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REVIEW

Clinical update

Direct oral anticoagulants in the treatment and long-term prevention of venous thrombo-embolism

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Direct oral anticoagulants (DOACs) specifically target factor IIa or Xa and represent a major step forward in the treatment of acute- and long-term prevention of venous thrombo-embolism (VTE). They are at least as effective and as safe as conventional therapy (heparins and vitamin-K inhibitors) and have practical advantages, such as fixed dosing and no need for laboratory monitoring. These antithrombotic agents introduce a new paradigm for the day-to-day management of VTE. Direct oral anticoagulants should streamline the management of most patients with VTE and will facilitate care in the outpatient setting. Nevertheless, it remains uncertain how to select specific DOACs for particular profiles of patients, and the optimal management of bleeding complications is evolving.

Keywords Pulmonary embolism • Deep venous thrombosis • Direct thrombin inhibitors • Direct factor Xa inhibitors • Anticoagulant

Introduction

During the past six decades, treatment of venous thrombo-embolism (VTE) utilized anticoagulants characterized by an indirect mode of action (such as heparins) or anticoagulants targeting several coagulation factors [vitamin-K antagonists (VKA)]. Direct oral anticoagulants (DOACs) differ in many respects, including fixed dosing, rapid onset of action, fewer food and drug interactions, and no need for laboratory coagulation monitoring.[1]

Direct oral anticoagulants can be categorized as either direct thrombin (FIIa) inhibitors (such as dabigatran) or direct factor Xa (FXa) inhibitors (such as rivaroxaban, apixaban, or edoxaban). Direct FIIa inhibitors bind to thrombin in the early phase of its generation and blunt the consecutive activation of factors V, VIII, and XI that are involved in the burst of thrombin production. They also inhibit the main function of thrombin, conversion of soluble fibrinogen into insoluble fibrin. Direct FXa inhibitors target the active site of FXa and thus inhibit the prothrombinase complex that leads to the formation of thrombin (*Figure 1*).

Direct oral anticoagulants share common pharmacological properties summarized in *Table 1*. In addition to their oral formulation, the onset of action is similar across all molecules, ranging from 2 to 4 h with an average half-life of 10 h.[1,2] The relatively short half-life of DOACs is consequently associated with a large intraday variability in the pharmacokinetic profile. For example, a pharmacokinetic model based on Phase II studies of rivaroxaban showed that the plasma concentration of the drug after administering 20 mg may range from >400 ng/mL at peak to <30 ng/mL 24 h later.[3]

Two important features differentiate DOACs. First, renal impairment has a strong impact on the pharmacokinetic and pharmacodynamic profile of dabigatran, whereas apixaban and edoxaban seem to be less affected by moderate renal insufficiency (*Table 1*).[2] Second, DOACs have different metabolisms, especially regarding the implication of cytochrome P450 (CYP)3A4 (*Table 1*). While all four DOACs are being eliminated via the P-glycoprotein (P-gp) transporter after absorption, CYP3A4 activity is involved in the rivaroxaban, apixaban, and edoxaban metabolisms but does not affect significantly the dabigatran pharmacokinetic profile.[4] This important feature is associated with potentially fewer drug–drug interactions with dabigatran.[5] However, the majority of the drugs that affects CYP3A4 function and also affects P-gp, since CYP3A4 and P-gp share many substrates and inhibitors and have a common tissue distribution.[6] Although many of these drugs also interact with VKA, the risk of concomitant treatment is mitigated by the availability of INR.[7]

