The recent clinical trials on use of the novel direct oral anticoagulants in patients with venous thromboembolism: a review

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Abstract

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, requires an immediate anticoagulation, that has been carried out so far by administering a parenteral anticoagulant drug (heparin or derivatives) overlapped with an oral vitamin K antagonist (VKA), more often warfarin. Several new direct oral anticoagulants (DOACs), with a mechanism of action completely different than VKA, have been developed in recent years. Recent clinical trials have investigated their use in VTE patients showing results at least equal for efficacy and safety, and sometime even better, as the standard anticoagulant treatment. There are differences in the design of the trials. In two cases the involved DOAC was administered immediately after VTE diagnosis as a single drug treatment (rivaroxaban and apixaban), whereas in the other trials (involving dabigatran and edoxaban) the DOAC was administered after an initial course of approximately 7 days with heparin or derivatives. Some clinical trials have also investigated the use of DOACs for extended anticoagulant treatment after the acute phase. Aim of this article is to review the results of the currently available clinical trials that have compared the use of DOACs versus the standard of care in patients with VTE.

Introduction

Venous thromboembolism (VTE), that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent disease whose incidence is estimated of about 1.5 per 1,000 inhabitants per year.[1] VTE is a potentially fatal disease and is associated with late complications such as the post thrombotic syndrome.[2] Consequently, VTE may be regarded as a major cause of morbidity and mortality, being the third cause of death due to cardiovascular diseases after myocardial infarction and stroke.[3] In order to prevent thrombus extension and its potential consequences, an immediate anticoagulation is necessary as soon as

diagnosis is made, by administering one of the available parenteral fast acting drug, such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux, and overlapping this therapy by associating an oral vitamin K antagonist (VKA, more frequently warfarin), which have a slow onset of action that requires 5 to 10 days before achieving an appropriate anticoagulant effect [*i.e.*, international normalized ratio (INR) between 2.0 and 3.0]. Current guidelines recommend giving effective anticoagulation to patients with acute VTE for at least 3 months; usually this performed by administering VKAs, at the exception of some special populations (such as patients with cancer or during pregnancy) in whom treatment with LMWH is recommended over VKA.[4] Since the risk of recurrence is not negligible, the duration of anticoagulation often lasts longer beyond the first 3 months, as it is suggested for high-risk patients such as those with an unprovoked VTE episode.

Treatment with VKA is very effective but is complex to carry out in a correct way. It is associated with noticeable burden for the health systems and demanding for the patients. VKA have several limitations, including: slow onset and offset of action, complex genetic control of their effect leading to highly variable individual sensitivity, narrow therapeutic window, and a metabolism affected by many factors, including diet, drugs, hepatic dysfunction, other co-morbid conditions and alcohol intake. The dose/response of VKA is unpredictable and frequent coagulation monitoring and dose-adjustments are needed to ensure efficacy of treatment and to minimize the risk of bleeding complications.

Several direct oral anticoagulants (DOAC) have been developed to overcome some limitations of VKAs and to improve the quality of life of patients who need anticoagulation. Recent large randomized clinical trials have investigated their use in VTE patients (as well as in other clinical indications, *e.g.* non valvular atrial fibrillation) showing results at least equal for efficacy and safety, and sometimes even better, as the standard anticoagulant treatment.

Aim of this article is to review the results of the currently available clinical trials that have compared the use of DOACs *versus* the standard of care in patients with VTE.

The novel direct oral anticoagulants

The DOACs are different drugs, with different characteristics and mechanisms of action. Dabigatran is a direct inhibitor of thrombin (factor IIa), while rivaroxaban, apixaban and edoxaban (still not available in

our country) are inhibitors of activated factor X (factor Xa) (some DOAC characteristics are shown in Table 1).[5-8] They do not need routine laboratory monitoring, they can be given in fixed doses once or twice daily per os, and have less food or drug interactions than VKA. However, they are not free from drawbacks. Their anticoagulant effect weakens quickly in case of poor compliance, and specific antidotes are not yet available.

