was associated with a significant lower VTE recurrence risk compared with placebo (1.3 vs. 7.1%, HR: 0.18, 95% CI: 0.09–0.39). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%) versus none in the placebo group.[6] EINSTEIN CHOICE study is a multicenter, randomized, double-blind study comparing the efficacy and the safety of two doses of rivaroxaban (20 and 10 mg, once daily) with aspirin (100 mg daily) for the prevention of recurrent VTE in patients who completed 6 to 12 months of anticoagulant therapy for acute VTE with intermediate risk of VTE recurrence.[9] A total of 1,107 patients were treated with rivaroxaban 20 mg, 1,127 with rivaroxaban 10 mg, and 1,131 with aspirin. Symptomatic

Table 2 DOACs clinical trials on extended treatment of VTE

Trial name	RE-SONATE	RE-MEDY	EINSTEIN extension	EINSTEIN	CHOICE	AMPLIFY	Extension	HOKUSAI extension
DOAC tested	Dabigatran (150 mg twice daily)	Dabigatran (150 mg twice daily)	Rivaroxaban (20 mg once daily)	Rivaroxaban (20 mg once daily)	Rivaroxaban (10 mg once daily)	Apixaban (5 mg twice daily)	Apixaban (2.5 mg twice daily)	Edoxaban (60 mg daily)
Design	Superiority	Noninferiority	Superiority	Superiority	Superiority	Superiority	Superiority	Noninferiority
Number of patients (DOACs/population)	681/1,343	1,430/2,856	602/1,196	1,107/3,365	1,127/3,365	813/2,486	840/2,486	3,633/8,292
Comparator	Placebo	Warfarin (NR 2–3)	Placebo	Aspirin	Aspirin	Placebo	Placebo	Warfarin (NR 2–3)
Treatment duration	6 mo	18–36 mo	6–12 mo	6–12 mo	6–12 mo	12 mo	12 mo	12 mo
Recurrent symptomatic VTE or related death, DOACs vs. comparator (%)	0.4 vs. 5.6	1.8 vs. 1.3	1.4 vs. 7.2	1.5 vs. 4.4	1.2 vs. 4.4	1.7 vs. 8.8	1.7 vs. 8.8	1.3 vs. 1.6[a]
Major bleeding, DOACs vs. comparator (%)	0.3 vs. 0.0	0.9 vs. 1.8	0.7 vs. 0.0	0.5 vs. 0.3	0.4 vs. 0.3	0.2 vs. 0.5	0.1 vs. 0.5	1.2 vs. 1.3
Major or CRNM bleeding, DOACs vs. comparator (%)	5.3 vs. 1.8	5.6 vs. 10.2	6.0 vs. 1.2	3.3 vs. 2.0	2.4 vs. 2.0	3.2 vs. 2.7	4.3 vs. 2.7	8.3 vs. 9.8

Abbreviations: CRNM, clinically relevant non major; DOACs, direct oral anticoagulants; VTE, venous thromboembolism.
[a]VTE-related deaths are not reported.

recurrent or nonfatal VTE occurred in 17 patients receiving 20 mg of rivaroxaban (1.5%), in 13 patients receiving 10 mg of rivaroxaban (1.2%) and in 13 of 1,127 patients receiving aspirin (4.4%; HR: 0.34, 95% CI: 0.20–0.59) for 20 mg of rivaroxaban versus aspirin; HR: 0.26, 95% CI: (0.14–0.47) for 10 mg of rivaroxaban versus aspirin ($p < 0.001$). Rates of major bleeding for the group receiving 20 mg of rivaroxaban, for the group receiving 10 mg of rivaroxaban, and for the aspirin group were 0.5, 0.4, and 0.3%, respectively.

Two doses of apixaban have been compared with placebo after 12 months of initial treatment.[10] The AMPLIFY extension study included 2,486 patients with intermediate risk of VTE recurrence and showed that both treatment doses (5 and 2.5 mg twice daily) reduced the risk of recurrent VTE compared with placebo (1.7% in both groups vs. 8.8% for placebo group). HRs for apixaban 2.5 mg group and apixaban 5 mg group versus placebo group were 0.19 (95% CI: 0.11–0.33) and 0.20, (95% CI: 0.11–0.34), respectively. These two doses (2.5 and 5 mg) were not associated with a higher risk of major bleeding compared with placebo (0.2 vs. 0.1 vs. 0.5%, respectively). HRs for apixaban 2.5 mg group and apixaban 5 mg group versus placebo group were 0.49 (95% CI: 0.09–2.64) and 0.25 (95% CI: 0.33–2.24), respectively.