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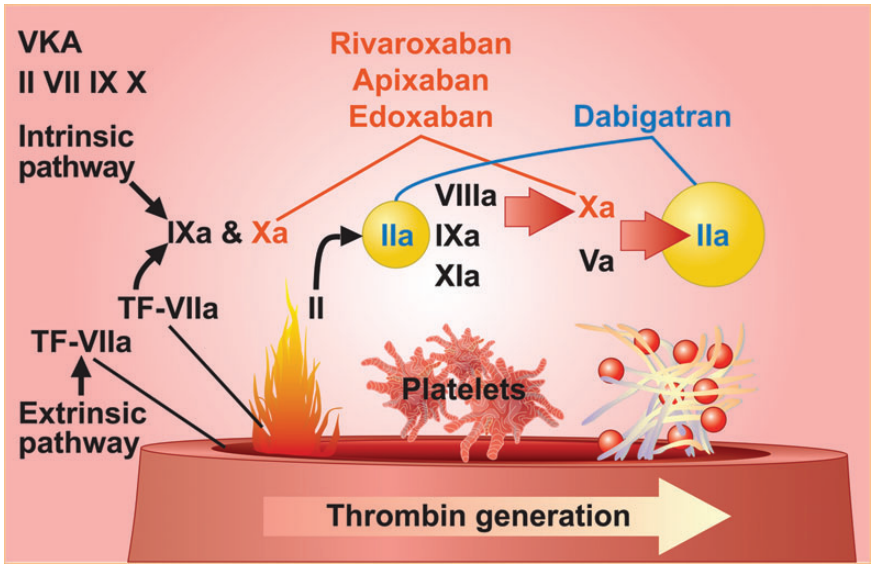

Figure 1 Coagulation process and targets of direct oral anticoagulants (DOACs). Contrarily to DOACs, vitamin-K antagonists (VKA) have multiple targets (including factors II, VII, IX and X).

Table 1 Pharmacological characteristics of direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	FIIa	FXa	FXa	FXa
Onset of action	2 h	2.5–4 h	3 h	1–5 h
Half-life	12–14 h	9–13 h	8–11 h	8–10 h
Renal clearance (%)	80	60	25	35
Metabolism	P-gp	P-gp/CYP3A4	P-gp/CYP3A4	P-gp/CYP3A4
Dosing	b.i.d.	b.i.d./qd	b.i.d.	b.i.d./qd

FIIa, factor IIa; FXa, factor Xa; P-gp, P-glycoprotein; CYP, cytochrome P450.

Acute and long-term treatment of venous thrombo-embolism

Conventional anticoagulant treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) consists of an initial course of at least 5 days of parenteral (usually s.c.) administration of unfractionated or low-molecular-weight heparin (LMWH) or fondaparinux (acute phase), overlapped and followed by VKA such as warfarin for at least 3 months, a period known as the long-term treatment phase.[8,9] This conventional treatment has been compared with various regimens of DOACs (*Figure 2*, and *Tables 2–5*).

Of note, Phase III trials addressing the efficacy and safety of rivaroxaban, dabigatran, and apixaban in acute and long-term treatment of VTE had a single-dose regimen for patients allocated to the study treatment. Among all four pivotal trials with DOACs for stroke prophylaxis in atrial fibrillation, a reduced dose option was available in patients with renal insufficiency, as it is the case with edoxaban in the VTE programme.

Dabigatran

Dabigatran etexilate (150 mg b.i.d.) has been compared with conventional anticoagulant treatment in the RE-COVER[10] and RE-COVER II studies. Patients could be included if they had symptomatic DVT and/or PE. Of note, in both studies, randomization was preceded by a mandatory phase of at least 5 days of LMWH. The two trials were randomized, double-blinded, and aimed at establishing non-inferiority. RE-COVER included 2564 patients and the still unpublished RE-COVER II (NCT 00680186) included 2589 patients. In RE-COVER, symptomatic VTE or death occurred in 2.4% of dabigatran-treated patients, compared with 2.1% receiving conventional therapy. The rate of major bleeding was similar in the two groups (1.6 and 1.9%, respectively). Of note, the treatment discontinuation rate was significantly higher in the dabigatran arm (9%) than in the control arm (6.8%), mainly due to dyspepsia attributed to dabigatran in 3% of patients. In RE-COVER II, non-inferiority was established for dabigatran with respect to efficacy [2.4% recurrent VTE, compared with 2.2% with conventional therapy, and major

