Therapeutics and Clinical Risk Management

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REVIEW

Using non-vitamin K oral anticoagulants in specific patient populations: a study of Korean cases

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Abstract: Non-vitamin K oral anticoagulants (NOACs) are increasingly used as alternatives to conventional therapies and have considerable accumulated real-world clinical data in patients with non-valvular atrial fibrillation (NVAF) or venous thromboembolism (VTE). However, it is not easy to make a complete changeover to NOACs in real-world clinical practice because NOACs still have challenges in specific patient populations (eg, Asian patients, NVAF patients presenting with acute coronary syndrome [ACS], dialysis patients with NVAF, patients with cancer-associated VTE, etc.). Clinical data on the optimal dose of NOACs in Asian patients with NVAF are not sufficient. The intensity of NOAC and antiplatelet treatment and the duration of antiplatelet treatment should be adjusted according to the bleeding and thrombotic risk profiles of the individual NVAF patient presenting with ACS. Increased bleeding risk and unclear efficacy of NOACs in dialysis patients with NVAF should be considered when making decisions on whether to give NOACs for these patients. If dialysis patients with NVAF require anticoagulant for stroke prevention, then apixaban could be considered while awaiting more clinical efficacy and safety data. Additional studies are needed to determine the utility of continuing treatment with reduced-dose NOACs for long-term therapy after VTE. We have enough experiences in using NOACs in cancer patients showing the benefit of antithrombotic treatment counterbalanced the bleeding risk; however, some challenges of cancer-associated VTE management exist due to differences in cancer types or chemotherapy regimens and comorbidities. Different dosing regimens among NOACs may impact on medication adherence; thus, individual patient preference should be considered in choosing a particular NOAC. A significant proportion of patients remain on warfarin because of the high price of NOACs and variability in reimbursement coverage. To compensate clinical-evidence and achieve optimal use of NOACs, we should pay attention to the outcomes of ongoing studies and evaluate more real-world data.

Keywords: non-valvular atrial fibrillation, venous thromboembolism, risk management plan, optimal dose, drug price, cost-effectiveness

Introduction

Atrial fibrillation (AF) affects 1–2% of the general population and is the most common type of arrhythmia, which is a problem with heart rhythm.[1,2] Patients with AF fail to pump all of the blood in the atria into the ventricle, causing some blood to contribute to thrombus formation. If the thrombus detaches and migrates to an artery in the brain, it can block the blood stream and cause a stroke.[3] The Framingham study reported that the incidence of stroke is more than 5-fold higher in the presence of AF, a greater increase than that observed in subjects with coronary heart disease (2-fold), hypertension (3-fold), or cardiac failure (4-fold).[4] Currently, the prevalence of AF is lower in Asians compared to Caucasians.[5]

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DovePress
http://doi.org/10.2147/TCRM.S204377

However, Asia has a larger elderly population than countries with predominantly Caucasian populations; thus, the incidence of chronic disease in Asia is predicted to rise, and the prevalence of AF is thus expected to increase further.[5] The predicted number of Asian AF patients in 2050 is 72 million, more than twice as many as in the United States (US) and Europe, and almost 2.9 million Asian patients will experience an AF-associated stroke if they do not take oral anticoagulants (OACs).[6]

Venous thromboembolism (VTE), requiring antithrombotic therapy as AF, comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE).[7] In DVT, blood clots form in the deep veins of the body, especially the lower leg or thigh.[8] These clots can break off, travel through the bloodstream to the lungs, and suddenly block a pulmonary artery.[9] This condition is called PE. The overall annual incidence rates of VTE range between 1.07 and 1.83 per 1000 individuals and the incidence rate of VTE in Asians was about 10–20% of that reported in the Caucasian population.[10,11] Although the incidence in the Asian population is lower than that in the Western population, the burden of VTE in the Asian population is expected to increase with the rapid aging and increased life expectancy of this population. In Korea, the incidence of VTE is gradually increasing yearly (eg, 0.21 and 0.29 per 1000 individuals in 2009 and 2013, respectively) and it is significantly higher in the older population than in the younger population.[12]

Considering the mechanisms of stroke in AF and the goal of VTE treatment (eg, prevent thrombus extension and new thrombus formation), antithrombotic therapy is required in patients with these diseases. OACs such as vitamin K antagonists (VKAs) are necessary to prevent thromboemboli in AF patients.[13,14] A parenteral anticoagulant overlapping with a VKA is a conventional antithrombotic therapy in patients with VTE.[15,16] However, these standard therapies have numerous disadvantages. Warfarin requires frequent international normalized ratio (INR) monitoring and dose adjustments, has multiple interactions with diet and drugs; multiple genetic polymorphisms are associated with warfarin metabolism, and parenteral anticoagulants should be administered by injection.[17–22]

These weaknesses of conventional therapies drove the development of non-vitamin K oral anticoagulants (NOACs) with new mechanisms of action, eg, direct thrombin inhibitor, dabigatran, and factor Xa (FXa) inhibitors, rivaroxaban, apixaban, and edoxaban. NOACs demonstrated efficacy and safety in comparison with warfarin in patients with non-valvular atrial fibrillation (NVAF), as well as parenteral therapy + VKA or placebo in patients with VTE.[23–36] Based on the clinical study data, NOACs are currently approved in various countries, eg, the US, Europe, Korea, and Japan, for the following indications: (1) reduction of the risk of stroke and systemic embolic events (SEE) in NVAF; (2) treatment of DVT and PE and reduced risk of recurrence of DVT and PE.[37] Approval status and dosing regimens in the label information of NOACs among the four regions are shown in Table 1.[37] The international clinical guidelines for NVAF or VTE management were updated to recommend NOACs as the preferred strategy for antithrombotic therapy.[14,15,38]

Currently, NOACs are increasingly used as alternatives to conventional therapies and have considerable accumulated real-world clinical data in patients with NVAF or VTE for at least 3–10 years after they have been released to the market. However, it is not easy to make a complete changeover to NOACs in real-world clinical practice because NOACs still have challenges in specific patient populations (eg, Asian patients, NVAF patients presenting with ACS, dialysis patients with NVAF, patients with cancer-associated VTE, etc.). Therefore, this narrative review aims to review recent data on the use of NOACs and discuss challenges when using NOACs in specific patient populations with NVAF or VTE.

Summary of pharmacological properties of NOACs compared with conventional treatments

Although warfarin has been approved for more than 60 years and is widely used in clinical practice, it has some characteristics hindering its compliance. The dose of warfarin is influenced by clinical factors, eg, age, race, concomitant medications, food, and genetic factors such as CYP2C9 and VKORC1 genotypes.[17] Warfarin inhibits multiple clotting factors in the coagulation cascade and has a slow onset of action, a narrow therapeutic range, and exhibits interactions with various drugs related to CYP450, dietary vitamin K, and botanical (herbal) products.[17] These features necessitate continuous INR monitoring.[17] Geriatric patients aged over 60 years exhibit increased anticoagulant effects, and they should have a lower dose of warfarin to have a beneficial level of anticoagulation.[17] Since Asian patients are more sensitive to warfarin, they require lower doses of warfarin and to have a lower INR range goal.[17,39]

Parenteral anticoagulants such as molecular-weight heparin (LMWH), unfractionated heparin (UFH), or

Table 1 Approval status and dosing regimens in the label information of NOACs in the US, Europe, Korea, and Japan[37]

Reduction of the risk of stroke in NVAF					
		FDA(US)	**EMA (Europe)**	**MFDS (Korea)**	**PMDA (Japan)**
Dabigatran	Date	2010.10.19. (2010.10.19.)[a]	2008.3.18. (2011.4.15.)[b]	2011.2.18. (2011.2.18.)[a]	2011.1. 21.(2011.1.21.)[a]
	Dose	•150 mg twice daily •75 mg twice daily ·CrCL 15 – 30 mL/min ·CrCL 30–50 mL/min with concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole	•150 mg twice daily •110 mg twice daily ·age ≥80 years ·concomitant use of verapamil •Daily dose of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding ·age 75–80 years ·CrCL 30–50 mL/min ·gastritis, esophagitis, gastroesophageal reflex ·increased risk of bleeding	•150 mg twice daily •110 mg twice daily ·age ≥75 years ·CrCL 30–50 mL/min ·concomitant use of moderate P-gp inhibitor or antiplatelet drug or NSAID or SSRI or SNRI ·body weight <50 kg ·gastritis, esophagitis, gastroesophageal reflex ·increased risk of bleeding ·intrinsic risk factors for thromboembolic events ·high surgical mortality risk	•150 mg twice daily •110 mg twice daily ·age ≥70 years ·CrCL 30–50 mL/min ·concomitant use of P-gp inhibitor ·history of gastrointestinal bleeding ·increased risk of bleeding
Rivaroxaban	Date	2011.7.1. (2012.11.2.)[a]	2008.9.30. (2011.9.22.)[b]	2009.4.13. (2012.2.29.)[a]	2012.1. 18. (2012.1.18.)[a]
	Dose	•20 mg once daily with the evening meal •15 mg once daily with the evening meal CrCL ≤50 mL/min	•20 mg once daily with food •15 mg once daily with food ·CrCL 15–49 mL/min		•15 mg once daily after a meal •10 mg once daily ·CrCL 15–49 mL/min
Apixaban	Date	2012.12.28. (2012.12.28.)[a]	2011. 5.18. (2012.9.20.)[b]	2011.11.30. (2013.1.8.)[a]	2012.12.25. (2012.12.25.)[a]
	Dose	•5 mg twice daily •2.5 mg twice daily with at least two of the following characteristics ·age ≥80 years ·body weight ≤60 kg ·serum creatinine ≥1.5 mg/dl			

(*Continued*)

Table 1 (Continued).

