REVIEW

Korean J Intern Med 2023;38:583-594
https://doi.org/10.3904/kjim.2023.035

Low-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Ki Hong Lee[1,2] and Hyung Wook Park[1,2]

[1]Department of Cardiovascular Medicine, Chonnam National University Hospital, Gwangju; [2]Department of Cardiovascular Medicine, Chonnam National University Medical School, Gwangju, Korea

In the last decade, non-vitamin K antagonist oral anticoagulants (NOACs), a new generation of OACs, were introduced to prevent thromboembolism in patients with atrial fibrillation. Although vitamin K-dependent anticoagulants have long been used as OACs, their inherent disadvantage of considerable bleeding complications has limited their use. NOACs demonstrate similar or superior clinical outcomes to those of warfarin. Although strict dose reduction criteria are recommended for NOACs, low-dose NOACs are frequently utilized, especially in Asian patients. Low-dose NOACs have shown clinical outcomes similar to those of warfarin in randomized controlled trials (RCTs) and real-world studies. However, off-label low-dose NOACs have shown inconsistent results compared with standard-dose NOACs and warfarin. Therefore, strict dose reduction criteria for NOACs should be followed until RCTs confirm the issues associated with NOAC underdosing.

Keywords: Off-label use; Anticoagulant agents; Atrial fibrillation

INTRODUCTION

Oral anticoagulants (OACs) are essential for patients with atrial fibrillation (AF) to prevent thromboembolism (TE), a catastrophic complication of AF. OACs prevent thrombus formation, which is associated with embolic risk and can result in complications including stroke. Before 2010, vitamin K-dependent anticoagulants (e.g., warfarin and vitamin K antagonists [VKAs]) were the only type of OAC. VKAs have the advantages of good availability and cost-effectiveness. However, the high risk of bleeding complications limits their use. Dose titration is essential to maintain optimal serum concentrations via blood sampling and thus decrease the risk of TE and bleeding complications [1-6]. Notably, the serum concentrations of VKAs are readily affected by food ingestion and other medications.

In the late 2000s, a new generation of OACs was introduced to overcome these disadvantages of VKAs: non-vitamin K antagonist oral anticoagulants (NOACs). Currently available NOACs include direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban). NOACs have several advantages, including no need for dose titration or caution when taken with food or certain herbal medications, and they have similar or even better efficacy and safety compared with traditional VKAs [4,7-9].

The optimal dosages of NOACs were determined by large-scale, worldwide prospective randomized controlled trials (RCTs) [10-13]. Most guidelines suggest similar dosing criteria across different ethnic groups [2-4,14]. Asians are more vulnerable to bleeding complications associated with OACs, partly because of their smaller body surface area and weight [15-18]. Therefore, low-dose NOACs are frequently used in Asian patients.

Evidence regarding the efficacy and safety of off-label low-dose NOACs is lacking. Nonetheless, some real-world data suggest that low-dose NOACs might be suitable in Asian populations. In this review, we identify how the standard doses of NOACs were determined and discuss whether low-dose NOACs have efficacy and safety comparable to that of standard doses.

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

NOACs IN RCTs

Dabigatran was compared with warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which had a non-inferiority design [10]. Rivaroxaban was compared with warfarin in the Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), which also had a non-inferiority design and had a primary endpoint of stroke or systemic embolism [11]. Apixaban was compared with warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which had a non-inferiority design and key secondary objectives of establishing superiority with respect to both the primary outcome and the rates of major bleeding and death from any cause [12]. Edoxaban was compared with warfarin in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, which had a non-inferiority design [13]. The NOACs in these trials had predefined dose reduction criteria (Table 1).

In the RE-LY trial, 150 mg dabigatran twice daily significantly reduced the risk of stroke and systemic embolism by 34% compared with warfarin, with a similar rate of major bleeding. In addition, 110 mg dabigatran was associated with a similar risk of stroke and systemic embolism and a lower risk of major bleeding compared with warfarin. Both doses were associated with a lower risk of hemorrhagic stroke and intracranial hemorrhage. Finally, 150 mg dabigatran had a lower risk of the composite clinical outcome of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding. However, a dose of 110 mg had a similar risk of this composite outcome compared with warfarin (Table 2).