Treatment of acute venous thromboembolism

All the four mentioned DOACs have results of randomized clinical trials in patients with acute VTE. All the trials were designed to show a non-inferior efficacy and safety versus the standard treatment. Some differences were present among the trials, regarding the studied population (patients with acute VTE, or acute DVT only, or acute non-hemodynamic PE), the treatment durations and the blinding. But the most important difference regarded the initial treatment: in the study with dabigatran[9] and that with edoxaban[10] the initial treatment was performed in all patients with heparin (unfractionated or LMWH) for an average period of 7 days, and then the patients were randomized to receive the investigated drug or the standard treatment (warfarin). In the trial with rivaroxaban (the two Einstein studies[11,12]) and in that with apixaban[13] the patients in the experimental arm received that single drug treatment since the beginning. Exclusion criteria in all the trials were the presence of contraindications to standard anticoagulation with heparin or VKAs, PE with hemodynamic instability, use of thrombectomy or of fibrinolysis, or positioning of a vena cava

filter. For details on results of the trials see Table 2.[9-15]

Dabigatran

In the randomized, double-blind, RE-COVER study,[9] were included 2564 patients with acute VTE who, after an initial treatment with parenteral anticoagulation therapy with LMWH or UFH (for a median of 9 days), were randomized to receive dabigatran at a dose of 150 mg *bis in die* (b.i.d.) or dose-adjusted warfarin to achieve an INR of 2.0 to 3.0. Duration of treatment was six months. The occurrence of primary outcome for efficacy was of 2.4% in patients treated with dabigatran and 2.1% in those receiving warfarin (time in therapeutic range 60%), confirming the non-inferiority of dabigatran *vs* warfarin (P<0.001). With regard to the safety, a major bleeding episode occurred in 1.6% and 1.9% of patients in dabigatran and warfarin groups, respectively [hazard ratio (HR) 0.82; 95% confidence interval (CI), 0.45 to 1.48]. The more frequent major bleeding event in the dabigatran group was gastrointestinal (nine events). Intracranial hemorrhage occurred in three patients treated with warfarin and in none receiving dabigatran.

Rivaroxaban

The Einstein VTE program consisted of two randomized trials of rivaroxaban: the Einstein-DVT[11] and the Einstein-PE[12] studies, that included patients with acute symptomatic DVT or PE, respectively; both studies allowed also different durations of treatment (3, 6 or 12 months), and after the completion of the initial acute treatment, patients could be included in the Continued Treatment Study, a double blind, randomized, superiority study that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months.

The Einstein-DVT study was a randomized, open-label, event-driven, trial that compared oral rivaroxaban alone (15 mg b.i.d. for 3 weeks, followed by 20 mg once daily) with the standard anticoagulation treatment (subcutaneous enoxaparin followed by VKA, INR 2.0-3.0) in 3449 patients with acute, symptomatic DVT and without symptomatic PE. The primary efficacy outcome occurred in 2.1% of patients who received rivaroxaban and in 3.0% of those who received LMWH+VKA (overall the time in therapeutic range for warfarin was 57.7%) and the HR was 0.68; 95% CI 0.44 to 1.04; with P<0.001 for non-inferiority. Major or clinically relevant non-major bleeds occurred in 8.1% and 8.1% of patients treated with rivaroxaban or standard therapy, respectively (HR with rivaroxaban, 0.97; 95% CI, 0.76-1.22; P=0.77).