Reduction of the risk of stroke in NVAF					
		FDA(US)	**EMA (Europe)**	**MFDS (Korea)**	**PMDA (Japan)**
Edoxaban	Date	2015.1.8. (2015.1.8.)[a]	2015.6.19. (2015.4.23.)[b]	2015.8.25. (2015.8.25.)[a]	2011.4.22.(2014.9.26.)[a]
	Dose	• 60 mg once daily • 30 mg once daily · CrCL 15 – 50 mL/min	• 60 mg once daily • 30 mg once daily ·CrCL 15–50 mL/min ·body weight ≤60 kg ·concomitant use of the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, or ketoconazole		• 60 mg once daily • 30 mg once daily ·CrCL15–50 mL/min ·body weight ≤60 kg ·concomitant use of the following P-gp inhibitors: cyclosporine, erythromycin, verapamil, or quinidine
	Warning and precaution	• Edoxaban should not be used in patients with CrCL >95 mL/min.	• Edoxaban should only be used in patients with NVAF and high CrCL after a careful evaluation of the individual thromboembolic and bleeding risk.		None
Treatment of DVT and PE and reduction of the risk of recurrence of DVT and PE					
		FDA (US)	**EMA (Europe)**	**MFDS (Korea)**	**PMDA (Japan)**

(*Continued*)

Table 1 (Continued).

Reduction of the risk of stroke in NVAF					
		FDA(US)	**EMA (Europe)**	**MFDS (Korea)**	**PMDA (Japan)**
Dabigatran	Date	2010.10.19. (2014.4.4.)[a]	2008.3.18. (2014.4.25.)[b]	2011.2.18. (2014.7.24.)[a]	-
	Dose	<Treatment> • 150 mg twice daily after 5–10 days of parenteral anticoagulation <Reduction of the risk of recurrence> • 150 mg twice daily	<Treatment> •150 mg twice daily following treatment with a parenteral anticoagulant for at least 5 days <Reduction of the risk of recurrence> •150 mg twice daily <Dosing adjustments> • 110 mg twice daily ·age ≥80 years ·concomitant use of verapamil •Daily dose of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding ·age 75 – 80 years ·CrCL 30 – 50 mL/min ·gastritis, esophagitis, gastroesophageal reflex ·increased risk of bleeding	<Treatment> •150 mg twice daily following treatment with a parenteral anticoagulant for at least 5 days <Reduction of the risk of recurrence> •150 mg twice daily <Dosing adjustments> • 110 mg twice daily · age ≥75 years · CrCL 30 – 50 mL/min ·concomitant use of moderate P-gp inhibitor or antiplatelet drug or NSAID or SSRI or SNRI ·body weight <50kg ·gastritis, esophagitis, gastroesophageal reflex ·increased risk of bleeding ·intrinsic risk factors for thromboembolic events ·high surgical mortality risk	Non-approved
Rivaroxaban	Date	2011.7.1. (2012.11.2.)[a]	2008.9.30. (2012.10.18.)[b]	2009.4.13. (2013.2.22.)[a]	2012.1. 18. (2015.9.24.)[a]
	Dose	<Treatment> •15 mg twice daily with food for the first 21 days •After 21 days, transition to 20 mg once daily with food <Reduction of the risk of recurrence> •20 mg once daily with food			<Treatment> •15 mg twice daily with food for the first 21 days •After 21 days, transition to 15 mg once daily with food <Reduction of the risk of recurrence> •15 mg once daily with food

(*Continued*)

Table 1 (Continued).

Reduction of the risk of stroke in NVAF					
		FDA(US)	**EMA (Europe)**	**MFDS (Korea)**	**PMDA (Japan)**
Apixaban	Date	2012.12.28. (2014.8.21.)[a]	2011. 5.18. (2014.6.26.)[b]	2011.11.30. (2014.9.4.)[a]	2012.12.25. (2015.12.21.)[a]
	Dose	<Treatment> •10 mg twice daily for the first 7 days, followed by 5 mg twice daily <Reduction of the risk of recurrence> •2.5 mg twice daily after at least 6 months of treatment			<Treatment and reduction of the risk of recurrence> •10 mg twice daily for the first 7 days, followed by 5 mg twice daily * This drug was not administered for more than 6 months in domestic clinical trials.
Edoxaban	Date	2015.1.8. (2015.1.8.)[a]	2015.6.19. (2015.6.19.)[b]	2015.8.25. (2015.8.25.)[a]	2011.4.22. (2014.9.26.)[a]
	Dose	<Treatment> •60 mg once daily following 5 to 10 days of initial therapy with a parenteral anticoagulant <Reduction of the risk of recurrence> • Non-approved <Dosing adjustments> •30 mg once daily ·CrCL 15–50 mL/min ·body weight ≤60 kg ·concomitant use of verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole	<Treatment> •60 mg once daily following initial therapy with a parenteral anticoagulant for at least 5 days <Reduction of the risk of recurrence> •60 mg once daily <Dosing adjustments> •30 mg once daily ·CrCL 15–50 mL/min ·body weight ≤60 kg ·concomitant use of the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, or ketoconazole		<Treatment> •60 mg once daily following initial therapy with a parenteral anticoagulant for at least 5 days <Reduction of the risk of recurrence> •60 mg once daily <Dosing adjustments> •30 mg once daily ·CrCL 15–50 mL/min ·body weight ≤60 kg ·concomitant use of the following P-gp inhibitors: cyclosporine, erythromycin, verapamil, or quinidine

Notes: [a]Date on which it was approved as a new molecular entity (date on which it was approved for the indication). [b]Date on which the European Commission granted a marketing authorization valid throughout the European Union (date on which the CHMP adopted a positive opinion on approval for the indication). Cho IY, Choi KH, Sheen YY, Therapeutic Innovation & Regulatory Science (53:2)pp. 233–242, copyright © 2019 by (SAGE Publications), Reprinted by Permission of SAGE Publications, Inc.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; CrCL, creatinine clearance; NOACs, non-vitamin K oral anticoagulants; DVT, deep vein thrombosis; EMA, European Medicines Agency; FDA, Food and Drug Administration; MFDS, Ministry of Food and Drug Safety; NSAID, nonsteroidal anti-inflammatory drug; NVAF, non-valvular atrial fibrillation; PE, pulmonary embolism; PMDA, Pharmaceuticals and Medical Devices Agency; P-gp, P-glycoprotein; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

fondaparinux are administered by subcutaneous or intravenous injection.[18–22] LMWHs such as enoxaparin, tinzaparin, dalteparin, and UFH are co-inhibitors of FXa and IIa (thrombin) in the blood coagulation cascade and fondaparinux is a selective inhibitor of FXa.[18–22] LMWH and fondaparinux need no routine monitoring of coagulation parameters.[18–20,22] On the other hand, UFH requires frequent monitoring of coagulation system status routinely done with the activated partial thromboplastin time (APTT) test.[21]

To overcome weaknesses of conventional treatments, target-specific NOACs inhibit a specific single step (eg, rivaroxaban, apixaban, and edoxaban inhibit FXa, and dabigatran inhibits thrombin directly) and do not require routine monitoring of coagulation parameters or INR.[40–47] NOACs are expected to replace parenteral anticoagulants because of their rapid onset/offset of action and possible switching of all-oral fixed dose regimens.[48] However, there will be clinical situations when a laboratory assessment of the anticoagulant effect of NOACs is required, although NOACs do not require routine monitoring (eg, a necessary reversal of anticoagulation or identification of subtherapeutic or supratherapeutic levels in special patients is needed, etc.).[49] The intensity of anticoagulation caused by dabigatran can be measured by the APTT and a dilute thrombin time can be used to measure dabigatran levels.[49] For the FXa inhibitor, a prothrombin time assay can measure the intensity of anticoagulation and anti-FXa assays can measure the FXa inhibitor level.[49]

Furthermore, specific reversal agents for NOACs exist. Idarucizumab binds all dabigatran with high affinity and neutralizes dabigatran activity as a monoclonal antibody fragment.[50] Today, idarucizumab is approved as a medicine to neutralize the effects of dabigatran in the US, Europe, Korea, and Japan. Andexanet alfa, which binds to the direct FXa inhibitors, is approved under Accelerated Approval in the US for patients treated with rivaroxaban and apixaban when reversal of anticoagulation is needed.[51] Those specific reversal agents are expected to reverse the anticoagulation effect of NOACs rapidly when life-threatening/uncontrolled bleeding occurs or an emergent surgery/urgent procedure is needed.