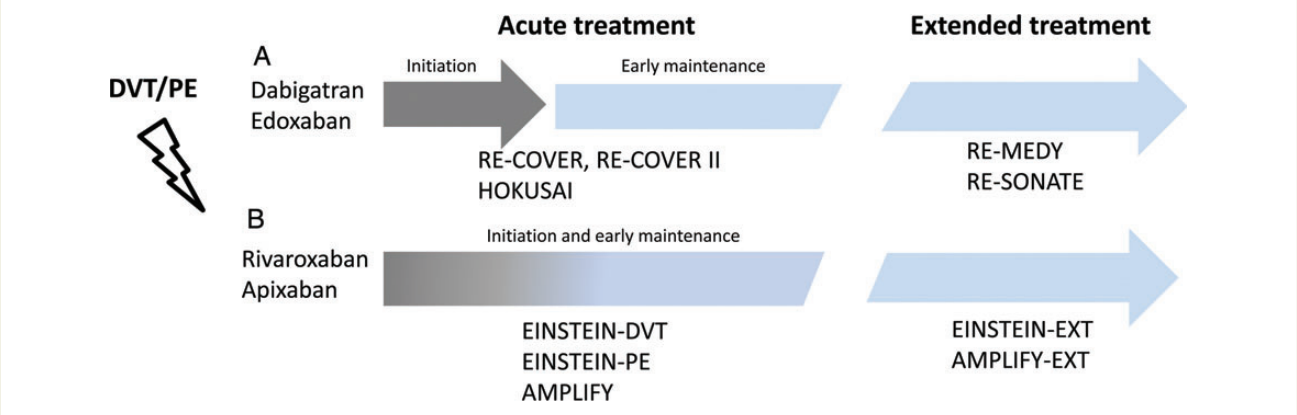

Figure 2 Summary of the main Phase III trials regarding acute and extended treatment of venous thrombo-embolism. Low-molecular-weight heparin has to be given upfront for the initiation of the treatment with dabigatran and edoxaban (*A*) while a single-drug approach drives the treatment with rivaroxaban and apixaban both in the initiation and the early maintenance phases (*B*).

Table 2 Selected characteristics of the studies with the DOACs in venous thrombo-embolism

Treatment/drug	Study	Dosage (mg)	Comparator	Indication	Design	Initial LMWH
Initial/dabigatran	RE-COVER	150 b.i.d.	Conventional	DVT or PE	DB	Mandatory
Initial/dabigatran	RE-COVER II	150 b.i.d.	Conventional	DVT or PE	DB	Mandatory
Initial/rivaroxaban	EINSTEIN-DVT	15 b.i.d./20 o.d.	Conventional	DVT	Open	Optional, <48 h
Initial/rivaroxaban	EINSTEIN-PE	15 b.i.d./20 o.d.	Conventional	PE	Open	Optional <48 h
Initial/apixaban	AMPLIFY	10 b.i.d./5 b.i.d.	Conventional	DVT or PE	DB	Optional <36 h
Initial/edoxaban	HOKUSAI-VTE	60 o.d.	Conventional	DVT or PE	DB	Mandatory
Extended/dabigatran	RE-SONATE	150 b.i.d.	Placebo	DVT or PE	DB	NA
Extended/dabigatran	RE-MEDY	150 b.i.d.	Warfarin	DVT or PE	DB	NA
Extended/rivaroxaban	EINSTEIN-EXT	20 o.d.	Placebo	DVT or PE	DB	NA
Extended/apixaban	AMPLIFY-EXT	5 b.i.d. OR 2.5 b.i.d.	Placebo	DVT or PE	DB	NA

O.d. and b.i.d., once or twice daily, respectively; DB, double-blind, NA, not applicable.