Dabigatran has been compared with conventional treatment with warfarin in RE-MEDY study and with placebo in RE-SONATE study.[8] RE-MEDY study showed that dabigatran was noninferior in preventing recurrent VTE compared with warfarin (1.8 vs. 1.3%, HR: 1.44, 95% CI: 0.78–2.64) with a nonsignificant lower risk of major hemorrhage (0.9 vs. 1.8%, HR: 0.52, 95% CI: 0.27–1.02) in patients with high risk of VTE recurrence. In the placebo-control study, recurrent VTE occurred in 3 of 681 patients in the dabigatran group (0.4%) and 37 of 662 patients in the placebo group (5.6%; HR: 0.08; 95% CI: 0.02–0.25). Major bleeding occurred in two patients in the dabigatran group (0.3%) and 0 patients in the placebo group. Major or clinically relevant bleeding occurred in 36 patients in the dabigatran group (5.3%) and 12 patients in the placebo group (1.8%; HR: 2.92; 95% CI: 1.52–5.60). Acute coronary syndromes occurred in one patient each in the dabigatran and placebo groups.

Edoxaban has also been compared with warfarin as extended VTE treatment in a post hoc analysis[11] of the Hokusai-VTE study.[4] Of the 3,633 patients receiving edoxaban, 1,076 (30%) received treatment between 3 and 6 months, 896 (25%) between 6 and less than 12 months, and 1,661 (46%) for a full 12 months. The cumulative incidence of recurrent VTE on treatment (day 1 to 12 months) was 1.3% in the edoxaban group and 1.6% in the warfarin group (HR: 0.83; 95% CI: 0.58–1.19). Major bleeding risk was 1.2% in the edoxaban group and 1.3% in the warfarin group (HR: 0.92; 95% CI: 0.62–1.37). A meta-analysis including the earlier-discussed studies assessing rivaroxaban, apixaban, and dabigatran as extended treatment has shown that DOACs are an effective treatment for prevention of VTE or VTE-related death in the extended treatment setting.[17]

These trials showed that extended therapy using DOACs was not inferior to warfarin or placebo in terms of efficacy. However, they did not demonstrate that low dose of DOACs is noninferior to full dose in terms of efficacy or superior in terms of safety in patients with high risk of recurrence. The optimal duration of anticoagulant treatment after the initial 3 months should depend on the weighing of the risk for recurrent VTE after anticoagulant therapy is stopped[18–22] and the risk of

anticoagulant therapy-associated hemorrhage.[23,24] For patients with PE provoked by a transient risk factor, anticoagulation is recommended for 3 months (recommendation Class I, Level B) since the recurrent risk is very low,[1,25,26] whereas for patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months[1,27,28] and extended anticoagulation should be considered for patients with a first episode of unprovoked PE (recommendation Class IIa, Level B) due to the high risk of recurrence.[1,29] Indeed, the PADIS-PE trial, extended treatment of 2 years, compared with 6 months, did not reduce VTE recurrence risk after anticoagulation has been stopped.[18] Three hundred and seventy-one patients with a first episode of symptomatic unprovoked PE, who had been treated initially for 6 months with VKA, were randomized to receive an additional 18 months of treatment with warfarin versus additional 18 months of treatment with placebo. The primary composite outcome of VTE recurrence or major bleeding after 18 months after randomization occurred in 6 of 184 patients (3.3%) in the warfarin group and in 25 of 187 (13.5%) in the placebo group (HR: 0.22; 95% CI: 0.09–0.55; $p = 0.001$). Major bleeding occurred in four patients in the warfarin group and in one patient in the placebo group (HR: 3.96; 95% CI: 0.44–35.89) and recurrent VTE occurred in three patients in the warfarin group and 25 patients in the placebo group (HR = 0.15; 95% CI: 0.05–0.43). After 42 months of follow-up, VTE recurrence was not significantly different and the bleeding rates were similar between the two groups. Extended anticoagulation should also be considered for patients with PE and active cancer as well until the cancer is cured (recommendation Class IIa, Level c).[1,30–32] The ESC guidelines published in 2014 recommended to consider dabigatran, rivaroxaban, and apixaban as an alternative to VKA in extended VTE anticoagulation,[1] whereas the recent ACCP guidelines published in 2016 recommend DOACs as long-term anticoagulant therapy over VKA therapy (Grade B).[2]

How to Use DOACs?

