Special Article

Treatment of Venous Thromboembolism in the Era of Non-Vitamin K Antagonist Oral Anticoagulants

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Venous thromboembolism (VTE) is a common cause of cardiovascular morbidity and mortality. Heparins and warfarin have been the standard treatment of VTE for decades, but they have several disadvantages, e.g. parenteral route, narrow therapeutic window and numerous drug interactions. The development of new, non-vitamin K antagonist oral anticoagulants (NOACs) that can overcome these problems is a significant breakthrough and may replace warfarin for treatment of VTE. However, NOACs have some limitations, e.g. the lack of antidotes and high cost. As a result, many physicians are uncomfortable to employ NOACs in daily practice. This review will briefly summarize and update pharmacological profiles, evidence base for VTE treatment from Phase III clinical trials and some clinical considerations of NOACs in treatment of VTE.

Keywords: *Venous thromboembolism, Treatment, Non-vitamin K antagonist oral anticoagulants*

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Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third cause of cardiovascular death in the United State but the most preventable death in hospitalized patients. The estimated incidence of VTE from several large American and European cohorts ranges from 71-192 cases per 100,000 person-years[1-4]. Although, the incidence of VTE in Thai population remains unknown, it is apparent that the incidence rates of VTE in some specific populations have significantly increased approaching to those of the western countries[5-9]. Prompt diagnosis and treatment of VTE are crucial for preventing several subsequent complications. The treatment aims of VTE are to prevent clot extension and embolization, reduce recurrence and fatality and avoid chronic complications such as post thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

Currently, the treatment phases of VTE are divided into these following phases: initial treatment, long-term treatment and extended treatment (Fig. 1).

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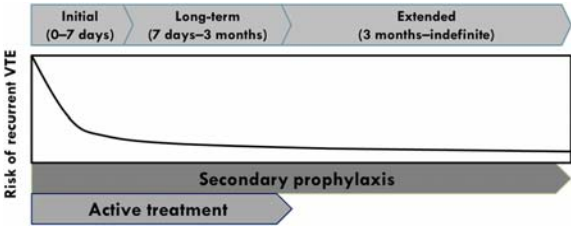

Fig. 1 Treatment phases of venous thromboembolism.

Conventionally, parenteral anticoagulants, primarily low molecular weight heparin (LMWH), overlapping with warfarin is administered in the initial phase followed by warfarin with a target INR of 2-3 for at least three months in the long-term treatment phase. These conventional anticoagulants have been considered as the standard treatment of VTE for several decades. Extended treatment using either warfarin with a standard INR of 2-3 or low-intensity warfarin with a target INR of 1.5-2 is able to significantly reduce recurrent VTE without increased major bleeding events in a low bleeding risk population. Prolonged anticoagulant therapy should be considered when the advantages from preventing the recurrence of VTE outweigh the bleeding risk in an individual patient[10]. Although these conventional anticoagulants are effective, they have several limitations, and new anticoagulants, therefore, have been recently developed.

Non-vitamin K antagonist oral anticoagulants (NOACs) are, currently, an alternative option using for management of thromboembolism. There have been several randomized clinical trials demonstrating their promising efficacy as well as safety in VTE management comparing to those of warfarin. Therefore, they confer a new treatment paradigm of VTE. This review will briefly focus on 1) pharmacological properties, 2) published evidence for NOACs in treatments of VTE and 3) special considerations of NOACs in clinical practice.

Pharmacological characteristics of NOACs

LMWHs, such as enoxaparin, tinzaparin, and fondaparinux, require daily subcutaneous injection until the anticoagulant effect of warfarin reaches the therapeutic level. In addition, LMWHs confer a risk of heparin-induced thrombocytopenia. Warfarin has been the only available oral anticoagulant for nearly 70 years. It has a narrow therapeutic margin and its effectiveness can be significantly interfered with by several drugs and food. Therefore, regular monitoring is mandatory. Furthermore, it has a slow onset. As a result, an administration overlapping with parenteral anticoagulants for a minimum of 5 days is required. Additionally, warfarin accounts for the greatest number of emergency hospitalization cases for adverse drug events in the American elderly[11].

These disadvantages of conventional antithrombotic agents result in the development of new oral anticoagulants, which are being comprised of 2 classes, a direct thrombin inhibitor (dabigatran) and a direct factor Xa inhibitor (rivaroxaban, apixaban and edoxaban)[12-14]. The different pharmacological characteristics between old and new oral anticoagulants are summarized in Table 1.