Table 3 Summary of the main results with the DOACs in venous thrombo-embolism: main efficacy endpoint

Treatment/drug	Study	Comparator	VTE recurrence (%) active/control	HR/RR (95% CI)
Initial/dabigatran	RE-COVER	Conventional	2.4/2.1	1.10 (0.60–1.84)
Initial/dabigatran	RE-COVER II[a]	Conventional	2.4/2.2	1.09 (0.65–1.81)
Initial/rivaroxaban	EINSTEIN-DVT	Conventional	2.1/3.0	0.68 (0.44–1.04)
Initial/rivaroxaban	EINSTEIN-PE	Conventional	2.1/1.8	1.12 (0.75–1.68)
Initial/apixaban	AMPLIFY	Conventional	2.3/2.7	0.84 (0.60–1.18)
Initial/edoxaban	HOKUSAI-VTE	Conventional	3.2/3.5	0.89 (0.70–1.13)
Extended/dabigatran	RE-SONATE	Placebo	0.4/5.6	0.08 (0.02–0.25)
Extended/dabigatran	RE-MEDY	Warfarin	1.8/1.3	1.44 (0.78–2.64)
Extended/rivaroxaban	EINSTEIN-EXT	Placebo	1.3/7.1	0.18 (0.09–0.39)
Extended/apixaban	AMPLIFY-EXT	Placebo	2.5 mg b.i.d.: 1.7/8.8 5 mg b.i.d.: 1.7/8.8	2.5 mg: 0.33 (0.22–0.48) 5 mg: 0.36 (0.25–0.53)

NA, not applicable; HR and RR, hazard ratio and relative risk, respectively.
[a]Full data yet unpublished.

Table 4 Summary of the main results with the DOACs in venous thrombo-embolism: bleeding endpoints

Study	Major bleeding (%) active/control	HR/RR (95% CI)	Major or clinically relevant non-major bleeding event (%)	HR/RR (95% CI)
RE-COVER	1.6/1.9	0.82 (0.45–1.48)	5.1/8.8	0.63 (0.47–0.84)
RE-COVER II[a]	1.2/1.7	0.69 (0.66–1.33)	NA	0.42 (0.45–0.84)
EINSTEIN-DVT[b]	0.8/1.2	0.65 (0.33–1.30)	8.1/8.1	0.97 (0.76–1.22)
EINSTEIN-PE[b]	1.1/2.2	0.49 (0.31–0.79)	10.3/11.4	0.90 (0.76–1.07)
AMPLIFY	0.6/1.8	0.31 (0.17–0.55)	4.3/9.7	0.44 (0.36–0.55)
HOKUSAI-VTE[b]	1.4/1.6	0.84 (0.59–1.21)	8.5/10.3	0.81 (0.71–0.94)
RE-SONATE	0.3/0	NA	5.3/1.8	2.92 (1.52–5.6)
RE-MEDY	0.9/1.8	0.52 (0.27–1.02)	5.6/10.2	0.54 (0.41–0.71)
EINSTEIN-EXT	0.7/0	NA	6.0/1.2	5.19 (2.3–11.7)
AMPLIFY-EXT	2.5: 0.2/0.5 5: 0.1/0.5	2.5:0.49 (0.09–2.64) 5: 0.25 (0.03–2.24)	2.5:3.2/2.7 5:4.3/2.7	2.5:1.20 (0.69–2.10) 5:1.62 (0.96–2.73)

Bleeding was defined as major if it was clinically overt and associated with a decrease in the haemoglobin level of 2.0 g/dL or more, if bleeding led to the transfusion of two or more units of red cells, or if bleeding occurred in a critical site, or contributed to death.
[a]Full data yet unpublished. NA, not applicable; HR and RR, hazard ratio and relative risk, respectively.
[b]In EINSTEIN-DVT, EINSTEIN-PE, and HOKUSAI-VTE, the principal safety outcome was not major bleeding but major bleeding plus clinically relevant non-major bleeding.