Although effective and safe, the disadvantages of conventional anticoagulant therapy with LMWH/VKAs include the numerous interactions with foods and drugs as well as a need for INR monitoring and dose adjustments.[33] In routine clinical practice, DOACs have simplified therapeutic management of VTE.[34] Indeed, DOACs can be given in fixed doses without routine monitoring and present minimal food and drug interaction.[35] The additional advantage of DOACs is a similarly rapid onset of action to LMWH with oral administration and the safety to switch from VKAs.[36] Moreover, DOACs facilitate home treatment in stable patients with PE, reducing healthcare cost. Indeed, a new ongoing trial (Home Treatment of Pulmonary Embolism—HoT-PE) aims to confirm that home treatment of acute low-risk PE with the oral factor Xa inhibitor rivaroxaban is effective, safe, and potentially cost-saving.[37]

Nevertheless, there are few contraindications for DOAC initiation: (1) creatinine clearance <30 mL/min, (2) moderate or severe hepatic impairment (Child–Pugh B and C), or hepatic disease associated with coagulopathy and (3) concomitant use of combined P-glycoprotein (amiodarone, quinidine, verapamil) and strong CYP3A4 inhibitors or inducers, and (4) and pregnancy or breastfeeding. Rivaroxaban and apixaban should be initiated in a higher starting dose for 21 and 7 days, respectively, without the need for preceding heparin therapy, whereas dabigatran or edoxaban is initiated after a previous 5-day parenteral anticoagulation phase. DOACs dosage and contraindications are summarized in ►**Table 3**. Efficacy and safety seem similar between different DOACs. DOACs have never been directly compared in randomized studies. Hence, today, there is no evidence to recommend one DOAC over another.[38]

As for DOAC reversal, several specific antidotes have been assessed.[39–44] DOACs reversal should be considered in case of urgent surgeries associated with a high risk of bleeding or during ongoing bleeding despite supportive measures. They should also be considered with life-threatening bleeding in case of intracranial hemorrhage or when it occurs into a critical organ (e.g., intraocular bleeding), or a closed space (e.g., retroperitoneal or pericardial bleeding). An ongoing prospective noninterventional registry including patients with life-threatening bleeding or emergency operations either treated with DOACs or VKAs will aim to evaluate effects of specific and unspecific reversal agents.[45] Idarucizumab is a humanized monoclonal antibody fragment derived from an IgG1 isotype molecule, whose target is the direct thrombin inhibitor dabigatran. Andexanet alfa is a recombinant modified human factor Xa decoy protein that has been shown to reverse the inhibition of factor Xa (rivaroxaban, apixaban, edoxaban, and heparin). Ciraparantag is a synthetic small molecule which binds DOACs via hydrogen bond formation (dabigatran, rivaroxaban, apixaban, edoxaban, and heparin) and reverses all of the DOACs and heparin. Most trials have been conducted in healthy volunteers and not had a comparator arm. Therefore, both reversal agents are currently not available for clinical practice. Only idarucizumab (dabigatran antidote) is licensed and widely available. The efficacy and the safety of idarucizumab was evaluated in an analysis of 90 patients and showed that it completely reversed the anticoagulant effect of dabigatran within minutes.[39] The phase 3, multicenter trial, assessing idarucizumab treated with dabigatran in 301 patients who had uncontrolled bleeding (Group A) and in 202 patients who required emergency surgery (Group B), has recently been published.[40] In Group A, the median time to the cessation of bleeding was 2.5 hours, whereas the median time to the initiation of the intended procedure was 1.6 hours in group B. At 90 days, thrombotic events occurred in 6.3% in group A and in 7.4% in group B. The mortality rate was 18.8 and 18.9%, respectively. Thus, idarucizumab reversed safely and rapidly the anticoagulant effect of dabigatran. Two phase 3 trials have reported good efficacy and good safety with andexanet alfa for reversal effect of apixaban, rivaroxaban, edoxaban, or enoxaparin.[41,42] A preliminary analysis from an ongoing prospective study (NCT02329327) including 67 patients with acute major bleeding after the administration of a factor Xa inhibitor showed that thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up. Clinical hemostasis was excellent or good in 37 of 47 patients in the efficacy analysis (79%; 95% CI: 64–89) 12 hours