NOACs have several more desirable characteristics when compared with those of warfarin. They have short time to peak effect as well as half-life. Therefore, they have both rapid onset and offset when the drugs are started and stopped, respectively. Theoretically, it is possible to give NOACs without an overlap with parenteral anticoagulants. However, only rivaroxaban and apixaban were given as single drug in the initial phase of VTE treatment, while dabigatran and edoxaban were introduced in the long-term treatment in clinical studies. In addition, they were administered at fixed doses without routine monitoring of anticoagulant effects. Therefore, they are much more convenient in use compared with warfarin. However, antidotes are currently unavailable for bleeding correction in patients taking NOACs. As a result, some physicians remain reluctant to use NOACs in clinical practice. Despite the lack of antidotes, several large well-designed Phase III randomized controlled trials demonstrated their clinical benefits in both efficacy and safety compared to those of traditional treatment, LMWH/warfarin. Hence, rivaroxan, dabigatran and apixaban have been approved for VTE treatment by the US FDA, while edoxaban is anticipated to be approved in near future.

Published evidence for NOACs in treatment of VTE

Several large Phase III randomized controlled trials have been designed to compare efficacy and safety of NOACs with warfarin in treatment of acute VTE. In addition, studies comparing NOACs with either warfarin or a placebo in the extended treatment have been recently published. The primary efficacy and safety outcomes of these trials were summarized in Table 2[15-21].

Currently, dabigatran and rivaroxaban have been approved by the US FDA for VTE treatment in all phases of treatment, while apixaban has been licensed for the initial and long-term treatment. Therefore, NOACs become a new option for VTE management. In addition, a single oral drug approach in all phases of anticoagulation is evolving as a new paradigm of VTE treatment (Fig. 2).

Special considerations of non-vitamin K antagonist oral anticoagulants in clinical practice

In large randomized clinical trials, NOACs demonstrated non-inferiority for efficacy and similar to or even lower major bleeding rates than those associated with warfarin. Their safety in the real clinical practice was confirmed from post marketing surveys and the large registry[22,23]. From post marketing reports to the US FDA database and the Dresden NOAC registry, both dabigatran and rivaroxaban, the first two NOACs approved and mostly used in the US and Europe, showed lower bleeding risks than those reported for warfarin. Furthermore, case fatality rates of bleeding leading to hospitalization of rivaroxaban were 5.1% and 6.3% at day 30 and day 90, respectively, compared to those of 15%-20% reported for warfarin.

However, many physicians remain reluctant to prescribe NOACs in their daily practice. The unavailability of antidotes is one of the most concerns as they might face active bleeding in patients taking NOACs. Although, a majority of cases was successfully treated with conservative approaches, the mortality rate

Table 1. Pharmacological properties of oral anticoagulants

Drug properties	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Vitamin K epoxide reductase	Thrombin	Factor Xa	Factor Xa	Factor Xa
Pro-drug	No	Yes	No	No	No
Bioavailability	>95%	6.5%	80%	66%	62%
Tmax (h)	72-96	1-3	2-4	1-3	1-2
Half-life (h)	40	14-17	7-11	8-15	5-11
Dosing	Once daily (INR-adjusted)	Fixed, once or twice daily[1]	Fixed, once or twice daily[2]	Fixed, twice daily	Fixed, once daily
Renal clearance	None	80%	66% (33% fecal)	25% (75% fecal)	35% (65% fecal)
Potential drug interactions	CYP 2C9, 3A4 and 1A2	Potent p-gp inhibitors[3]	Potent CYP 3A4, p-gp inhibitors[3]	Potent CYP 3A4, p-gp inhibitors[3]	Potent CYP 3A4, p-gp inhibitors[3]
Pregnancy category[4]	Category X	Category C	Category C	Category B	No data

Tmax: time to peak concentration

[1] Once daily in prevention of venous thromboembolism and twice daily in other indications

[2] Twice daily in acute coronary syndrome and once daily in other indications

[3] Potent inhibitors of both CYP3A4 and P-glycoprotein transporter (p-gp): azole antifungals such as ketoconazole, itraconazole, voriconazole and posaconazole; protease inhibitors such as ritonavir; potent inhibitors of CYP3A4 such as azole antifungals, macrolide antibiotics such as clarithromycin and protease inhibitors such as atanazavir

[4] US FDA pregnancy category, B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

in patients with intracranial bleeding was still substantially high. Most recommendations for management of bleeding in patients taking NOACs are based on animal study models as well as studies in healthy volunteers[24-28]. Until their specific antidotes, of which several have been investigated in the Phases I and II studies, are available, this issue remains an important drawback limiting their clinical use.