The inhibition sites of conventional treatments and NOACs in the blood coagulation cascade are shown in Figure 1 and their pharmacological properties are outlined in Table 2.

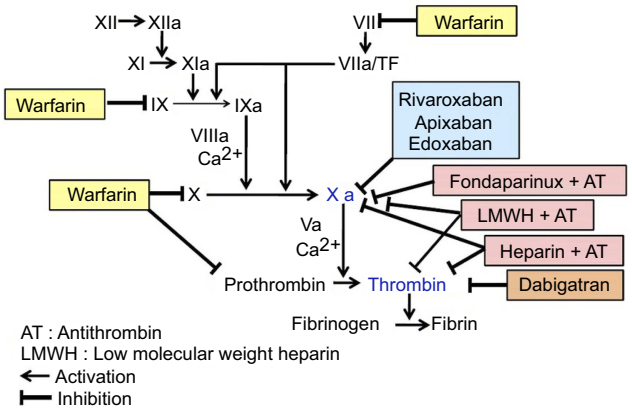

Figure 1 Inhibition sites of conventional treatments and NOACs in the blood coagulation cascade
Abbreviation: NOACs, non-vitamin K oral anticoagulants.

Summary of clinical efficacy and safety of NOACs

The main efficacy and safety data of NOACs in premarketing development programs require review when used in specific patient populations with either NVAF or VTE. Regulatory approvals of NOACs for each indication are based on these clinical data. Main outcomes of the pivotal clinical studies are summarized as follows:

Reduction of the risk of stroke in NVAF

Each NOAC was compared to warfarin in patients with NVAF in a confirmatory Phase III global clinical study (eg, RE-LY with dabigatran, ROCKET-AF with rivaroxaban, ARISTOTLE with apixaban, and ENGAGE AF-TIMI with edoxaban).[23–28] NOACs were non-inferior or superior to warfarin with regard to prevention of stroke and SEE and had a comparable or significantly reduced major bleeding risk compared to warfarin in patients with NVAF. Table 3 shows the design and main outcomes of those pivotal clinical studies.

Treatment of VTE and reduction of the risk of recurrence of VTE

Each NOAC was compared to conventional anticoagulation therapy (eg, parenteral anticoagulant followed by VKA) for treatment of VTE in confirmatory Phase III global clinical studies (eg, RE-COVER and RE-COVER II with dabigatran EINSTEIN-DVT and EINSTEIN-PE with rivaroxaban, AMPLIFY with apixaban, HOKUSAI-VTE with edoxaban).[29,30,32–34,36] NOACs were as effective as the parenteral/VKA regimen and had comparable or significantly reduced major or clinically relevant non-major

Table 2 Outline of the pharmacological properties of conventional treatments and NOACs

Generic name	Conventional treatments				NOACs			
	LMWH[18–21]	UFH[21]	Fondaparinux[22]	Warfarin[17]	Dabigatran[40,41]	Rivaroxaban[42,43]	Apixaban[44,45]	Edoxaban[46,47]
Administration rout	Parenteral	Parenteral	Parenteral	Oral	Oral	Oral	Oral	Oral
Inhibition site	Factor IIa, Xa	Factor IIa, Xa	Factor Xa	Prothrombin, Factor VII, IX, X	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability	Completely absorbed	20–30%	Completely absorbed	Completely absorbed	3–7%	80–100%	50%	62%
Time to peak concentration level	–	–	2–3 hrs	4 hrs (Time to peak effect: 72 – 96 hrs)	1 hr	2–4 hrs	3–4 hrs	1–2 hrs
Half-life	1.5–4.5 hrs	30–60 mins	17–21 hrs	40 hrs	12–17 hrs	5–13 hrs	12 hrs	10–14 hrs
Clearance	Urinary	Urinary	Urinary (77%)	Urinary (92%)	Urinary (80%)	Urinary (67%, 33% active), fecal (33%)	Urinary (27%), biliary/intestinal (73%)	Urinary (50%), biliary/intestinal (50%)
Laboratory monitoring	Not required	Essential	Not required	Essential	Not required	Not required	Not required	Not required
Reversal agents	Protamine sulfate	Protamine sulfate	Not available	Vitamin K	Idarucizumab	Andexanet alfa51	Andexanet alfa51	Not available

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Table 3 Comparison of the design and main outcomes of the pivotal clinical studies for reduction of stroke risk in NVAF

Generic name	**Dabigatran**			**Rivaroxaban**		**Apixaban**		**Edoxaban**		
Study	**RE-LY**[23–25]			**ROCKET-AF**[26]		**ARISTOTLE**[27]		**ENGAGE AF-TIMI 48**[28]		
Design	Randomized, open-label for warfarin, blinded for dabigatran			Randomized, double-blind		Randomized, double-blind		Randomized, double-blind		
Follow up period, years	2.0			1.9		1.8		2.8		
Warfarin, TTR, % (mean)	64			55		62		65		
Dose group	Warfarin	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60 mg	Edoxaban 30 mg
Number of patients	6022	6076	6015	7133	7131	9081	9120	7036	7035	7034
Age, years	71.6±8.6 (mean ± SD)	71.5±8.8 (mean ± SD)	71.4±8.6 (mean ± SD)	73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]		72 (64–78) [median (interquartile range)]		
Male sex, %	63.3	63.2	64.3	60.3	60.3	65.0	64.5	62.5	62.1	61.2
$CHADS_2$, score (mean ±SD)	2.1±1.1	2.2±1.2	2.1±1.1	3.5±1.0	3.5±1.0	2.1±1.1	2.1±1.1	2.8±1.0	2.8±1.0	2.8±1.0
	Event rate, %/year	Event rate, %/year (RR vs Warfarin)	Event rate, %/year (RR vs Warfarin)	Event rate, %/year	Event rate, %/year (HR vs Warfarin)	Event rate, %/year	Event rate, %/year (HR vs Warfarin)	Event rate, %/year	Event rate, %/year (HR vs Warfarin)	Event rate, %/year (HR vs Warfarin)
Stroke/ systemic embolism[a]	1.72	1.12 (0.65, 0.52–0.81; *P* for NI and SUP <0.001)	1.54 (0.89, 0.73–1.09; *P* for NI <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for NI <0.001, *P* for SUP =0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* for NI <0.001, *P* for SUP =0.01)	1.80	1.57 (0.87, 0.73–1.04; *P* for NI <0.001, *P* for SUP =0.08)	2.04 (1.13, 0.96–1.34; *P* for NI =0.005, *P* for SUP =0.10)

(*Continued*)

Table 3 (Continued).

Generic name	Dabigatran			Rivaroxaban		Apixaban		Edoxaban		
Study	RE-LY[23–25]			ROCKET-AF[26]		ARISTOTLE[27]		ENGAGE AF-TIMI 48[28]		
NNT/year[122](95% CI)	–	182 (118 to 397)	–	–	367 (−1031 to 161)	–	303 (169 to 1501)	–	481 (−2398 to 219)	–
Major bleeding[b]	3.61	3.40 (0.94, 0.82–1.08; P=0.41)	2.92 (0.80, 0.70–0.93; P=0.003)	3.4	3.6 (1.04, 0.90–1.20; P=0.58)	3.09	2.13 (0.69, 0.60–0.80; P<0.001)	3.43	2.75 (0.80, 0.71–0.91; P<0.001)	1.61 (0.47, 0.41–0.55; P<0.001)
NNT/year[122] (95% CI)	–	475(−427 to 153)	–	–	−1166 (−178 to 256)	–	120 (85 to 200)	–	185 (119 to 420)	–

Notes: [a]This efficacy outcome was analyzed in the intention-to-treat population. [b]This safety outcome was analyzed in the safety population.
Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke (double weight); HR, hazard ratio; NI, non-inferiority; NNT, number needed to treat; NVAF, non-valvular atrial fibrillation; RR, relative risk; SUP, superiority; TTR, time in therapeutic range.