Table 3 DOACs doses and contraindications

Direct oral anticoagulant	Initial dose	Standard dose	Contraindications
Edoxaban	At least 5 d combined with parenteral anticoagulation	60 mg once daily 30 mg once daily can be considered in patients with one or more of the following factors: CrCl 30–49 mL/min; body weight ≤60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole	CrCl <15 mL/min Moderate or severe hepatic impairment (Child–Pugh B and C), or hepatic disease associated with coagulopathy Concomitant treatment with rifampicin Pregnancy and breastfeeding[a]
Apixaban	First 7 d, 10 mg twice daily	5 mg twice daily	CrCl <15 mL/min Severe hepatic impairment (Child–Pugh C) or hepatic disease associated with coagulopathy Strong dual inhibitors or inducers of CYP3A4 and P-gp Pregnancy and breastfeeding[a]
Dabigatran	At least 5 d with parenteral anticoagulation	150 mg twice daily 110 mg if high bleeding risk or comedication (e.g., verapamil)	CrCl <30 mL/min Concomitant treatment with P-gp inhibitors[a] in patients with CrCl <50 mL/min Concomitant treatment with P-gp inducers (i.e., rifampicin) Pregnancy and breastfeeding[a]
Rivaroxaban	First 3 wk 15 mg twice daily	20 mg once daily 15 mg once daily if CrCl 30–49 mL/min	CrCl <30 mL/min Moderate or severe hepatic impairment (Child–Pugh B and C), or hepatic disease associated with coagulopathy Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers Pregnancy and breastfeeding[a]

[a]No assessment during pregnancy and breastfeeding.

after the andexanet alfa infusion.[41] Ciraparantag has been assessed in a double-blind phase 2, placebo-controlled trial among 80 healthy adult patients. The results showed an immediate and sustained full reversal of edoxaban.[43] Similar results have been reported for enoxaparin.[44]

Real-Life Registries

Real-world studies with DOACs including unselected patients with DVT and PE are of particular interest to support and to evaluate the reproducibility of the phase 3 trial findings. We will discuss the largest studies published to date.[46–50] The results of these noninterventional studies are summarized in ►**Table 4**.

XALIA study is a multicenter, prospective, noninterventional study, including 2,619 patients treated with rivaroxaban and 2,149 patients treated with standard anticoagulation therapy.[47] All included patients diagnosed with DVT had an indication to be treated for at least 3 months. Patients with isolated PE were excluded. The rate of major bleeding was 0.8% (19/2505) in the rivaroxaban group and 2.1% (43/2,010) in the standard anticoagulation group (HR: 0.77, 95% CI: 0.40–1.50; $p = 0.44$). The rates of frequency of recurrent VTE in the rivaroxaban and standard anticoagulation group were 1.4% (36/2,505) and 2.3% (47/2,010), respectively (HR: 0.91, 95% CI: 0.54–1.54, $p = 0.72$). The rate of all-cause mortality was 0.4% (11/2,505) in the rivaroxaban group and 3.4% (69/2,010) in the standard anticoagulation group (HR: 0.51; 95% CI: 0.24–1.07). The rate of fatal PE was <0.1% in both groups.

The DRESDEN study included 1,776 patients with DVT, PE, or atrial fibrillation (AF) treated with rivaroxaban in routine practice.[48] The rates of major bleeding (4.1%) and mortality (6.3%) were higher than recorded in XALIA study. The main reasons of this difference are the older age and the higher proportion of patients with renal impairment in the DRESDEN registry. Despite the lack of comparator group treated with VKA, bleeding rates with rivaroxaban were lower and the outcome of major bleeding at 90 days is better than that reported for VKA.

The REMOTEV cohort included 499 patients with DVT and PE.[49] The rates of major bleeding, and recurrent DVT with rivaroxaban were coherent with those reported in XALIA registry, 1.4 versus 3.1%, respectively. The frequency of major bleeding was 1.1% in rivaroxaban group versus 3.1% in the warfarin group.