Table 5 Numbers of patients with deep vein thrombosis only or pulmonary embolism (with or without deep vein thrombosis) in the various trials with direct oral anticoagulants in venous thrombo-embolism

Treatment/drug	Study	Patients (*n*)	With DVT (*n*)	With PE (*n*)
Initial/dabigatran	RE-COVER	2534	1749	785
Initial/dabigatran	RE-COVER II	2589	[a]	[a]
Initial/rivaroxaban	EINSTEIN-DVT	3428	3405	23
Initial/rivaroxaban	EINSTEIN-PE	4832	0	4832
Initial/apixaban	AMPLIFY	5368	3532	1836
Initial/edoxaban	HOKUSAI-VTE	8240	4921	3319
Extended/dabigatran	RE-SONATE	1315	872	443
Extended/dabigatran	RE-MEDY[b]	2854	1860	994
Extended/rivaroxaban	EINSTEIN-EXT	1196	742	454
Extended/apixaban	AMPLIFY-EXT	2482	1622	860

[a]Details unpublished yet.
[b]Comparator in this study was warfarin, in all other studies on extended treatment, comparator arm was placebo.

bleeding (1.2 vs. 1.7%, respectively)]. Overall, the RE-COVER trials demonstrated non-inferiority of efficacy compared with conventional therapy, with similar safety.

Rivaroxaban

Rivaroxaban (15 mg b.i.d. during the first 3 weeks, then 20 mg o.d.) has been compared with conventional anticoagulant treatment in the EINSTEIN-DVT[11] and EINSTEIN-PE[12] studies. In the former, patients were included if they had symptomatic DVT with or without asymptomatic PE and in the latter, patients had to have symptomatic PE with or without DVT. The two trials were randomized, open, and aimed at establishing non-inferiority of the two regimens. Their results have been pooled in a pre-specified analysis on 8281 patients that allowed for studying clinically important high-risk subgroups, including frail patients, patients with cancer, moderate renal insufficiency, recurrent VTE events, or a large clot burden. Although these patients had an increased risk of thrombo-embolic recurrence and of major bleeding, the efficacy and safety of rivaroxaban was at least as good as conventional therapy.[13] Of note, rivaroxaban could be given upfront without initial administration of LMWH in both studies that encompassed 3449 patients (EINSTEIN-DVT) and 4832 patients (EINSTEIN-PE). In EINSTEIN-DVT, symptomatic VTE or VTE-related death occurred in 2.1% of rivaroxaban-treated patients, compared with 3.0% in the controls. The corresponding figures were 2.1 and 1.8% in EINSTEIN-PE. In EINSTEIN-DVT, the principal safety outcome (major bleeding plus clinically relevant non-major bleeding) was observed in 8.1% in both arms. In EINSTEIN-PE, the corresponding figures were 10.3% (rivaroxaban-treated

patients) and 11.4% (controls). The rates of major or clinically relevant nonmajor bleeds are displayed in *Table 4*. Surprisingly, in the pooled analysis, the reduction in major bleeding in favour of rivaroxaban was most pronounced in patients aged 75 years or more (1.2 and 4.5% in rivaroxaban-treated patients and control, respectively, $P < 0.05$) as well as in those with moderate renal impairment with a creatinine clearance <50 mL/min (0.9 and 4.1% in rivaroxaban-treated patients and control, respectively, $P < 0.05$).[13]

Overall, the EINSTEIN-DVT and EINSTEIN-PE studies demonstrated non-inferiority in terms of efficacy, compared with conventional therapy, with similar safety.

Apixaban

Apixaban (10 mg b.i.d. during the first 7 days, followed by 5 mg b.i.d.) was compared with conventional anticoagulant treatment in AMPLIFY.[14] Patients were included if they had symptomatic DVT and/or PE, and apixaban could be given upfront without initial administration of LMWH. The study was randomized, double-blinded, and aimed at establishing non-inferiority of apixaban. The study included 5395 patients. During the treatment period, symptomatic VTE recurrence or VTE-related death occurred in 2.3% of apixaban-treated patients and in 2.7% of patients treated with the conventional regimen, resulting in non-inferiority of the apixaban regimen. Major bleeding was less frequent among the apixaban-treated patients (0.6%), compared with 1.8% in the conventional therapy group ($P < 0.001$). Likewise, the combined outcome of major and clinically relevant non-major bleeding was less frequent in the apixaban arm (4.3%) than in the conventional treatment arm (9.7%, $P < 0.001$).

Overall, AMPLIFY demonstrated that apixaban is non-inferior to conventional anticoagulant therapy with significantly less bleeding.