(CRNM) bleeding risk compared to the parenteral/VKA regimen for treatment of VTE. In particular, rivaroxaban and apixaban had efficacy and safety as a single oral drug without initial treatment with a parenteral anticoagulant. Table 4 shows the design and main outcomes of those pivotal clinical studies.

Three NOACs were evaluated for extended treatment of VTE in comparison with warfarin or placebo in patients already treated with anticoagulant for a specified period in separate extension clinical studies (eg, RE-MEDY and RE-SONATE with dabigatran, EINSTEIN-Extension with rivaroxaban, AMPLIFY-EXT with apixaban).[31,32,35] NOACs were as effective as warfarin or superior to placebo for secondary prevention of VTE after initial treatment. Although no extra extension clinical study with edoxaban existed, the HOKUSAI-VTE study with clinical-practice-based design (eg, patients with broad spectrum, various treatment duration for each patient, active comparator) and statistical analysis (eg, the primary efficacy outcome was confirmed in the modified intention-to-treat population for both of the overall study period and the on-treatment period) covered the evaluation of the extended treatment.[37,52,53] Table 5 shows the design and main outcomes of those pivotal clinical studies.

Challenges of using NOACs in specific patient populations

The optimal dose of NOACs in Asian patients with NVAF

Dabigatran

In the RE-LY study, both doses of dabigatran 110 mg and 150 mg showed non-inferior or superior efficacy and favorable safety compared to warfarin.[23–25] The European Medicines Agency (EMA), the Korean Ministry of Food and Drug Safety (MFDS), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) approved the 150-mg dose as a full-dose and the 110-mg dose as a reduced-dose for fragile patients (eg, geriatric, lower body weight, increased risk of bleeding, moderate renal impairment, and concomitant use of the P-glycoprotein 1 (P-gp) inhibitor).[41,54,55] Unlike the other medical regulatory agencies, the US Food and Drug Administration (FDA) did not approve the 110-mg dose.[37] The FDA emphasized the result of the RE-LY study that the dabigatran 150-mg dose was superior to warfarin for efficacy and similar for bleeding, but the 110-mg dose was non-inferior to warfarin for efficacy and caused less bleeding.[56] The events of ischemic stroke in the 110-mg

Table 4 Comparison of the design and main outcomes of the pivotal clinical studies for the treatment of VTE

Generic name	Dabigatran				Rivaroxaban				Apixaban		Edoxaban	
Study	**RE-COVER**[29]		**RE-COVER II**[30]		**EINSTEIN-DVT**[32]		**EINSTEIN-PE**[33]		**AMPLIFY**[34]		**HOKUSAI-VTE**[36]	
Design	randomized, double blind, non-inferiority		randomized, double blind, non-inferiority		randomized, open-label, non-inferiority		randomized, open-label, non-inferiority		randomized, double blind, non-inferiority		randomized, double-blind, non-inferiority	
Treatment duration	6 months		6 months		3, 6, or 12 months		3, 6, or 12 months		6 months		Variable, 3–12 months	
Warfarin, TTR, % (mean)	60		57		58		63		61		64	
Dose group	Parenteral therapy /Warfarin	Parenteral therapy /Dabigatran	Parenteral therapy /Warfarin	Parenteral therapy /Dabigatran	Enoxaparin /VKA	Rivaroxaban	Enoxaparin /VKA	Rivaroxaban	Enoxaparin /Warfarin	Apixaban	Parenteral therapy /Warfarin	Parenteral therapy /Edoxaban
Number of patients	1265	1274	1289	1279	1718	1731	2413	2419	2704	2691	4122	4118
DVT only, %	68.6	69.1	67.8	68.5	–	–	–	–	65.9	65.0	59.5	59.9
PE only, %	21.4	21.2	23.1	23.3	–	–	75.5	74.9	25.2	25.2	30.7	30.1
Both DVT and PE, %	9.8	9.5	9.1	8.1	–	–	24.5	25.1	8.3	9.4	9.8	10.0
	Rate of patients, %	Rate of patients, % (HR with dabigatran)	Rate of patients, %	Rate of patients, % (HR with dabigatran)	Rate of patients, %	Rate of patients, % (HR with rivaroxaban)	Rate of patients, %	Rate of patients, % (HR with rivaroxaban)	Rate of patients, %	Rate of patients, % (RR with apixaban)	Rate of patients, %	Rate of patients, % (HR with edoxaban)
Recurrent VTE or fatal VTE	2.1	2.4 (1.10, 0.65–1.84; *P* for NI <0.001)	2.2	2.3 (1.08, 0.64–1.80; *P* for NI <0.001)	3.0	2.1 (0.68, 0.44–1.04; *P* for NI <0.001, *P* for SUP =0.08)	1.8	2.1 (1.12, 0.75–1.68; *P* for NI =0.003, *P* for SUP =0.57)	2.7	2.3 (0.84, 0.60–1.18; *P* for NI <0.001)	3.5	3.2 (0.89, 0.70–1.13; *P* for NI <0.001)

(*Continued*)

Table 4 (Continued).

Generic name	Dabigatran			Rivaroxaban			Apixaban		Edoxaban	
Study	**RE-COVER**[29]		**RE-COVER II**[30]	**EINSTEIN-DVT**[32]		**EINSTEIN-PE**[33]	**AMPLIFY**[34]		**HOKUSAI-VTE**[36]	
Major bleeding	1.9	1.6 (0.82, 0.45–1.48)	1.7	1.2	0.8 (0.65, 0.33–1.30; *P*=0.21)	2.2	1.1 (0.49, 0.31–0.79; *P*=0.003)	1.8	0.6 (0.31, 0.17–0.55; *P* for SUP <0.001)	1.6	1.4 (0.84, 0.59–1.21; *P* for SUP =0.35)
Major or CRNM bleeding	8.8	5.6 (0.63, 0.47–0.84; *P*=0.002)	7.9	8.1	8.1 (0.97, 0.76–1.22; *P*=0.77)	11.4	10.3 (0.90, 0.76–1.07; *P*=0.23)	9.7	4.3 (0.44, 0.36–0.55; *P*<0.001)	10.3	8.5 (0.81, 0.71–0.94; *P* for SUP =0.004)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; CRNM, clinically relevant non-major; HR, hazard ratio; RR, relative risk; NI, non-inferiority; SUP, superiority; TTR, time in therapeutic range; VTE, venous thromboembolism.

group (1.3% per year) outnumbered the events in the warfarin group (1.1% per year).[56] Moreover, the post-hoc analysis showed that the 150-mg dose was statistically superior to the 110-mg dose in preventing stroke, and the exploratory analysis by reviewers in the US FDA confirmed subjects who experienced a major bleeding event and subsequently received the higher dabigatran dose were at no greater risk of experiencing a subsequent major bleeding event than those receiving the lower dose.[37,56,57] Therefore, the US FDA judged approval of the 110-mg dose provides the average patient with the option of taking a dose with reduced efficacy, leading to additional strokes and disability.[56] Finally, the US FDA approved only the 150-mg dose.[37,57] In not approving the 110-mg dose, the US FDA limited the dosing options for fragile patients (eg, severe renal impairment, moderate renal impairment with concomitant use of the P-gp inhibitor). Therefore, the US FDA recommended a dose of 75 mg to provide these patient populations with access to dabigatran, based not on efficacy and safety data, but on pharmacokinetic and pharmacodynamic modeling.[37,57]

Recently, considerable data on the optimal dabigatran dose for real-world patients have been published. A post-hoc simulation analysis of the RE-LY study revealed that patients' efficacy and safety outcomes using the EU label information would be more favorable compared to warfarin, and it supported the EU label information of dabigatran.[58] Furthermore, another prospective observational study in Canada supported approval of both dabigatran doses examined in the RE-LY study because drug exposures were observed to be similar in patients treated with either 110- or 150-mg dose as indicated in the label information.[59]