Due to their predictable pharmacokinetics and pharmacodynamics, NOACs are administered at fixed dose and do not require routine monitoring of anticoagulant effects. However, the lack of reliable simple tests for measuring their activities turns to be a major disadvantage of NOACs in some special circumstances. The assessment of their anticoagulant effects may be indicated in the following clinical scenarios:

1. Patients with active bleeding.
2. Patients with deteriorating renal function.
3. Patients with an extreme body weight.
4. Patients taking known drugs that significantly alter pharmacokinetics of NOACs.
5. Suspicion of overdose.
6. Patients requiring emergent and/or urgent surgery.
7. Assessment of compliance.

Screening coagulation assays, such as prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT), are unreliable to evaluate anticoagulant effects of NOACs. Therefore, specific tests that are able to quantify anticoagulant effects of NOACs are required. For example, TT is a very sensitive assay for dabigatran. A low plasma concentration of dabigatran results in markedly prolonged TT, while normal TT indicates no anticoagulant effects of dabigatran. More comprehensive assays such as diluted TT or a dabigatran-specific anti-thrombin assay are helpful for the quantitative assessment. However, these assays are not widely available and may not be in a timely

Table 2. Designs and primary clinical outcomes of trials comparing non-vitamin K antagonist oral anticoagulants and conventional treatment in VTE treatment

Clinical trial	Patient population (cohort size)	Dose of NOACs	Recurrent VTE (NOACs vs. control)	Major bleeding (NOACs vs. control)
Treatment of acute VTE				
RE-COVER (dibigatran)	Acute VTE initially treated with parenteral anticoagulants (2,482)	150 mg bid	2.4% vs. 2.1%, (non-inferiority)	1.6% vs. 1.9% (HR, 0.82; 95% CI, 0.45-1.48)
EINSTEIN-DVT (rivaroxaban)	Acute symptomatic DVT (3,449)	15 mg bid for 3 weeks, followed by 20 mg od	2.1% vs. 3.0%, (non-inferiority)	0.8% vs. 1.2%, $p = 0.21$
EINSTEIN-PE (rivaroxaban)	Acute symptomatic PE with or without DVT (4,832)	15 mg bid for first 3 weeks followed by 20 mg od	2.1% vs. 1.8%, (non-inferiority)	1.1% vs. 2.2%, $p = 0.003$
AMPLIFY (apixaban)	Acute symptomatic VTE (5,395)	10 mg bid for 7 days, followed by 5 mg bid	2.3% vs. 2.7%, (non-inferiority)	0.6% vs. 1.8%, $p<0.001$
Hokusai-VTE (edoxaban)	Acute symptomatic VTE initially treated with parenteral anticoagulant (8,240)	60 mg od or 30 mg od (CrCl 30-50 mL/min or BW <60 kg)	3.2% vs. 3.5%, (non-inferiority)	1.4% vs. 1.6%, $p = 0.35$
Extended treatment of VTE				
RE-MEDY (dabigatran)	VTE, already completed 3 months of therapy, compared to warfarin (2,856)	150 mg bid	1.8% vs. 1.3%, (non-inferiority)	0.9% vs. 1.8%, $p = 0.06$
RE-SONATE (dabigatran)	VTE, already completed 3 months of therapy, compared to placebo (1,343)	150 mg bid	0.4% vs. 5.6%, $p<0.001$ (superiority)	0.3% vs. 0.0%, $p = 1$
EINSTEIN-EXT (rivaroxaban)	Patients with VTE who completed 6-12 months of anticoagulation therapy, compared to placebo (1,198)	20 mg od	1.3% vs. 7.1%, $p<0.001$ (superiority)	0.7% vs. 0.0%, $p = 0.11$
AMPLIFY-EXT (apixaban)	Patients with VTE who completed 6-12 months of anticoagulation therapy, compared to placebo (2,482)	2.5 mg bid or 5 mg bid	1.7% (2.5 mg), 1.7% (5 mg) vs. 8.8%, $p<0.001$ (superiority)	0.2% (2.5 mg), 0.1% (5 mg) vs. 0.5%; RR 0.49, 95%CI 0.09-2.64 (2.5 mg), RR 0.25, 95%CI 0.03-2.24 (5 mg)

VTE = venous thromboembolism; NOAC = non-vitamin K antagonist oral anticoagulant; CrCl = creatinine clearance; BW = body weight

fashion. Different assays and their utility of measuring anticoagulant effects of NOACs are summarized in Table 3[29-31].

