



Direct Oral Anticoagulants for the Treatment of Venous Thromboembolism in Japan

Mashio Nakamura, Norikazu Yamada and Masaaki Ito

Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan

Direct oral anticoagulants (DOACs) were developed to compensate for the demerits of warfarin. In Japan, three factor Xa inhibitors are used for the treatment of venous thromboembolism (VTE): edoxaban, rivaroxaban, and apixaban. Despite problems, such as the inability to monitor their effect and the lack of an antidote, these inhibitors have the same efficacy as conventional treatment with warfarin, and they are associated with a significantly high degree of safety in relation to hemorrhagic complications. East Asians, including Japanese, suffer from hemorrhage more frequently; therefore, DOACs are considered to be highly effective. Although there is no evidence to date, DOACs may be effective in a wide variety of ways, including the possibility that they prevent recurrence over the long term, reduce the length of hospitalization, allow treatment to be started on an outpatient basis, and be effective in cancer patients.

Key words: Apixaban, Direct oral anticoagulant, Edoxaban, Rivaroxaban

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Introduction

The main conventional anticoagulant treatments have included parenteral drugs, such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Because of their molecular chemical characteristics, heparins are not absorbed easily in the gastrointestinal tract; however, parenteral drugs are very poorly suited for long-term anticoagulant therapy. In contrast, since its commercialization in the 1960s, the vitamin K antagonist warfarin has contributed to clinical medicine through its use as the only oral anticoagulant. However, warfarin is limited in many ways, and its use entails a large burden. Specifically, warfarin has delayed drug efficacy, requires careful monitoring and frequent dose adjustments, requires different doses for each individual according to CYP2C9 activity, has a narrow safety range, is interactive with food-derived vitamin K and a large number of drugs, and requires

patient education.

In recent years, activated factor X (factor Xa), which is an important serine protease in the coagulation cascade, and nonpeptide low molecular weight compounds that interfere with thrombin have been developed as oral anticoagulants designed to replace warfarin. These drugs do not require monitoring, and there is hope that they can be used as new anticoagulants that overcome the aforementioned problems with warfarin. Their clinical targets are the prevention of thromboembolism in atrial fibrillation, primary prevention of venous thromboembolism (VTE) in orthopedic surgery, and treatment of VTE. In Japan, dabigatran, rivaroxaban, apixaban, and edoxaban are used to prevent thromboembolism in atrial fibrillation; only edoxaban is used in the primary prevention of VTE in orthopedic surgery, and edoxaban, rivaroxaban, and apixaban are used in the treatment of VTE (Table 1)¹⁻⁴.

Here, we provide an outline of these new oral anticoagulants; that is, the direct oral anticoagulants (DOACs), and in particular their efficacy in the treatment of VTE and future prospects for their use.

Address for correspondence: Mashio Nakamura, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174, Edobashi, Tsu 514-8507, Japan
E-mail: mashio@clin.medic.mie-u.ac.jp

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Table 1. Large clinical trials of direct oral anticoagulant for venous thromboembolism

	Hokusai-VTE	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY
Product Name (Generic Name)	Lixiana (Edoxaban)	Xarelto (Rivaroxaban)		Eliquis (Apixaban)
Trial Method	Double blind	Open-label		Double blind
Regimen	60 mg (30 mg) once daily	15 mg twice daily for 3 weeks followed by 20 mg once daily		10 mg twice daily for a weeks followed by 5 mg twice daily
Dose Reduction	Body weight ≤ 60 kg Creatinine clearance: 30–50 mL/min Combination with P-glycoprotein inhibitor	N/A		N/A
Initial Heparin Use	5–12 days	72%	92%	87%
Population	8,292	3,449	4,832	4,816
Warfarin TTR (%)	63.50%	57.70%	62.70%	60.90%
Treatment Period	3–12 months	3, 6, 12 months		6 months
Japanese Patients	209 patients	N/A	N/A	N/A
Primary Efficacy Outcome	Non-inferiority (VTE recurrence)	Non-inferiority (VTE recurrence)	Non-inferiority (VTE recurrence)	Non-inferiority (VTE recurrence or VTE related death)
Primary Safety Outcome	Superiority (Major bleeding + CRNM)	Non-inferiority (Major bleeding + CRNM)	Non-inferiority (Major bleeding + CRNM)	Superiority (Major bleeding))

CRNM, clinically relevant no major bleeding; N/A, not available; TTR, Target Therapeutic Range; VTE, venous thromboembolism
From ref. 1-4.