Edoxaban

Edoxaban (60 mg o.d.) has been compared with conventional anticoagulant treatment for VTE in the HOKUSAI-VTE study,[15] the largest study ever for VTE treatment. Patients were included if they had symptomatic DVT and/or PE. The study was randomized, double-blinded, and aimed at establishing non-inferiority of the two regimens. A minimal initial 5-day period with parenteral administration of LMWH was mandatory in the two arms. HOKUSAI-VTE enrolled 8292 patients. Recurrent VTE during the study period occurred in 130 of 4118 patients (3.2%) in the edoxaban group and in 146 of 4122 patients (3.5%) in the warfarin group, resulting in non-inferiority of the edoxaban regimen. Among the pre-specified subgroup of patients with PE and evidence of right ventricular dysfunction (NT-pro-BNP level of ≥500 pg/mL), recurrent VTE occurred in 15 of 454 patients (3.3%) in the edoxaban group and in 30 of 484 patients (6.2%) in the warfarin group (hazard ratio: 0.52; 95% confidence interval: 0.28–0.98). Similar results were observed among patients with right ventricular dysfunction as assessed by means of computed tomography.[15] Major bleeding did not differ between groups (1.4% among the edoxaban-treated patients and 1.6% in the warfarin-treated group, $P = 0.35$). However, the primary safety outcome of major plus clinically relevant non-major bleeding was less frequent in the edoxaban arm (8.5%), compared with 10.3% in the conventional therapy group ($P = 0.004$).

Extended treatment of venous thrombo-embolism

Following the first 3 months of anticoagulant treatment, it is often difficult to determine whether treatment should be continued. Clinical equipoise surrounding this decision led to 'extension' studies in which the DOACs were compared with placebo (except in one case with warfarin). These extension studies were randomized, double-blinded, and aimed at establishing superiority (non-inferiority in the RE-MEDY study that used warfarin as comparator) of the DOAC, after an initial phase of at least 3 months of treatment with an approved anticoagulant regimen (*Tables 2–4*).

Dabigatran

RE-MEDY ($n = 2856$) assessed dabigatran (150 mg b.i.d.) vs. warfarin, and RE-SONATE ($n = 1343$) assessed dabigatran vs. placebo in separate extension studies published together in the same manuscript.[16] The patients included must have received an initial phase of at least 3 (RE-MEDY) or 6 (RE-SONATE) months of anticoagulation. In the dabigatran and warfarin arms of RE-MEDY, the principal efficacy outcome occurred in 1.8 and 1.3% of patients, respectively ($P = 0.01$ for non-inferiority). The corresponding figures in RE-SONATE were 0.4 and 5.6% in the dabigatran-treated patients and placebo controls, respectively ($P < 0.001$ for superiority). Major bleeding occurred in 0.9% (dabigatran-treated patients) and 1.8% (warfarin controls, $P = 0.06$) in RE-MEDY, and 0.3% (dabigatran-treated patients) and 0% (placebo controls) in RE-SONATE. If major plus clinically relevant non-major bleeding was assessed, this outcome was recorded in 5.2% of dabigatran-treated patients, compared with 10.6% of warfarin-treated patients in RE-MEDY ($P < 0.001$). In RE-SONATE, the corresponding figures were 5.3% (dabigatran-treated patients) and 1.8% (placebo controls, $P < 0.001$). In RE-MEDY, 0.9% of dabigatran-treated patients experienced an acute coronary syndrome compared with 0.2% in warfarin-treated patients ($P < 0.02$).

Overall, dabigatran was effective and safe in the extended treatment of VTE.

Rivaroxaban

The EINSTEIN-Extension study ($n = 1197$) is a randomized and double-blind superiority study that was published together with the EINSTEIN-DVT study.[11] Patients were eligible for the extension study if they had completed an initial course of at least 6 months of anticoagulation and if the treating physician had clinical equipoise as to whether anticoagulation should be continued. They received either rivaroxaban (20 mg o.d.) or placebo for 6–12 months. Recurrent symptomatic VTE occurred in 1.3% of rivaroxaban-treated patients, compared with 7.1% of placebo patients ($P < 0.0001$), an 82% relative and a 5.8% absolute risk reduction. Major bleeds were observed 0.7% of rivaroxaban-treated patients and in none of the patients receiving placebo ($P = 0.106$). Clinically, relevant non-major bleeding was more frequent with rivaroxaban (5.4%) than placebo (1.2%).