Another disadvantage of NOACs but might be one of the most important limitation is the much higher cost of NOACs compared with that of warfarin. In addition, NOACs are out of the National List of Essential Drugs. Therefore, a majority of Thai patients are unable to afford NOACs for the long-term as well as the extended treatment of VTE.

In summary, NOACs become a new standard treatment of VTE and allow a single oral agent approach. Large randomized clinical trials demonstrated their promising efficacy and safety benefits in all phases of VTE treatment when compared to conventional treatment with LMWH and warfarin. However, the lack of antidotes as well as availability of quantitative laboratory assessment remains their disadvantages and limit their use widely in general practice. Therefore, physicians who decide to use NOACs in VTE treatment need a deep understanding of pharmacological properties as well as clinical profiles of each drug before prescription.

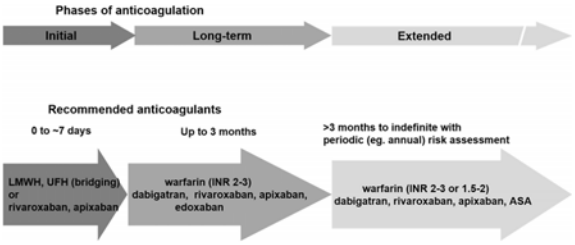

Fig. 2 Phases of anticoagulation in VTE treatment and evidence-based recommendation for antithrombotic treatment.

Potential conflicts of interest

None.

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Table 3. Laboratory assessment of non-vitamin K antagonist oral anticoagulants

Test	Availability	Dabigatran	Rivaroxaban	Apixaban
Coagulation assay				
PT	Widely available	Not useful	Useful for qualitative assessment	Not useful
APTT	Widely available	Useful for qualitative assessment	Not useful	Not useful
TT	Widely available, but turnaround time may vary	Useful for qualitative assessment	Not useful	Not useful
Dilute TT	Not widely available assessment	Useful for quantitative	Not useful	Not useful
Chromogenic assay				
Anti-Xa assay	Widely available, but turnaround time may vary	No effect	Useful for quantitative assessment	Useful for quantitative assessment
Anti-thrombin assay	Not widely available assessment	Useful for quantitative	No effect	No effect

PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time

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การรักษาภาวะลิ่มเลือดอุดตันในหลอดเลือดดำในยุคของยาต้านการแข็งตัวของเลือดชนิดรับประทานที่ไม่ได้ออกฤทธิ์ผ่านวิตามินเค

นภชาญ เอื้อประเสริฐ

ภาวะลิ่มเลือดอุดตันในหลอดเลือดดำเป็นสาเหตุความพิการและการตายจากหัวใจและหลอดเลือดที่พบบ่อย เฮปารินและวาร์ฟารินเป็นการรักษามาตรฐานของภาวะนี้มาหลายทศวรรษ แต่ยาเหล่านี้ยังมีข้อเสียหลายประการเช่น ให้ด้วยวิธีฉีด มีช่วงของประสิทธิภาพยาในการรักษาแคบและถูกรบกวนจากยาหลายชนิด การพัฒนายาต้านการแข็งตัวของเลือดแบบรับประทานชนิดใหม่ที่ไม่ได้ออกฤทธิ์ผ่านวิตามินเคสามารถแก้ไขข้อบกพร่องเหล่านี้ได้ นับเป็นความก้าวหน้าสำคัญและอาจจะมาทดแทนวาร์ฟารินในการรักษาภาวะลิ่มเลือดอุดตันในหลอดเลือดดำ อย่างไรก็ตามยาต้านการแข็งตัวของเลือดชนิดรับประทานที่ไม่ได้ออกฤทธิ์ผ่านวาร์ฟารินยังคงมีข้อจำกัดบางประการ เช่น การขาดยาต้านฤทธิ์และมีราคาแพง ทำให้แพทย์จำนวนมากยังไม่สะดวกใจที่จะใช้ยากลุ่มนี้ในเวชปฏิบัติ บทความนี้จะสรุปเนื้อหาที่ทันสมัยของคุณสมบัติทางเภสัชวิทยา หลักฐานเชิงประจักษ์และข้อพิจารณาทางคลินิกบางประการของยาต้านการแข็งตัวของเลือดชนิดรับประทาน ที่ไม่ได้ออกฤทธิ์ผ่านวิตามินเคในการรักษาภาวะลิ่มเลือดอุดตันในหลอดเลือดดำ