Pharmacological Characteristics of DOACs

The new anticoagulants that overcome the problems associated with conventional drugs boast assured efficacy with little individual variation in only a single dose and they do not require monitoring. In addition, they are extremely safe, have a wide therapeutic range, are less hemorrhagic, and have rapid onset action. In Japan, all of the DOACs used for VTE therapy are factor Xa inhibitors (**Fig. 1**). Factor Xa is further upstream in the coagulation cascade compared to thrombin, and one molecule of factor Xa produces 1000 molecules of thrombin. Therefore, rather than inhibiting the enzymatic activity of thrombin, it is thought that inhibiting this production would be a more efficient way to suppress the coagulation response. In addition, although thrombin has a negative feedback action on blood coagulation systems other than blood coagulation activation, because factor Xa is selective to the blood coagulation system, it is more appropriate for use as a drug discovery target

molecule.

In the search for drugs that could be used as anti-coagulants that do not have the same problems as warfarin, compounds with high oral absorbability were discovered and investigated. However, because most are strongly basic in nature, they have insufficient oral absorbability. Before oral factor Xa, indirect factor Xa inhibitor, fondaparinux, which is injectable and dependent upon antithrombin, was available for use in the treatment and prevention of VTE. Then, in recent years, compounds that maintain Xa activity due to their reduced alkalinity and that have excellent oral absorbability were discovered and developed into multiple direct factor Xa inhibitors.

Table 2 shows the pharmacokinetic characteristics of edoxaban, rivaroxaban, and apixaban^{5, 6}. Rivaroxaban and edoxaban are administered once a day, and apixaban is administered twice a day. Each drug reaches maximum blood concentration within 4 h after administration, and their short half-life of approximately half a day means that they act

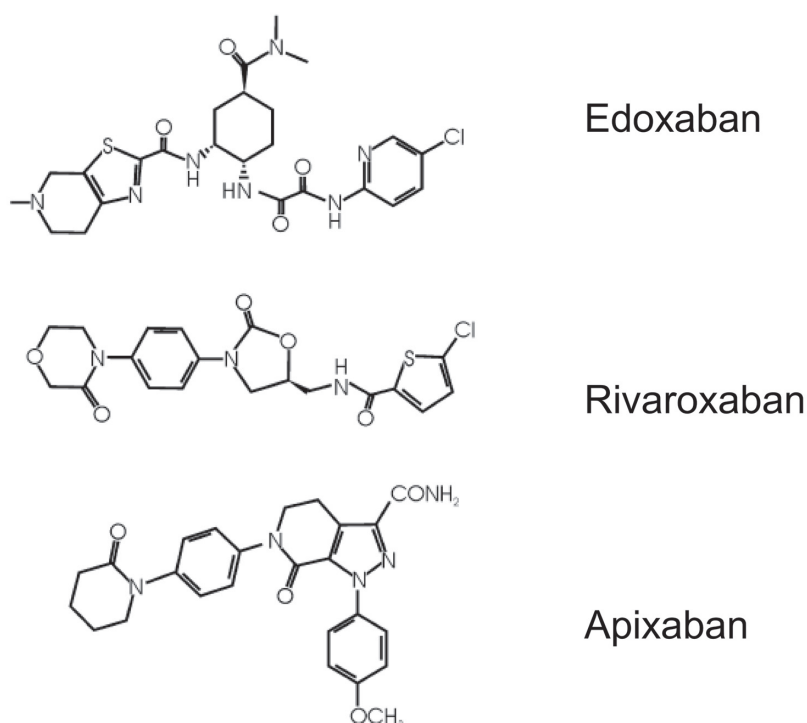


Fig. 1. Structures of the oral factor Xa inhibitors edoxaban, rivaroxaban, and apixaban

Table 2. Pharmacokinetic features of direct oral anticoagulants^{5, 6)}

	Edoxaban	Rivaroxaban	Apixaban
Target	Factor Xa	Factor Xa	Factor Xa
Molecular Weight (Da)	548	436	460
Clinical Development in Japan	DAIICHI SANKYO CO., Ltd.	Bayer Yakuhin, Ltd.	BMS K.K/ Pfizer Japan Inc.
Dosing	Once daily	Once daily	Twice daily
Time of maximum concentration (h)	1–2	2–4	1–3
CYP metabolism (%)	< 4	~ 66	25
Bioavailability (%)	62	80	66
Interaction with P-Glycoprotein-inhibitors	Yes	Yes	Yes
Protein binding (%)	40–59	90 ~	87
Half-life (h)	9–11	9–13	8–15
Renal excretion (%)	35–39	66	25

extremely quickly and exhibit anticoagulant effects from the day of administration. Most are metabolized in the liver by cytochrome P450, which means that the renal excretion rate of unaltered substances is relatively low.