Table 1. Dose reduction criteria for NOACs

Rivaroxaban
Creatinine clearance 30–49 mL/min
Apixaban
More than 2 of the following:
1) Age ≥ 80 years
2) Body weight ≤ 60 kg
3) Serum creatinine ≥ 1.5 mg/dL
Edoxaban
Any of the following:
1) Creatinine clearance 30–50 mL/min
2) Body weight ≤ 60 kg
3) Concomitant use of verapamil or quinidine (P-glycoprotein inhibitors)

NOAC, non-vitamin K antagonist oral anticoagulant.

In ROCKET-AF, rivaroxaban was associated with a similar risk of stroke or systemic embolism, and no difference in the risk of major bleeding, compared with warfarin. Nonetheless, rivaroxaban significantly reduced the risk of hemorrhagic stroke and intracranial hemorrhage. Rivaroxaban was associated with a lower risk of the composite clinical outcome of stroke, non-central nervous system embolism, vascular death, and myocardial infarction (Table 2).

In the ARISTOTLE trial, 5 or 2.5 mg apixaban twice daily significantly reduced the risk of stroke and systemic embolism, as well as major bleeding and death from any cause, compared with warfarin. Although the rates of hemorrhagic stroke and intracranial hemorrhage were lower with apixaban, the rate of ischemic stroke was similar to that of warfarin. Both doses were associated with a lower risk of the composite clinical outcome of stroke, systemic embolism, myocardial infarction, and death from any cause (Table 2).

In the ENGAGE AF-TIMI 48 trial, 60 mg edoxaban was not inferior to warfarin for the prevention of stroke or systemic embolism and was associated with significantly lower rates of major bleeding and death from cardiovascular causes. A dose of 30 mg edoxaban showed similar results. Both doses of edoxaban were associated with a lower risk of poor clinical outcomes. The rate of ischemic stroke was similar with 60 mg edoxaban, whereas 30 mg edoxaban significantly increased the risk of ischemic stroke. Therefore, only 60 mg edoxaban has been approved for stroke prevention in patients with AF (Table 2).

In a pooled analysis of 42,411 patients treated with NOACs and 29,272 patients treated with warfarin, NOACs significantly reduced the risk of stroke/systemic embolism, hemorrhagic stroke, intracranial hemorrhage, and death from any cause [7]. Although NOACs did not show superiority in terms of reducing the risk of stroke and systemic embolism events, they significantly reduced the risk of major bleeding compared with warfarin in a subpopulation of patients whose drug concentration was within the therapeutic range < 66% of the time (Table 3).