The Einstein-PE study was a randomized, open-label, event-driven, trial that involved 4832 patients with acute symptomatic non-hemodynamic PE with or without DVT. Rivaroxaban (at the dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared with standard therapy with LMWH followed by an adjusted-dose VKA for 3, 6, or 12 months. The primary efficacy outcomes in 2.1% of the rivaroxaban group and 1.8% of the standard therapy group (HR 1.12; 95% CI, 0.75-1.68; P=0.003 for non-inferiority). The principal safety outcome, that included major or clinically relevant non-major bleeding, occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard therapy group (HR 0.90; 95% CI, 0.76-1.07; P=0.23), with major bleeding events in 1.1% of patients treated with rivaroxaban and 2.2% in those receiving standard therapy

Apixaban

The double blind, double dummy Amplify study[13] enrolled 5395 patients with acute DVT and/or PE who were randomized to receive apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily) or LMWH + warfarin (2.0-3.0 INR) for 6 months. The primary efficacy outcome, that included recurrent symptomatic VTE or death VTE-related occurred in 2.3% in the apixaban group and 2.7% in the standard-therapy group (HR, 0.84; 95% CI 0.60-1.18; P<0.001 for non-inferiority). Principal safety outcomes included major bleeding alone and major bleeding plus clinically relevant non-major bleeding. Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received standard therapy (HR, 0.31; 95% CI, 0.17-0.55; P<0.001 for superiority). The composite outcome occurred in 4.3% of the patients in the apixaban group and in 9.7% of those in the conventional-therapy group (HR, 0.44; 95% CI, 0.36 to 0.55; P<0.001).

Edixaban

The Hokusai study[10] was a randomized, double-blind, in which all patients included with acute VTE (4921 presented with DVT, and 3319 with PE) initially received heparin (or LMWH) and then were randomized to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (*e.g.*, in the case of creatinine clearance of 30-50 mL/min or body weight below 60 kg), or to receive warfarin (time in the therapeutic range was 63.5%) for a duration of treatment of 3 to 12 months.

Primary efficacy outcome (recurrent symptomatic VTE) occurred in 3.2% and in 3.5% of patients in the experimental arm and in the standard treatment group, respectively (HR 0.89; 95% CI, 0.70 to 1.13; P<0.001 for non-inferiority). The rate of recurrent VTE was particularly low (3.3%) in PE patients with right ventricular dysfunction (assessed by measurement of N-terminal pro-brain natriuretic peptide levels) who received edoxaban group versus those treated with warfarin (6.2%; HR 0.52; 95% CI, 0.28-0.98).

Table 1. Main pharmacological characteristics of the new drugs.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct, selective factor IIa inhibitor	Direct, selective factor Xa inhibitor	Direct, selective factor Xa inhibitor	Direct, selective factor Xa inhibitor
Prodrug	Yes	No	No	No
Hours to Cmax	2[5]	2-4[6]	1-3[7]	1-2[8]
Half-life (hours)	12-14[5]	9-13[6]	8-15[7]	9-11[8]
Elimination	80% renal 20% biliary	1/3 renal 1/3 renal (as inactive metabolites) 1/3 biliary	25% renal 75% biliary	35% renal 65% biliary
Interactions	P-Glycoprotein	P-Glycoprotein and CYP3A4	P-Glycoprotein (minimal) and CYP3A4	P-Glycoprotein
Food effect	Absorption delayed	Absorption delayed	Not reported	Not or minimal
Protein binding (%)	35	90	87	40-59
Dosing	b.i.d.	Once daily	b.i.d.	Once daily

b.i.d., *bis in die.*

Table 2. Rates (no./100 patient-year) of primary outcomes and major bleedings with direct anticoagulants or comparators in recent trials in patients treated for venous thromboembolism.