Clinical Effectiveness of DOACs When Used in VTE Therapy

Edoxaban was shown to be effective and safe in the international clinical Hokusai-VTE trial, which

included Japanese patients¹⁾. A subanalysis of the East Asian population, including Japanese, also found that they are effective⁷⁾. Rivaroxaban was effective and safe in the international clinical EINSTEIN Pulmonary Embolism (PE)/Deep Vein Thrombosis (DVT) Trial^{2, 3)}, and apixaban was effective and safe in the international clinical AMPLIFY Trial⁴⁾. They were found to be safe for Japanese patients in the J-EINSTEIN Trial⁸⁾ and the AMPLIFY-J Trial⁹⁾.

The Hokusai-VTE Trial began treating subjects with edoxaban after administering parenteral antico-

agulants for at least 5 days to early-phase patients and then assessed the effectiveness and safety. The EINSTEIN PE/DVT Trial conducted treatment in the initial phase after onset of VTE using only oral drugs by administering rivaroxaban during the initial 3 weeks at 1.5-fold the usual dose. The J-EINSTEIN Trial of Japanese subjects administered rivaroxaban 3 weeks after onset at a reduced dose that was three-quarters that used in the EINSTEIN PE/DVT Trial. The AMPLIFY Trial conducted treatment in the initial phase after onset of VTE using only oral drugs by administering apixaban during the initial week at 2-fold the usual dose.

Comparisons in all these trials of DOACs and warfarin indicated that the effectiveness (that is, the recurrence rate of symptomatic VTE) was not inferior and that safety (that is, the onset rate of hemorrhagic complications) of DOACs was superior. A subanalysis of the Hokusai-VTE Trial on PE at NT-proBNP \geq 500 pg/mL indicated that edoxaban showed significantly more reduction in the onset of symptomatic VTE than warfarin (but less than heparin)¹⁰. When East Asians, including Japanese, were compared to non-East Asians, DOACs showed equal incidences for hemorrhagic complications, while warfarin had markedly higher incidence. This suggests that DOACs have a great deal of merit for East Asians⁹.

Problems with VTE Therapy Using DOACs

Efficacy monitoring was impossible for all DOACs. Therefore, administration to patients whose DOACs blood levels may rise, such as the elderly, underweight patients, and patients with renal dysfunction, requires that sufficient attention be paid to the risk of hemorrhage. In addition, it must be kept in mind that there is no antidote at present; therefore, when interventional procedures are being considered, the use of UFH and other drugs with shorter half-lives should be considered. Currently, antidotes for Xa inhibitors are being developed, and we look forward to their early clinical application¹¹. There are also reports indicating that VTE often has complications in patients who are at risk of arteriosclerosis^{12, 13}. In such cases, the combined use of antiplatelet drugs and DOACs is likely to be frequent. Because the combined use of antiplatelet drugs and DOACs increases the frequency of hemorrhage, the benefits and risks must be considered; thus, lower doses of DOACs should be considered.

Although three DOACs can now be used in VTE therapy, there are major differences in the initial administration regimens for each of them. Because there is currently no evidence regarding this topic, it is

very difficult to determine which DOAC should be used for which type of VTE (Fig. 2). In addition, although dose reduction criteria for edoxaban have been established and its effectiveness has been verified in Phase III trials, there are no dose reduction criteria for rivaroxaban or apixaban. There is a strong sense that dose reduction criteria for Japanese, a population with many underweight and elderly members, are required, but there is no evidence regarding this issue at present. Thus, many issues regarding DOACs have not been elucidated in large-scale clinical trials, and there are many issues in which Japanese and patients of European descent differ. It is necessary to conduct further clinical trials designed to provide answers to these unanswered questions.