PREFER VTE registry is a large international, noninterventional database including 3,455 patients with PE and DVT,

Table 4 DOACs real-world studies

Registry name	XALIA	DRESDEN	REMOTEV	PREFER	GARFIELD[a]
DOACs	Rivaroxaban	Rivaroxaban	Rivaroxaban	DOACs[b]	DOACs[c]
Sponsor	Bayer Health Care Pharmaceutical, Janssen Research & Development, LLC	Bayer Health Care, Boehringer Ingelheim, Pfizer	None	Daiichi Sankyo	Bayer Pharma AG
Method	Multicenter, prospective, noninterventional study	Prospective, noninterventional study	Prospective, noninternational study	Multicenter, prospective, noninterventional study	Multicenter, prospective, noninternational study
Population	DVT	DVT, EP, AF	DVT, EP	DVT, EP	DVT, EP
Population size	4,768	1,776	499	3,455	10,329
Rate of active cancer, % in DOACs group vs. comparator group	6 vs. 19%	NP	2.6 vs. 8.1%	8.5%[d]	9.1%
Follow-up	> 12 mo	3 mo	6 mo	12 mo	3 y
Comparator	Standard anticoagulation therapy[e]	No comparator	Standard anticoagulation therapy[f]	No comparator	No comparator
Major bleeding, DOACs vs. comparator	0.8 vs. 2.1%	4.1%	1.1 vs. 3.1%	1.5%[d]	2.8%[g]
Recurrent VTE, DOACs vs. comparator	1.4 vs. 2.3%	NP	1.4 vs. 3.1%	3.5%[d]	3.6%[g]
All-cause mortality, DOACs vs. comparator	0.4 vs. 3.4%	6.3%[h]	1.8 vs. 5.2%	6.7%[d]	11.1%g

Abbreviations: AF, atrial fibrillation; DOACs, direct oral anticoagulants; DVT, deep venous thrombosis; LMWH, low-molecular-weight heparin; NP, not provided; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.
[a]GARFIELD VTE study results are not yet published. They are extracted from ISTH Congress abstract.
[b]Type of DOACs not provided.
[c]In GARFIELD registry, 50.5% of patients are treated with DOACs.
[d]No distinction between DOACS and standard anticoagulation therapy.
[e]Unfractioned heparin–LMWH or fondaparinux followed by VKAs.
[f]Major bleeding rate in VTE population.
[g]No distinction provided in the abstract between DOACS and other treatment.
[h]No distinction between AF and VTE population.

one quarter of who received DOACs.[50] This study did not compare patients according DOACs versus standard anticoagulation, but according VTE presentation (DVT vs. PE vs. DVT ± PE). The rate of major bleeding was not higher than reported in other registries (1.5%, 33/2,326). The high rate of mortality (6.7%, 230/3,455) could be explained by the high proportion of patients with active cancer (8.5%).

The Global Anticoagulant Registry in the FIELD-Venous Thromboembolism (GARFIELD-VTE) is a prospective, multicenter, observational study that will enroll 10,329 patients treated for acute VTE in 28 countries.[46] Patients included in GARFIELD-VTE have been treated with DOACs in 50.5% of cases. The incidence of all causes of death, recurrent VTE, and major bleeding of the overall cohort after 6 months of follow-up were 11.1, 3.6, and 2.8%, respectively.

Thus, real-world registries have shown consistently that the rate of major bleeding and recurrent VTE under DOAC therapy is low. These data reinforce the findings of the phase 3 studies that DOACs are efficient and safe in the therapeutic management of acute VTE.

Conclusion

Phase 3 trials have shown that DOACs have comparable efficacy but a better safety profile than conventional anticoagulant treatment with LMWH and VKA in patients with acute VTE. Moreover, DOACs are effective and safe for the extended treatment of VTE as well. Results of real-word cohort studies and registries have confirmed the results of the phase 3 trials, supporting the guideline recommendations that acute VTE should be preferably treated with DOACs, except for patients with cancer-associated VTE, high risk of bleeding, during pregnancy or breast feeding, and severe renal insufficiency (creatinine clearance <30 mL/min).

References

1 Konstantinides SV, Torbicki A, Agnelli G, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35(43):3033–3069, 3069a–3069k

2 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149(02):315–352

3 Schulman S, Kakkar AK, Goldhaber SZ, et al; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129 (07):764–772

4 Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369(15):1406–1415

5 Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369(09):799–808

6 Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499–2510

7 Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287–1297

8 Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368(08):709–718

9 Weitz JI, Lensing AWA, Prins MH, et al; EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017;376(13):1211–1222

10 Agnelli G, Buller HR, Cohen A, et al; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368(08):699–708

11 Raskob G, Ageno W, Cohen AT, et al. Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. Lancet Haematol 2016;3(05):e228–e236