Trial	DOAC agent; design; no. patients; initial therapy; dosing	Rates of primary efficacy outcomes		Rates of major bleeding events	
		DOAC	Comparator	DOAC	Comparator
Acute phase treatment					
RE-COVER[9]	Dabigatran; treatment of acute DVT or PE; 2564; initial treatment with LMWH (median 9 d); 150 mg b.i.d. x 6 months	1.8 HR=1.44 (0.78-2.64) P<0.01*	1.3%	1.6% HR=0.82 (0.45-1.48)	1.9% LMWH + W
Einstein-DVT[11]	Rivaroxaban; acute and extended treatment of DVT patients; 3449, single drug treatment since the beginning (3, 6 or 12 months); 15 mg b.i.d. x 21 d then 20 mg o.i.d.	2.1% HR=0.68 (0.44-1.04) P<0.001*	3.0%	0.8% HR=0.65 (0.33-1-30)	1.2% LMWH + W
Einstein-PE[12]	Rivaroxaban; acute and extended treatment of PE patients; 4833; single drug treatment since the beginning (3, 6 or 12 months); 15 mg b.i.d. x 21 d then 20 mg o.i.d.	2.1% HR=1.12 (0.75-1.68) P=0.003*	1.8%	1.1% HR=0.49 (0.31-0.79; 0.003)	2.2% LMWH + W
Amplify[13]	Apixaban; treatment of acute DVT or PE; 2609; single drug treatment since the beginning; 10 mg b.i.d. x 7 d then 5 mg b.i.d. x 6 months	2.3% HR=0.84 (0.60-1.18) P<0.001*	2.7%	0.6 RR=0.31 (0.17-0.55) P<0.001°	1.8% LMWH + W
Hokusai[10]	Edoxaban; acute and extended treatment of DVT or PE; 8240; initial treatment with LMWH (median 7 d); 60 mg o.i.d.	3.2% HR = 0.89 (0.70-1.13) P<0.001*	3.5%	1.4% HR=0.84 (0.59-1.21)	1.6% LMWH + W
Extended treatment					
RE-MEDY RE-SONATE[14]	Dabigatran; extended treatment after the first 3 months; 150 mg b.i.d. RE-MEDY: 2866; comparator W RE-SONATE: 1363; comparator placebo	1.8% HR=1.44 (0.78-2.64) P<0.01* 0.4 HR=0.08 (0.02-0.25) P<0.001°	1.3% W 5.6 placebo	0.9% HR=0.52 (0.27-1.02) P=0.06° 0.3%	1.8% W 0 placebo
Amplify Extension[15]	Apixaban; extended treatment with 2 different doses: 2.5 mg b.i.d. or 5 mg b.i.d.; 2482; comparator placebo	2.5 mg b.i.d.=3.8 HR=0.33 (0.22-0.48) 5 mg b.i.d.=4.2 HR=0.36 (0.25-0.53) P<0.001° for both comparisons	11.6 placebo	2.5 mg b.i.d=0.2% HR=0.49 (0.09-2.64) 5 mg b.i.d.=0.1% HR=0.25 (0.03-2.24)	0.5% placebo

DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin; b.i.d., *bis in die*; HR, hazard ratio; o.i.d., optimal immunomodulating dose; RR, relative risk. *Statistical significance for superiority. §Statistical significance for non-inferiority; °statistical significance for superiority.

The principal safety outcomes (major or clinically relevant non-major bleeding) occurred in 8.5% of patients in the edoxaban group and in 10.3% of those treated with warfarin (HR 0.81; 95% CI, 0.71 to 0.94; P=0.004 for superiority).

Studies on extended treatment

Some clinical trials have investigated the effects of DOACs in VTE patients treated for extended therapy after an initial therapy of at least 3 months from the index event. Among these studies, only the RE-MEDY (dabigatran) study[14] had warfarin as comparator, while the others [Einstein-DVT Extended Treatment (rivaroxaban),[11] the RE-SONATE (dabigatran)[14] and Amplify Extension (apixaban)[15] had placebo as comparator (Table 2).[9-15]

The Einstein-DVT continued-treatment study (rivaroxaban)

In the Einstein-DVT it was carried out, in parallel, a double-blind superiority study that included 1196 patients who had completed 6 to 12 months of therapy after the index VTE event.[11] They were randomized to receive rivaroxaban (20 mg once daily) or placebo for an additional 6 or 12 months. Recurrent events occurred in 1.3% of patients treated with rivaroxaban and in 7.1% of those receiving placebo (HR 0.18; 95% CI, 0.09-0.39; P<0.001). The principal safety outcome of major bleeding occurred in 4 patients (0.7%) in the rivaroxaban group and in none in the placebo group (P=0.11). However, major or clinically relevant non-major bleeds occurred in 6.0% and 1.2% in the rivaroxaban and placebo groups, respectively (P<0.001)