New Developments in VTE Therapy in the Age of DOACs

The possibility of recurrence during the chronic phase of VTE means that it is necessary to consider the long-term use of anticoagulants, particularly in cases of unprovoked VTE, in which this possibility remains at a constant rate for as long as 3 months after onset¹⁴. DOACs are safe anticoagulants that have a lower risk of hemorrhage than warfarin; as a result, they can be used for longer periods of time in VTE therapy. To further reduce the risk of hemorrhage with long-term use, the possibility of reducing the DOAC dose should be examined. The AMPLIFY-EXT Trial¹⁵ indicated that apixaban administered continuously at a reduced dose of 2.5 mg per dose twice a day after 6 months after VTE onset was effective.

Because DOACs are effective immediately after administration, they do not have the same onset delay as seen in warfarin, which leads to reduced hospitalization during the acute phase of VTE. Patients whose conditions are stable and in whom the risk of VTE recurrence and hemorrhage is low may be discharged early and shifted to outpatient care. In addition, there seem to be no major problems with the use of DOAC therapy at VTE onset in moderate or mild cases of DVT. However, it is necessary to emphasize the reliability of treatment in cases of symptomatic PE; therefore, further studies are required to determine whether oral drug therapy alone at onset is sufficient for these cases.

Cancer patients commonly experience VTE as a complication¹⁴. The prognostic improvement effect of LMWH in cases of VTE complicating cancer has been elucidated¹⁶, and LMWH is recommended for cancer patients with VTE in Europe and the United States. However, LMWH cannot be used as a VTE therapy in Japan, which means that only warfarin can

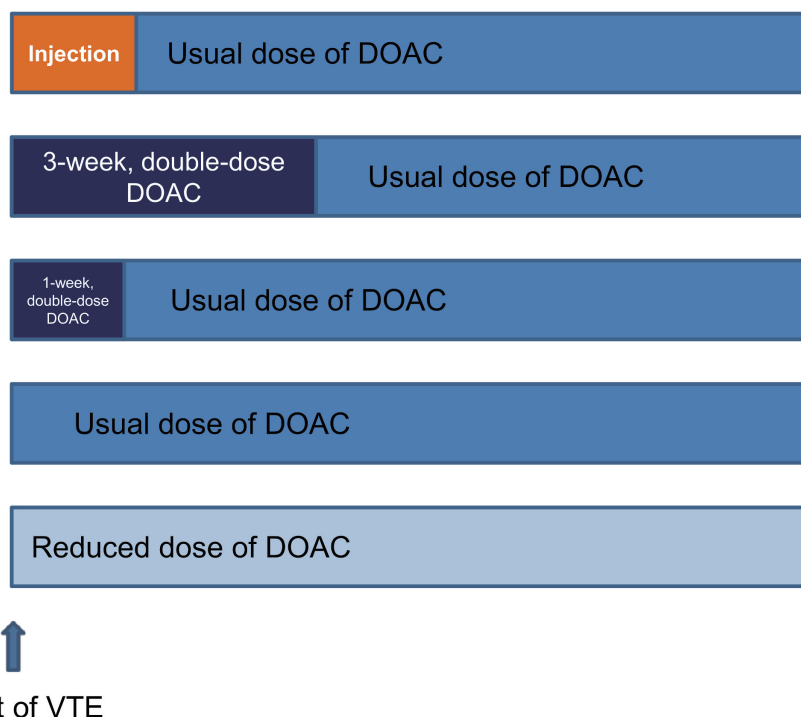


Fig. 2. Options for the regimen of direct oral anticoagulants for the initial treatment of venous thromboembolism in Japan

Patients at a greater risk of thrombosis are more prone to choosing the dosing regimens in the upper regimen, while patients at a greater risk of bleeding are more prone to choosing the dosing regimens in the lower regimen.

Table 3. Clinical questions in therapeutic application for the treatment of VTE with DOAC

What is the duration of administration of DOAC for VTE patients? What patients can receive outpatient DOAC? How is the safety of DOAC ensured in fragile patients? Does DOAC have the utility for cancer patients? What is the regimen of DOAC for isolated calf DVT?

DOAC, direct oral anticoagulant, VTE, venous thromboembolism

be used for long-term therapy. However, it is often difficult to adjust the dose of warfarin when used in combination with chemotherapy and because of fluctuations in platelet count. DOACs can be administered more safely to cancer patients than warfarin, and currently, their clinical effectiveness is being investigated worldwide¹⁷⁾.

Conclusion

When used as VTE therapy, DOACs are highly effective and have a great deal of potential. However, because there is little evidence regarding a variety of clinical questions (**Table 3**), further clinical trials and clinical data are required for the development of DOACs into safer drugs that are easier to use.

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