12 Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361(24):2342–2352

13 Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(04):692–694

14 van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12(03):320–328

15 Brekelmans MP, Ageno W, Beenen LF, et al. Recurrent venous thromboembolism in patients with pulmonary embolism and right ventricular dysfunction: a post-hoc analysis of the Hokusai-VTE study. Lancet Haematol 2016;3(09):e437–e445

16 Weitz JI, Bauersachs R, Beyer-Westendorf J, et al; EINSTEIN CHOICE Investigators. Two doses of rivaroxaban versus aspirin for prevention of recurrent venous thromboembolism. Rationale for and design of the EINSTEIN CHOICE study. Thromb Haemost 2015;114(03):645–650

17 Cohen AT, Hamilton M, Bird A, et al. Comparison of the non-VKA oral anticoagulants apixaban, dabigatran, and rivaroxaban in the extended treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. PLoS One 2016;11(08):e0160064

18 Couturaud F, Sanchez O, Pernod G, et al; PADIS-PE Investigators. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. JAMA 2015;314(01):31–40

19 van der Hulle T, Tan M, den Exter PL, et al. Recurrence risk after anticoagulant treatment of limited duration for late, second venous thromboembolism. Haematologica 2015;100(02):188–193

20 Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007;92(02):199–205

21 Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362 (9383):523–526

22 Schulman S, Granqvist S, Holmström M, et al; The Duration of Anticoagulation Trial Study Group. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med 1997;336(06):393–398

23 Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003;139(11):893–900

24 Klok FA, Kooiman J, Huisman MV, Konstantinides S, Lankeit M. Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review. Eur Respir J 2015; 45(01):201–210

25 Agnelli G, Prandoni P, Becattini C, et al; Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003;139(01):19–25

26 Campbell IA, Bentley DP, Prescott RJ, Routledge PA, Shetty HG, Williamson IJ. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. BMJ 2007;334(7595):674

27 Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost 1995;74(02):606–611

28 Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Lancet 1992;340(8824):873–876

29 Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340 (12):901–907

30 van der Hulle T, den Exter PL, van den Hoven P, et al. Cohort study on the management of cancer-associated venous thromboembolism aimed at the safety of stopping anticoagulant therapy in patients cured of cancer. Chest 2016;149(05):1245–1251

31 Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349 (02):146–153

32 Lee AY, Bauersachs R, Janas MS, et al; CATCH Investigators. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. BMC Cancer 2013;13:284

33 Carlquist JF, Anderson JL. Using pharmacogenetics in real time to guide warfarin initiation: a clinician update. Circulation 2011;124 (23):2554–2559

34 Kvasnicka T, Malikova I, Zenahlikova Z, et al. Rivaroxaban - metabolism, pharmacologic properties and drug interactions. Curr Drug Metab 2017;18(07):636–642

35 Ageno W, Eikelboom J, Lip GY. Dabigatran in clinical practice: contemporary overview of the evidence. Int J Cardiol 2016;220:417–428
36 Beyer-Westendorf J, Gelbricht V, Förster K, et al. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care–results from the Dresden NOAC registry. Br J Clin Pharmacol 2014;78(04):908–917
37 Barco S, Lankeit M, Binder H, et al. Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the HoT-PE Trial. Thromb Haemost 2016;116(01):191–197
38 Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35 (45):3145–3146
39 Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373(06):511–520
40 Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med 2017; 377(05):431–441
41 Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;375(12):1131–1141
42 Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373(25): 2413–2424
43 Ansell JE, Bakhru SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. Thromb Haemost 2017;117(02):238–245
44 Ansell JE, Laulicht BE, Bakhru SH, Hoffman M, Steiner SS, Costin JC. Ciraparantag safely and completely reverses the anticoagulant effects of low molecular weight heparin. Thromb Res 2016; 146:113–118
45 Lindhoff-Last E. Direct oral anticoagulants (DOAC) - management of emergency situations. Rationale and design of the RADOA-Registry. Hamostaseologie 2017. Doi: 10.5482/HAMO-16-11-0043
46 Weitz JI, Haas S, Ageno W, et al. Global Anticoagulant Registry in the Field - Venous Thromboembolism (GARFIELD-VTE). Rationale and design. Thromb Haemost 2016;116(06):1172–1179
47 Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 2016;3(01):e12–e21
48 Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood 2014;124(06):955–962
49 Gaertner S, Cordeanu EM, Nouri S, 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
50 Cohen AT, Gitt AK, Bauersachs R, et al. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. Thromb Haemost 2017;117 (07):1326–1337