On the other hand, patients treated with the 75-mg dose, approved only in the US for patients with severe renal impairment on the basis of pharmacokinetic modeling, had no significantly different outcomes (eg, effect on risk of ischemic stroke, major gastrointestinal bleeding, and mortality) compared to patients with warfarin except for a lower risk of intracranial hemorrhage in an observational study using the US Medicare database.[60] This result suggested that the 75-mg dose was suboptimal or patients were treated off-label and under-dosed with the 75-mg dose.[60] Moreover, there is a recommendation that the US FDA should reconsider approving the 110-mg dose to give flexible choices to patients who would benefit most by this intermediate dose.[61]

Regarding the optimal dose in Asians, a retrospective study to determine the optimal dose of dabigatran in

Table 5 Comparison of the design and main outcomes of the pivotal clinical studies for secondary prevention of VTE

Generic name	**Dabigatran**				**Rivaroxaban**		**Apixaban**		
Study	**RE-MEDY**[31]		**RE-SONATE**[31]		**EINSTEIN-Extension**[32]		**AMPLIFY-EXT**[35]		
Design	randomized, double blind, active control, non-inferiority		randomized, double blind, placebo control, superiority		randomized, double blind, placebo control, superiority		randomized, double blind, placebo control, superiority		
Treatment duration	6–36 months		6 months		6–12 months		12 months		
Dose group	Warfarin	Dabigatran	Placebo	Dabigatran	Placebo	Rivaroxaban	Placebo	Apixaban 5 mg	Apixaban 2.5 mg
Number of patients	1426	1430	662	681	594	602	829	813	840
DVT only, %	64.7	65.6	66.6	63.3	–	–	–	–	–
PE only, %	23.5	22.7	26.9	26.9	–	–	–	–	–
Both DVT and PE, %	11.8	11.7	5.3	6.9	–	–	–	–	–
	Rate of patients, %	Rate of patients, % (HR with dabigatran)	Rate of patients, %	Rate of patients, % (HR with dabigatran)	Rate of patients, %	Rate of patients, % (HR with rivaroxaban)	Rate of patients, %	Rate of patients, % (RR with apixaban)	Rate of patients, % (RR with apixaban)
Recurrent VTE or fatal VTE	1.3	1.8 (1.44, 0.78–2.64; *P* for NI =0.01)	5.6	0.4 (0.08, 0.02–0.25; *P* for SUP <0.001)	7.1	1.3 (0.18, 0.09–0.39, *P* for SUP <0.001)	8.8	1.7 (0.20, 0.11–0.34)	1.7 (0.19,0.11–0.33)
Major bleeding	1.8	0.9 (0.52, 0.27–1.02; *P*=0.06)	0	0.3 (Not estimated; *P*=1.0)	0	0.7 (Not estimated; *P*=0.11)	0.5	0.1 (0.25, 0.03–2.24)	0.2 (0.49, 0.09–2.64)
Major or CRNM bleeding	10.2	5.6 (0.54, 0.41–0.71; *P*<0.001)	1.8	5.3 (2.92, 1.52–5.60; *P*=0.001)	1.2	6.0 (5.19, 2.3–11.7; *P*<0.001)	2.7	4.3 (1.62, 0.96–2.73)	3.2 (1.20, 0.69–2.10)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; CRNM, clinically relevant non-major; HR, hazard ratio; RR, relative risk; NI, non-inferiority; SUP, superiority; VTE, venous thromboembolism.

Korean patients with NVAF suggested a fixed dose of 110 mg might be sufficient regardless of dose-reduction criteria based on the comparable efficacy and favorable safety of the 110-mg dose to 150-mg dose.[62] This finding in Korea is consistent with the observational study of real-world data in Taiwan that did not show a benefit of the 150-mg dose over the 110-mg dose.[63] Also, those results support the real-world clinical practice for dabigatran in Asia that the 110-mg dose is preferred because of a concern about bleeding risk in Asian patients with a higher dose.[62,63]

The recommendation for dabigatran dose reduction to 110 mg in fragile patients is supported by real-world clinical data as well as the RE-LY study. However, clinical data on the optimal dabigatran dose in Asian patients with NVAF are not sufficient. More data are required to evaluate whether dabigatran 150 mg or 110 mg is a desirable dose in Asian patients. Additionally, we should also consider that subgroup analyses by Asian and non-Asian populations in the RE-LY study showed that favorable treatment effects of both doses of dabigatran compared to warfarin did not show a significant difference between Asian and non-Asian patients.[64] The US FDA has maintained the approved dabigatran regimen without a compromised intermediate dose and more intensive treatment is required for stroke prevention in Asia where the burden of AF is expected to increase.[6]

Rivaroxaban

The smaller body size and lower renal clearance in Asians compared to non-Asians, as well as ethnic differences in pharmacokinetic and pharmacodynamic features, render physicians to prefer reduced-dose NOACs for their patients.[62,63,65] Mirroring that tendency, especially among Asians, reduced-dose rivaroxaban has been used more frequently than the full-dose in patients without dose-reduction criteria (eg, renal dysfunction).[65,66] However, concerns remain about the insufficient net clinical benefit of off-label underdosing and the optimal dose of rivaroxaban for Asian NVAF patients.[66,67]

Rivaroxaban was approved at a lower dose in Japan than in the US, Europe, and Korea as shown in Table 1. Distribution of rivaroxaban with the 15-mg dose in Japanese patients was predicted to be equivalent to that in Caucasian patients with the 20-mg dose in pharmacokinetic modeling data.[37,68] Therefore, Japanese patients were not included in the global, pivotal ROCKET-AF study but were instead enrolled in a domestic Phase III clinical study with a lower dose because of the risk of bleeding complications with the full dose.[37,39] Although the Japanese PMDA approved the lower dose based on the results of that local study, it was underpowered due to small sample size and showed borderline statistical significance for the primary efficacy endpoint; thus, it is uncertain that using a lower dose can be generalized to the entire Asian patient population.[66]

A Taiwanese nationwide cohort study showed that almost 95% of patients received reduced-dose rivaroxaban (eg, 10–15 mg once daily) regardless of renal function and this reduced-dose had a significantly lower risk of stroke, major bleeding, intracranial hemorrhage, and mortality when compared with warfarin.[69] This study did not show a trend of insufficient efficacy in patients who took reduced-dose rivaroxaban. Furthermore, this result from reduced-dose rivaroxaban was comparable to the subgroup analysis of Asians from the ROCKET-AF study using full-dose rivaroxaban.[69] This study had a limit to determine whether those patients with reduced-dose rivaroxaban were correctly adjusted by dose-reduction criteria or were off-label underdosed.[69]

Meanwhile, a retrospective, observational study using the Korean National Health Insurance Service (NHIS) database revealed that both on-label 20 mg and off-label 15 mg were associated with a lower risk of stroke, major bleeding, and all-cause death compared with warfarin in patients with NVAF and normal or mildly impaired renal function.[66] On-label 20 mg showed a nonsignificant trend toward lower risks of stroke, hospitalization for gastrointestinal bleeding or major bleeding, and all-cause death compared with off-label 15 mg.[66] Overall, on-label 20 mg showed significantly better results for the composite clinical outcome compared with off-label 15 mg.[66] On the other hand, another retrospective, observational study using the Korean NHIS database demonstrated that off-label use of reduced-dose rivaroxaban had comparable efficacy and safety outcomes compared to full-dose rivaroxaban in patients who were subject to full-dose rivaroxaban.[65] However, both studies should be interpreted cautiously due to patient selection bias (eg, elderly patients or patients with multimorbidity or high thromboembolic risk were not included).[65,66]

Although several studies were conducted in various Asian regions to examine the efficacy and safety of full- and reduced-dose rivaroxaban, the optimal dose for Asian patients with NVAF remains still uncertain. Considering the highest proportion of patients treated with rivaroxaban among patients treated with NOAC in Asia, issues related

to the optimal dose of rivaroxaban for Asian patients are important.[65,66,69] For that reason, further studies are required to identify the desirable dose of rivaroxaban; careful evaluation of the individual's thromboembolic and bleeding risk is needed at the dose selection level.[65,66,69]

Apixaban

Among the four NOACs, only apixaban has an identical dosing regimen for patients with NVAF in both Western and Asian countries. Unlike dabigatran and rivaroxaban, recent studies indicated that off-label underdosing of apixaban was associated with less clinical benefit over warfarin in Asian patients.[65] In a retrospective, observational study using the Korean NHIS database, reduced-dose apixaban in patients whom the full-dose might be indicated showed a notable reduction in efficacy and loss of superiority over warfarin, although the safety profile was better in comparison with warfarin.[65] In addition, this finding in Korea is supported by the result from a study using the US administrative database that off-label underdosing of apixaban had a considerably higher risk of stroke but a similar risk of major bleeding compared with full-dose apixaban.[70] These findings suggest unjustified underdosing of apixaban causes insufficient stroke prevention without safety benefits.[65,70]