The RE-MEDY and RE-SONATE study (dabigatran)

In the RE-MEDY study[14] 2866 patients, who had received 3 to 12 months of anticoagulant therapy after a VTE episode, were randomized to treatment with dabigatran 150 mg twice daily or with warfarin (INR 2.0 to 3.0) for an additional period of 6 to 36 months. Recurrent symptomatic VTE occurred in 1.8% and 1.3% of patients treated with dabigatran and warfarin, respectively (HR 1.44; 95% CI 0.78 to 2.64; P=0.01 for non-inferiority). Major bleeds occurred in 0.9% and 1.8% in dabigatran- and warfarin-treated patients, respectively (HR 0.52; 95% CI, 0.27 to 1.02). Major or clinically relevant bleeding was less frequent with dabigatran (HR 0.54; 95% CI, 0.41 to 0.71). More acute coronary syndromes occurred in the dabigatran (0.9%) than in the warfarin group (0.2%) (P=0.02). The authors concluded that dabigatran was as effective as warfarin in the extended treatment of VTE; it was associated with a reduced risk for bleeding but an increased incidence of acute coronary events.

In the double-blind, placebo-controlled RE-SONATE study[14] 1363 patients with VTE who had completed 6-18 months of anticoagulant therapy were randomized to receive dabigatran 150 mg b.i.d. daily or placebo for 6 more months. Recurrent VTE occurred in 0.4% of patients in the dabigatran group and in 5.6% in the placebo group (HR 0.08; 95% CI, 0.02-0.25; P<0.001 for superiority). Major bleeding occurred in 2 patients (gastrointestinal bleeding in both cases) in the dabigatran group (0.3%) and 0 patients in the placebo group. Major or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran group (5.3%) and in 1.8% in the placebo group (HR 2.92; 95% CI, 1.52-5.60). One patient each in the dabigatran and placebo groups had an acute coronary syndrome. The authors concluded that an extended treatment with dabigatran was highly effective in reducing the rate of VTE recurrences as compared with placebo, and was associated with only a low risk for major bleeding.

The Amplify-Ext study (apixaban)

This was a randomized, double-blind study that compared the effects during one year of treatment with two doses of apixaban (2.5 mg and 5 mg, twice daily) or placebo in 2486 patients with VTE who had already received anticoagulation for 6-12 months. Primary efficacy outcomes occurred in 11.6% of patients treated with placebo, and in 3.8% who received 2.5 mg b.i.d. of apixaban and in 4.2 % of those who were treated with 5 mg b.i.d. of apixaban; with both apixaban doses the reduction of events was highly statistically significant (P<0.001). The rates of major bleeding were not different in the placebo group (0.5%), than in the 2.5-mg apixaban group (0.2%), and in the 5-mg apixaban group (0.1%). The authors concluded that the extended anticoagulation with apixaban at both adopted doses reduced the risk of recurrent VTE without increasing the rate of major bleeding.

Conclusions

The clinical trials on the use of DOACs in patients with acute VTE have all shown that the efficacy of these drugs on prevention of thrombotic complications was non-inferior to the standard treatment, consisting of initial administration heparin (or derivatives) followed by warfarin. Moreover, all the treatments with DOACs proved at least as safe and sometimes even better than the comparator treatment.

As regards the long-term therapy, it should be pointed-out that only one study (RE-MEDY[14]) was performed versus warfarin as comparator, while in all the others the comparator was placebo. While the one DOAC (dabigatran) that was compared with warfarin proved similarly effective and with less major bleeding complications (though not reaching the statistical significance), the other DOACs compared to placebo proved more effective and with no higher rates of major bleeding.

It is of interest to notice that altogether the results of these trials showed substantially lower bleeding rates in VTE patients compared with results in recent clinical trials on DOACs use in patients with non valvular atrial fibrillation, a finding that could be due to the usually older age of the latter *versus* VTE patients (with more chronic medical conditions and concurrent medications) and the shorter duration of the studies in VTE patients.

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