Overall, rivaroxaban was effective in the extended treatment of VTE but had a higher bleeding risk than placebo.

Apixaban

The AMPLIFY-Extension study[17] included 2486 patients who had completed an initial course of at least 6 months of anticoagulation. The study was randomized, double-blinded, and placebo-controlled. Two active groups were compared with placebo: apixaban 2.5 and 5 mg b.i.d. for 12 months. During the treatment period, recurrent symptomatic VTE occurred in 1.7% (2.5 mg b.i.d.), 1.7% (5 mg b.i.d.), and 8.8% (placebo), resulting in a relative risk of recurrence of 0.33 (2.5 mg b.i.d.) and 0.36 (5 mg b.i.d.) against placebo. The corresponding rates of major bleeding were 0.2% (2.5 mg b.i.d.), 0.1% (5 mg b.i.d.), and 0.5% (placebo). In addition, no difference was found in non-major clinically relevant bleeding between placebo and the lower dosage of apixaban.

Overall, apixaban was effective in the extended treatment of VTE, with the lower 2.5 mg b.i.d. dose showing an advantage over the 5 mg b.i.d. dose with respect to safety.

Lessons from the development programme of the direct oral anticoagulants in venous thrombo-embolism

A meta-analysis has summarized the data from randomized controlled trials of DOACs compared with VKA for the acute treatment of VTE, with data on >16 000 patients,[18] but not including HOKUSAI-VTE. There were no significant differences in efficacy when comparing DOACS vs. conventional therapy. Rivaroxaban and apixaban reduced the risk of major bleeding compared with conventional treatment, whereas dabigatran did not.

Data on the extended treatment of VTE showed that DOACs were associated with a favourable safety profile, even when compared with placebo,[11,17] except for dabigatran at 150 mg twice daily.[16] The two apixaban regimens tested (2.5 and 5 mg b.i.d.) were as safe as placebo for major bleeding, and the lower dosage was as safe as placebo for non-major clinically relevant bleeding. Of note, the term 'clinically relevant bleeding' usually includes major bleeding that was defined the same way across studies, adhering to the recommendations of the International Society on Thrombosis and Haemostasis, and thus allowing comparison of trials (*Table 4*). The non-major component is less strictly defined, and therefore a comparison across studies becomes more problematic.

Vitamin-K antagonists or direct oral anticoagulants for my next venous thrombo-embolism patient?

Besides these main data that favour DOACs, some practical differences may be considered when selecting a DOAC in day-to-day practice. Those include the need for an upfront administration of LMWH (dabigatran and edoxaban regimens, *Figure 2*), twice daily dosing (dabigatran and apixaban regimens), and a change in the dosing of the drug during the treatment (rivaroxaban and apixaban) that may influence adherence by patients and acceptance by clinicians. The absence of drug monitoring may also influence adherence to treatment and practitioners may be reluctant to prescribe a critical treatment without any regular and objective information on compliance.

Although a fixed dose regimen would favour these drugs in third world countries, the cost associated with DOACs is a major limitation. Cost-effectiveness studies are indeed lacking regarding VTE treatment for most of these DOACs but pioneered evaluation of rivaroxaban based on data of the EINSTEIN trials and on the US healthcare system studies suggest that rivaroxaban would be cost-effective most of the time.[19] Cost-effectiveness issues will certainly influence the decision regarding the choice of anticoagulant treatment. Large registries suggest that the risk/benefit ratio of anticoagulation may vary over time;[20] this may also influence drug selection or dosage for long-term prophylaxis. The relative weight of an often reversible haemorrhagic event compared with the recurrence of a venous thrombotic event that may be associated with long-term consequences should also be taken into account. Finally, a VKA-treated patient with excellent INR control has probably little to gain by switching to DOACs since the net clinical benefit may not favour these drugs, at least in atrial fibrillation patients treated with dabigatran.[21]