Edoxaban

Real-world clinical data are required to evaluate edoxaban in patients with NVAF with supranormal renal function to determine the optimal dose of edoxaban needed to protect patients against stroke. In the ENGAGE AF-TIMI study, the efficacy of edoxaban decreased with increasing CrCL as compared to well-managed warfarin and the medical regulatory agencies adopted different approaches regarding this issue.[37] The US FDA included a warning on the label information and mentioned that patients with CrCL >95 mL/min should not use edoxaban as a risk mitigation strategy.[37,71] In contrast, the EMA did not prevent edoxaban use in patients with supranormal renal function but emphasized edoxaban should be used only after a careful evaluation of each individual's thromboembolic and bleeding risk.[37,47] An additional study entitled "Evaluation of Lixiana (edoxaban) in patients with non-valvular atrial fibrillation and high creatinine clearance" is ongoing in Europe to investigate whether a higher dose of edoxaban advances prevention against stroke in those patients as a measure of the risk management plan (RMP).[72]

The Korean MFDS took a comparable stance with the EMA on this issue.[37,53] However, Korea could not be included in that post-authorization study because the approval application for edoxaban was submitted prior to the introduction of the RMP system there. Recently, the first study was published reporting the efficacy and safety of edoxaban compared with warfarin, focusing on Korean patients with NVAF and good kidney function.[73] In this retrospective cohort study using the Korean NHIS data, edoxaban showed a statistically nonsignificant trend toward reduced stroke risk in both patients with CrCl >80–95 mL/min and >95 mL/min compared with warfarin, although the small sample size and short-term follow-up duration may have caused some statistical nonsignificance in the analysis results.[73] Nevertheless, the recent Korean AF Management Guideline prefers dabigatran, rivaroxaban, and apixaban to edoxaban in NVAF patients with CrCL >90mL/min.[74] Approved label information of edoxaban in Japan where it was first released for prevention of stroke in patients with NVAF has no precaution related to decreased efficacy with increasing CrCL.[75] Therefore, Korean and Japanese regulatory agencies should notice the upcoming results of that post-authorization study and evaluate the need to modify the label information and clinical guidelines of edoxaban.

Choice of NOAC in NVAF patients presenting with ACS and/or undergoing PCI

Up to one-third of all patients with AF eventually develop vascular disease, and up to one-fifth of all patients with AF are likely to undergo stenting at some point.[76] Therefore, it is important to carefully consider antithrombotic therapies by balancing their associated bleeding risk, stroke risk, and acute coronary syndrome (ACS) risk.[14] Conventional triple antithrombotic therapies, including warfarin, clopidogrel, and aspirin, are associated with high bleeding risk.[77–79] The WOEST study evaluated the safety and efficacy of clopidogrel versus clopidogrel plus aspirin in patients receiving OACs and undergoing percutaneous coronary intervention (PCI) revealing that dual therapy is associated with a lower bleeding risk than triple therapy without an increase of thrombosis risk.[80] Although this study was too small to evaluate thrombotic outcomes, it supports the hypothesis that dual therapy with OAC and clopidogrel may be an alternative to triple therapy in AF patients undergoing PCI.[80]

There was a subgroup analysis of RE-LY study with dabigatran suggesting that the benefits of NOACs are not affected regarding efficacy and safety compared to warfarin in the setting of triple therapy.[81] However, until recently most guidelines limited adding NOACs to antiplatelets in patients with NVAF with ACS and/or PCI with stenting due to limited clinical evidence.[14,38,82] Now, the most recently

revised guidelines are recommending NOACs over a VKA based on the PIONEER AF-PCI and the RE-DUAL PCI study.[83–85] Both studies showed lower bleeding risk among patients who received NOAC and a $P2Y_{12}$ inhibitor than among those who received triple therapy, with no apparent increase in cardiovascular events, although the studies were not powered to evaluate them.[77,78]

Each of the four NOACs has been studied or is being assessed for combination therapy with antiplatelets in NVAF patients presenting with ACS and/or undergoing PCI. The PIONEER AF-PCI study with rivaroxaban showed that two rivaroxaban groups significantly lowered the rates of clinically significant bleeding than the triple therapy group (group 1: rivaroxaban 15 mg once daily + $P2Y_{12}$ inhibitor for 12 months, group 2: rivaroxaban 2.5 mg twice daily + dual antiplatelet therapy for 1, 6, or 12 months, group 3: VKA + dual antiplatelet therapy for 1, 6, or 12 months).[77] It is important to note that both doses of rivaroxaban used in this study were lower than dose known to reduce the risk of stroke and SEE in NVAF.[77,83]

Two different dabigatran dose regimens (either 110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor significantly lowered the major or CRNM bleeding risk more than the triple therapy in the RE-DUAL PCI study.[78] Furthermore, the combined dual therapy group with dabigatran and a $P2Y_{12}$ inhibitor was noninferior regarding the cardiovascular outcomes in the triple therapy group.[78] Although this study was not powered to access the risk of thrombosis by dabigatran dose, it revealed that both dabigatran doses balanced the risk of bleeding with the prevention of thromboembolic events in NVAF patients presenting with ACS and/or undergoing PCI and it proved the concept of the WOEST study with greater statistical power.[78]

In the AUGUSTUS study, a dose of apixaban with proven efficacy for reducing stroke risk in NVAF patients significantly lowered the rates of major or CRNM bleeding without significant differences in ischemic events; this was compared to a regimen of a VKA, aspirin, or both in patients with AF and recent ACS or PCI treated with a $P2Y_{12}$ inhibitor.[79] Moreover, this study directly evaluated the benefits and risks of omitting aspirin with both apixaban and VKA and revealed that the effect of dropping aspirin on the rate of bleeding events is greater than the benefit of using apixaban instead of a VKA.[79]

The ongoing ENTRUST AF-PCI study of edoxaban (NCT02866175, EudraCT Number: 2016–002683-14) is expected to provide appropriate approaches for antithrombotic therapy in patients in whom both edoxaban and antiplatelet treatment are indicated.[86] The intensity of NOAC and antiplatelet treatment and the duration of antiplatelet treatment should be adjusted according to the bleeding and thrombotic risk profiles of the individual patient.[84]

Use of NOACs in dialysis patients with NVAF

The risk of NVAF, ischemic stroke, and serious bleeding increases more in patients with chronic kidney disease (CKD) compared to people with normal renal function, and the relative risk of each of them increases progressively with advancing CKD, being greatest in dialysis patients.[87] Furthermore, NVAF in dialysis patients increases the risk of mortality and stroke.[88]

However, although VKAs have been used as prophylaxis against embolic complications of AF in the general population and in early stage CKD, the efficacy is unclear and the bleeding risk increases significantly in severe CKD, particularly in dialysis patients.[87] Furthermore, there are no clinical data that demonstrate the efficacy and safety of NOACs in dialysis patients because these severe CKD patients were excluded in the premarketing pivotal clinical studies of NOACs.[23,26–28,87] Increased bleeding risk and unclear efficacy of OACs in dialysis patients with AF should be considered when making decisions on whether to give OACs for these patients.[89]

A recent "Kidney Disease: Improving Global Outcomes Controversies Conference" suggests that if dialysis patients with NVAF require OAC for stroke prevention, then an apixaban 2.5 mg twice-daily regimen could be considered while awaiting more clinical efficacy and safety data.[87,90] NOACs may have advantages over VKAs in dialysis patients with NVAF, although two ongoing studies of apixaban versus VKA (AXADIA and RENAL-AF, NCT02933697, and NCT02942407) will evaluate the relative merits of NOAC vs VKA.[89,90]

Option to use reduced- or full-dose NOACs in the extended treatment of VTE

Extended anticoagulant therapy for reducing VTE recurrence is accompanied by bleeding risk and leading to hesitate for continuing anticoagulant therapy beyond 6–12 months.[91] Therefore, using lower-dose anticoagulant therapy can be considered to lower the bleeding risk when treatment is extended.[92] Several studies using reduced-dose NOACs revealed that they may effectively balance the benefit-to-risk profile with respect to recurrent VTE and bleeding when the risk of recurrent VTE decreases.[35,91,93]

In the AMPLIFY-EXT study, the risk of recurrent VTE was significantly reduced with extended anticoagulation with apixaban at either a full-dose (5 mg twice daily) or a reduced-dose

(2.5 mg twice daily) than with placebo, without a significant increase in bleeding rates.[35] In the EINSTEIN CHOICE study, extended anticoagulation with rivaroxaban at either a full-dose (20 mg once daily) for treatment and prophylaxis of VTE or a reduced-dose (10 mg once daily) significantly lowered the risk of recurrent VTE without increasing the bleeding rate.[91] Meta-analysis of these two similar extension studies suggests that reduced-dose NOACs are as effective as full-dose DOACs in reducing the risk of recurrent thrombotic events at 1 year without a significant increase in bleeding as compared with aspirin or placebo, unlike full-dose DOACs.[93] Therefore, reduced-dose NOACs may be considered as an attractive option for long-term therapy after VTE in patients in whom there is clinical equivalence for continuation or cessation of anticoagulant treatment.[93]

However, there are several limitations related to the use of reduced-dose NOACs to patients with VTE. Both extension studies treated patients for up to 12 months; thus, the safety and efficacy of reduced-dose NOACs is unknown beyond 1 year.[35,91,93] Furthermore, patients requiring ongoing anticoagulant therapy with therapeutic doses (eg, active cancer or recurrent VTE) were excluded; thus, it is unknown whether reduced-dose NOACs would be sufficient to prevent recurrence in such patients.[35,91,93] Additionally, it is unclear whether the meta-analysis results are applicable to all NOACs as a class effect or only to apixaban and rivaroxaban.[93] Additional studies are needed to determine the utility of continuing treatment with reduced-dose NOACs for a longer period, and in patients with an indication for ongoing anticoagulant therapy.[35,91,93]

Regarding the approved dose of rivaroxaban for preventing recurrent VTE, the maintenance dose after initial treatment in Japan is lower than in Korea as shown in Table 1. The Korean MFDS approved the maintenance dose based on the global, pivotal EINSTEIN-Extension study but the Japanese PMDA approved the lower dose based on a separate domestic study because the Japanese clinical guidelines recommended using lower-intensity anticoagulant therapy because of the bleeding risk.[37,94,95] Considering concerns about the bleeding risk with full-dose rivaroxaban in Asian patients, the optimal thromboprophylactic dose reflecting the characteristics of Korean VTE patients should be evaluated as in Japan.

Use of NOACs in patients with cancer-associated VTE

The risk for VTE is 4-fold higher in patients with cancer alone and the risk is higher more than 6-fold in cancer patients receiving chemotherapy as compared to healthy people.[96] Moreover, the risk of recurrent VTE is 2–5 times greater during anticoagulant treatment in patients with cancer than those without cancer and the risk of serious bleeding is similarly 2–6 times greater.[97] Therefore, treatment and secondary prevention of VTE with indefinite anticoagulant treatment are indispensable in patients with cancer-associated VTE (CAT).[16] Current clinical practice guidelines recommend administration of LMWH in the acute phase and the first 3–6 months as first-line therapy because indirect comparison suggests that NOACs are less effective than LMWH in patients with VTE and cancer.[15,16,98] However, the preferable treatment after the first 6 months is unclear, and no preference has been established for either LMWH or VKA or NOAC after the first 6 months.

NOACs have a number of advantages including oral administration, lack of interactions with foods or other medicines, and no need for monitoring drug levels, whereas injection of more expensive LMWH can cause pain and bruising at the injection site, and result in adverse effects like heparin-induced thrombocytopenia in patients with cancer.[99] However, limited evidence is available to confirm the efficacy and safety of NOACs in patients with VTE and cancer because these patients were excluded from the pre-marketing pivotal clinical studies and few cancer patients with a low risk of recurrent VTE and major bleeding were included in those clinical studies.[29,30,32–34,36] Therefore, it was unclear previously whether NOACs could be used safely in patients with CAT.[99] However, recently, several prospective clinical studies comparing NOACs with LMWH directly resolved uncertainties about using NOACs in these patients.

In the open-label ADAM VTE Trial, a fixed oral apixaban dose showed a very low rate of bleeding events with a significantly lower rate of VTE recurrence and better quality of life (eg, concern for excess bruising, stress, irritation, burden of delivery, and overall satisfaction with anticoagulant therapy) compared to subcutaneous injections of dalteparin at 6 months.[100] In the open-label Hokusai VTE Cancer study, a fixed oral edoxaban dose was noninferior to parenteral dalteparin with regard to the composite primary outcome of recurrent VTE or major bleeding for up to 12 months.[101] However, the rate of major bleeding as a secondary outcome was significantly higher with edoxaban compared to dalteparin due to the higher rate of upper gastrointestinal (GI) bleeding in patients with GI cancer.[101] In the open-label, pilot SELECT-D study, a fixed oral rivaroxaban dose was related not only to relatively low VTE recurrence within 6 months but to a 3-fold relative increase in CRNM bleeding compared with dalteparin.[102] Patients with

esophageal or gastroesophageal cancer experienced more rivaroxaban-associated major bleeding because most of the major and CRNM bleeding occurred in GI.[102] Even though these studies had some limitations including their open-label designs, the relatively small number of enrolled patients, and not powered to evaluate the risk of recurrent VTE, they support the clinical use of NOACs for the acute treatment of VTE in patients with CAT.[100–102] A recently published meta-analysis based on these studies showed that NOACs (especially direct Xa inhibitors) were more effective to reduce VTE recurrence for up to 6 months with better compliance when compared to LMWH; however, they had a significantly higher rate of major bleeding as well as a trend toward more CRNM bleeding.[103] Thus, NOACs can be potential alternatives to LMWH in treating CAT despite the increased risk of CRNM bleeding.[104]

Although chemotherapy is a risk factor of VTE, routine thromboprophylaxis in ambulatory patients undergoing chemotherapy is not clinically recommended because LMWH or VKA are not effective for VTE risk reduction.[16,105–107] They are associated with an increased major bleeding risk, and parenteral thromboprophylaxis is not only expensive but also inconveniently requires daily injections.[16,105–107] However, two recently published studies evaluating oral direct Xa inhibitors may provide clinically valuable information for reducing the risk of VTE in ambulatory patients with cancer at intermediate-to-high risk for VTE.[107,108]

In the placebo-controlled, double-blind CASSINI study, rivaroxaban did not show a significantly lower rate of VTE or death due to VTE for up to 6 months although these events occurred in a lower percentage of patients in the rivaroxaban group.[108] However, during the intervention period, defined as the time from receipt of the first dose of rivaroxaban or placebo to the last dose plus 2 days, rivaroxaban resulted in a more favorable benefit than placebo with regard to VTE or VTE-related death, with a low incidence of major bleeding.[108] In the placebo-controlled, double-blind AVERT study, thromboprophylaxis with apixaban resulted in a significantly lower VTE rate than placebo in the 6-month trial period.[107] The major bleeding rate was significantly higher with apixaban than with placebo, but the rate of severe major bleeding events was similar in the apixaban group and the placebo group.[107] Although these studies had a small sample size and did not conduct subgroup analysis by individual tumor types or chemotherapy regimens, they support the benefit of antithrombotic prophylaxis against bleeding risk with oral direct Xa inhibitors in ambulatory cancer patients receiving chemotherapy at intermediate-to-high risk for VTE.[107,108]

Taken together, we have enough experiences in using NOACs in cancer patients showing the benefit of antithrombotic treatment counterbalanced the bleeding risk with NOACs. Therefore, NOACs can be considered in patients with cancer after careful evaluation of thrombotic and bleeding risk, patient's underlying disease, and treatment preference. Currently, some challenges of CAT management exist due to differences in cancer types or chemotherapy regimens and comorbidities including renal impairment, GI problems, and thrombocytopenia; hence, more studies with various designs and a much larger sample are required to address these challenges.[104] Furthermore, all studies previously mentioned have evaluated oral direct Xa inhibitors; thus, findings and conclusions from these studies may not be extrapolated to a direct thrombin inhibitor.