Practical considerations

Laboratory testing

Although the pro-thrombin time is relatively more sensitive to oral FXa inhibitors and the activated partial thromboplastin time to dabigatran, the usual coagulation tests routinely available do not precisely reflect the anticoagulation effect of DOACs,[22] especially in the low range of values. Moreover, these results are highly dependent on the reagents used and may thus differ from one laboratory to another.[23] The subcommittee on control of anticoagulation of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis recommends that the dilute thrombin time in combination with dabigatran calibrants should be used to determine dabigatran level (Hemoclot assay[24]), while anti-Xa assays with rivaroxaban calibrants can be used to determine rivaroxaban plasma levels.[25] It is likely that determination of other direct oral FXa inhibitor such as apixaban or edoxaban should be possible with an anti-Xa assay using dedicated calibrants. The interpretation of the results will remain challenging and will be more qualitative than quantitative until 'therapeutic ranges' are determined.[26]

Bleeding and bleeding management

When major bleeding occurs with DOACs, optimal management remains uncertain. American College of Chest Physician guidelines recommend reversal of warfarin by using 4-factor pro-thrombin complex concentrates (PCC) in conjunction with vitamin K.[27] However, the reversal of bleeding from DOACs is not addressed. Most studies conducted of DOAC reversal agents were performed in healthy volunteers using laboratory coagulation endpoints or clinical endpoints in animal models. Moreover, the available data are mostly related to rivaroxaban and dabigatran, with few data regarding apixaban and edoxaban. Thus, recommendations regarding bleeding management result more from experts' opinions rather than clinical experience. For example, the European Heart Rhythm Association[28] a multidisciplinary French[29] and American group[30] provide guidance

that may help the practitioner in managing bleeding events in patients treated with DOACs.

Overall, since DOACs have a short half-life, time is an efficient way to eliminate the anticoagulant effect. When a life-threatening bleeding occurs, non-specific agents such as PCC (25–50 U/kg) or activated PCC (30–50 U/kg) should be considered as a first-line treatment. Reserve recombinant activated factor VII as a second-line treatment. Adjunctive therapy such as desmopressin or tranexamic acid may also be considered, although the data regarding their efficacy in DOAC-associated bleeding are even more scarce. Specific antidotes are in development[31,32] and may dramatically change the bleeding management of these patients in the next future.

Perioperative management

Surgery is a well-known risk factor for VTE. The management of invasive procedures in patients with previous DVT and/or PE is particularly challenging since it may require modification or temporary discontinuation of the anticoagulant. One should perform for each patient a careful assessment of the bleeding risk associated with the continuation of the anticoagulant (procedure specific) and the thrombotic risk in case of discontinuation (both patient and procedure specific).[33]

Since renal function is a major determinant of the DOACs elimination (*Table 1*), creatinine clearance is a key factor in deciding how long to wait between DOAC withdrawal and the invasive procedure. In patients with normal renal function who undergo a low-haemorrhagic risk procedure such as a colonoscopy without removal of large polyps, a stop of the DOAC 24 h before surgery is proposed.[7] If renal function is impaired (Cockcroft creatinine clearance $<$50 mL/min) and/or the haemorrhagic and thrombotic risks are moderate to high, withdrawal of the DOAC for 2–5 days may be warranted, with a bridging procedure in selected cases.[34–37]

Conclusion

Direct oral anticoagulants represent a major step forward in the treatment and long-term prevention of VTE. Fixed dosing, few food and drug interactions, and no need for laboratory coagulation monitoring are major advantages compared with VKA. However, this simplification of treatment, along with a shift towards outpatient management of VTE, may inappropriately trivialize the importance of VTE and its treatment. Recurrence of VTE as well as bleeding events has serious consequences that should not be overlooked. Finally, some issues remain unanswered, such as the effects of DOACs in the setting of cancer, their use in patients with mechanical heart valve, and the availability of a specific reversal agent.

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