Adherence and persistence of NOACs

Poor adherence and persistence (that is, adherence during the whole treatment period) to anticoagulant medication may result in increased rates of both thromboembolism and bleeding as well as worse morbidity and mortality.[109,110] NOACs have an advantage of fixed oral dosing but also shorter half-lives than VKA and difficulty in checking adherence without blood level monitoring.[109,111]

Different dosing regimens among NOACs may impact on medication adherence; thus, individual patient preference should be considered in choosing a particular NOAC.[109] For VTE, rivaroxaban, and apixaban as a simple single-drug approach in initial treatment phase do not require previous treatment with parenteral anticoagulant, although dabigatran and edoxaban should be administered after parenteral anticoagulant for at least 5 days.[40–47] Therefore, rivaroxaban and apixaban should be recommended for patients avoiding or hesitating parenteral therapy. For patients with NVAF or VTE, rivaroxaban should be taken with food, unlike dabigatran, apixaban, and edoxan, which can be taken with or without food.[40–47] Rivaroxaban and edoxaban are administered once-daily (OD) but dabigatran and apixaban are dosed twice-daily (BID).[40–47]

However, reducing the dosing complexity and frequency from multiple dosing to OD dosing might not necessarily result in better adherence.[112–114] Furthermore, OD dosing might be more disadvantageous than BID dosing regarding non-adherence because a single missed OD dose equals to 2–3 consecutively missed doses from a BID dosing regimen.[109] Therefore, the Korean AF Management Guideline recommends that OD vs BID regimens should

not be considered as a primary factor in choosing a particular NOAC but considered with patient preference and situation (eg, on multiple medications).[74] In addition, a structured follow-up of patient adherence, evaluation of contributing risk factors for non-adherence, and sufficient patient education are necessary to enhance NOAC adherence in clinical practice.[74,109]

Switching to NOACs: focusing on the drug price and cost-effectiveness of NOACs

Although many patients have switched to NOACs, a significant proportion of patients remain on warfarin because of the high price of NOACs.[115] The drug price of each NOAC is much higher (23- to 70-fold) than that of warfarin in various countries as shown in Table 6.[116–119] Additional cost considerations affecting the choice of warfarin over NOACs include variability in reimbursement coverage. This section would examine a case of Korea to investigate whether economic factors and cost-effectiveness affect the use of DOACs.

In Korea, the high cost of NOACs contributed to strict reimbursement guidelines and preference of warfarin.[120] Before 2015, patients with NVAF with a history of thromboembolism or age ≥75 years or at least two of the following (heart failure, hypertension, diabetes, age 65–74 years, female gender, vascular disease) could take NOACs with reimbursement coverage only if warfarin was not suitable for these patients. In July 2015, reimbursement guidelines were revised to choose NOACs as the first therapy in these patients (Ministry of Health and Welfare notification No 2015–118, 29 June 2015). This drove a voluntarily decrease in the cost of NOACs and an increase in the prescription rate of NOACs between 2014 and 2015 (from 9% in 2014 to 38% in 2015).[121] Annual relative prescription rates of warfarin and LMWH for VTE decreased with NOACs with reimbursement coverage between 2012 and 2013 (warfarin, from 63.9% in 2012 to 42.6% in 2013; LMWH, from 25.8% in 2012 to 22.5% in 2013).[12] However, the reimbursement guidelines for VTE seem to remain strict in that patients with VTE can take NOACs only for 6 months with reimbursement coverage, and only the cost of warfarin can be reimbursed in Korea beyond 6 months (Ministry of Health and Welfare notification No 2012–173, 27 December 2012). Therefore, patients with a high risk of relapse, such as those with cancer, must pay the cost of NOACs by themselves after the first 6 months and the actual prescription rate of NOACs after the first 6 months cannot be identified using the Korean Health Insurance Review and Assessment Service (HIRA) databases.[12]

Absolute benefits and harms of NOACs in NVAF patients using the number needed to treat (NNT) and/or number needed to harm (NNH) were addressed in several reports including a study conducted by Kumana et al.[122] Kumana et al showed absolute benefits of NOACs for primary-outcome prevention were modest in terms of NNT/year value (eg, 182–481, Table 3) with greater acquisition costs compared to warfarin.[122] However, these findings should be considered with benefits from avoidance of INR monitoring and its impact on the quality of life, etc.[122] Therefore, we need to focus on the long-term cost-effectiveness of NOACs.

Table 6 Drug prices and reimbursement of OACs for patients with NVAF in the US, UK, Korea, and Japan

Oral anticoagulant	Dosage/day (mg)	US (cost/day, $)[116]	UK (cost/day, £)[117]	Korea (cost/day, $)[118]	Japan (cost/day, $)[119]
Warfarin tabs (X1 daily)	1 3 5	0.6 0.6 0.6	0.03 0.03 0.03	0.03[a] 0.06	0.09 0.18 0.27
Dabigatran caps (X2 daily)	300	16	1.7	2.2	5.1
Rivaroxaban tabs (X1 daily)	20	17	1.8	2.2	4.9[b]
Apixaban tabs (X2 daily)	10	17	1.9	2.2	4.8
Edoxaban tabs (X1 daily)	60	14	1.9	2.1	5.1
Reimbursement of NOACs[120]		Non-reimbursement	$CHADS_2$ score ≥1	$CHADS_2$ score ≥2	Full reimbursement

Notes: [a]Dosage/day (mg) =2; [b]Dosage/day (mg) =15.
Abbreviations: NOACs, non-vitamin K Oral Anticoagulants; OACs, oral Anticoagulants; UK, United Kingdom; US, United States; NVAF, non-valvular atrial fibrillation.

Table 7 Cost-effectiveness results of base case analyses for patients with NVAF receiving NOACs

	Study	Strategy	Cost($)[a]	QALYs	Incremental Costs($)	Incremental QALYs	ICER
2014	Lee et al.[123]	Warfarin	9280	6.77	reference		
		Rivaroxaban	12,550	7.03	3270	0.26	12,550
2014	Kim et al.[124]	Warfarin	8807	7.28	reference		
		Dabigatran	15,381	7.49	6574	0.21	18,711
2018	Kim et al.[125]	Warfarin	17,151	11.43	reference		
		Rivaroxaban	20,886	11.81	3735	0.38	9707

Notes: [a]All costs were calculated in Korean won (KRW). Therefore, they are converted into US dollar (1$ =1000 KRW).
Abbreviations: NOACs, non-vitamin K Oral Anticoagulants; NVAF, non-valvular atrial fibrillation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

To our knowledge, three studies assessed the cost-effectiveness of NOACs compared to warfarin in Korean patients as shown in Table 7. Both studies conducted by Lee et al and Kim et al obtained data (eg, the baseline of patients, clinical event rates, costs, etc.) based on the results of pivotal clinical trials, literature, research data, and interviews with health care professionals.[123,124] Another study conducted by Kim et al used specific real-world data from the Korean HIRA database.[125] All of these cost-effectiveness analyses demonstrate that NOACs, including other NOACs which are not evaluated in these studies, may be cost-effective alternatives to warfarin in Korean patients with NVAF.[123–125]

It is expected that annual prescription rates of NOACs in Korea will steadily increase, therefore, that the drug price of NOACs will be dropped by the "prescription rate-drug price interoperation policy."[121] Furthermore, generic drugs will emerge in the near future to expand the market of NOACs.[121] Cost-effective NOACs with lower drug prices will effectively reduce the burden of NVAF-related stroke in Asia where the burden of AF is expected to increase with a large elderly population and increased life expectancy.

Conclusion

NOACs have been approved for risk reduction of stroke and SEE in NVAF, treatment of VTE and risk reduction in the recurrence of VTE in various countries based on their comparable or favorable efficacy and safety profiles compared to the conventional anticoagulation therapy in NVAF or VTE patients.[37] Target-specific NOACs with predictable, reversible anticoagulant effects without a need for invasive monitoring are increasingly used as substitutes to conventional anticoagulation therapy and provide a wide range of patient treatment choices.[126] However, it is difficult to make a complete change to NOACs in specific patient populations due to the challenges discussed in this review. To compensate clinical-evidence and achieve optimal use of NOACs, we should pay attention to the outcomes of ongoing studies and evaluate more real-world data. Most of all, NOAC use should be regulated in individual patient to have a sufficient benefit for antithrombotic treatment or prophylaxis over bleeding risk.

Abbreviations

ACS, acute coronary syndrome; AF, atrial fibrillation; APTT, activated partial thromboplastin time; BID, twice-daily; CAT, cancer-associated VTE; CHMP, Committee for Medicinal Products for Human Use; CKD, chronic kidney disease; CrCL, creatinine clearance; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; EMA, European Medicines Agency; FDA, Food and Drug Administration; FXa, factor Xa; HIRA, Health Insurance Review and Assessment Service; HR, hazard ratio; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MFDS, Ministry of Food and Drug Safety; NI, non-inferiority; NOACs, non-vitamin K oral anticoagulants; NVAF, non-valvular atrial fibrillation; OACs, oral anticoagulants; OD, once-daily; PCI, percutaneous coronary intervention; PE, pulmonary embolism; P-gp, P-glycoprotein 1; PMDA, Pharmaceuticals and Medical Devices Agency; RMP, risk management plan; RR, relative risk; SEE, systemic embolic event; SUP, superiority; TTR, time in therapeutic range; UFH, unfractionated heparin; US, United States; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

Disclosure

The author reports no conflicts of interest in this work.

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