https://doi.org/10.3904/kjim.2023.035

Table 2. Comparison of clinical outcomes between NOACs and warfarin in RCTs

Variable	Dabigatran [10]			Rivaroxaban [11]		Apixaban [12]		Edoxaban [13]		
Mechanism	Direct thrombin inhibitor			Factor Xa inhibitor		Factor Xa inhibitor		Factor Xa inhibitor		
Number of patients	18,113			14,264		18,201		21,105		
	D150 (n = 6,076)	D110 (n = 6,015)	Warfarin (n = 6,022)	Rivaroxaban (n = 7,131)	Warfarin (n = 7,133)	Apixaban (n = 9,120)	Warfarin (n = 9,081)	E60 (n = 7,035)	E30 (n = 7,034)	Warfarin (n = 7034)
$CHADS_2$ score, mean ± SD	2.2 ± 1.2	2.1 ± 1.1	2.1 ± 1.1	3.5 ± 0.9	3.5 ± 1.0	2.1 ± 1.1	2.1 ± 1.1	2.8 ± 1.0	2.8 ± 1.0	2.8 ± 1.0
	RR vs. warfarin (95% CI), *p* value			HR vs. warfarin (95% CI), *p* value		HR vs. warfarin (95% CI), *p* value		HR vs. warfarin (95% CI), *p* value		
	D150 vs. warfarin	D110 vs. warfarin						E60 vs. warfarin	E30 vs. warfarin	
Stroke/systemic embolism	0.66 (0.53–0.82), < 0.001[a]	0.91 (0.74–1.11), < 0.001[b]		0.79 (0.66–0.96), < 0.001[b]		0.79 (0.66–0.95), 0.01		0.79 (0.63–0.99), < 0.001[b]	1.07 (0.87–1.31), 0.005[b]	
Ischemic stroke	1.11 (0.89–1.40), 0.03[a]	0.76 (0.60–0.98), 0.35[a]		0.94 (0.75–1.17), 0.581[a]		0.92 (0.74–1.13), 0.42		1.00 (0.83–1.19), 0.97[a]	1.41 (1.19–1.67), < 0.001[a]	
Hemorrhagic stroke	0.26 (0.14–0.49), < 0.001[a]	0.31 (0.17–0.56), < 0.001[a]		0.59 (0.37–0.93), 0.024[a]		0.51 (0.35–0.75), < 0.001		0.54 (0.38–0.77), < 0.001[a]	0.33 (0.22–0.50), < 0.001[a]	
Major bleeding	0.93 (0.81–1.07), 0.31	0.80 (0.69–0.93), 0.003		1.04 (0.90–1.20), 0.58[a]		0.69 (0.60–0.80), < 0.001		0.80 (0.71–0.91), < 0.001	0.47 (0.41–0.55), < 0.001	
Intracranial hemorrhage	0.40 (0.27–0.60), < 0.001	0.31 (0.20–0.47), < 0.001		0.67 (0.47–0.93), 0.02[a]		0.42 (0.30–0.58), < 0.001		0.47 (0.34–0.63), < 0.001	0.30 (0.21–0.43), < 0.001	
Myocardial infarction	1.38 (1.00–1.91), 0.07[a]	1.35 (0.98–1.87), 0.048[a]		0.81 (0.63–1.06), 0.121[a]		0.88 (0.66–1.17), 0.37		0.94 (0.74–1.19), 0.60[a]	0.87 (0.79–0.96), 0.006[a]	
Death from any cause	0.88 (0.77–1.00), 0.13[a]	0.91 (0.80–1.03), 0.051[a]		0.85 (0.70–1.02), 0.073[a]		0.89 (0.80–0.998), 0.047		0.92 (0.83–1.01), 0.08[a]	0.87 (0.79–0.96), 0.006[a]	
Net clinical outcomes	0.91[c] (0.80–1.00), 0.04	0.92[c] (0.84–1.02), 0.10		0.85[d] (0.74–0.99), 0.010[a]		0.88[e] (0.80–0.97), 0.01		0.89[f] (0.83–0.96), 0.003	0.83[f] (0.77–0.90), < 0.001	

CI, confidence interval; D150, dabigatran 150 mg; D110, dabigatran 110 mg; E60, edoxaban 60 mg; E30, edoxaban 30 mg; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RR, relative risk.

[a] *p* value for superiority.

[b] *p* value for non-inferiority.

[c] The composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

[d] The composite of stroke, non-central nervous system embolism, vascular death and myocardial infarction.

[e] The composite of stroke, systemic embolism, myocardial infarction, or death from any cause.

[f] The composite of stroke, systemic embolism, major bleeding, or death from any cause.

DEFINITION OF LOW-/REDUCED-DOSE NOACs

NOAC dosing is classified as either appropriate or inappropriate. Appropriate dosing indicates that NOACs are being prescribed according to dose reduction criteria (Table 1); this is defined as on-label dosing. A reduced dose is a low dose of NOACs in accordance with the dose reduction criteria. Inappropriate dosing indicates that NOACs are not being prescribed according to the dose reduction criteria; this is defined as off-label dosing. Inappropriate dosing can be divided into underdosing and overdosing. Underdosing is defined as the administration of a low dose of NOACs despite the recommendation for a standard dose. Overdosing is defined as the administration of a standard dose of NOACs despite the recommendation for a low dose. Low-dose NOAC therapy indicates the use of a low dose of NOACs irrespective of whether the dosing is on-label or off-label.

ON-LABEL LOW-DOSE (REDUCED-DOSE) NOAC THERAPY IN RCTs

The efficacy and safety of on-label low- or reduced-dose NOAC therapy were reviewed in a meta-analysis of four RCTs [7]. Low-dose therapy showed similar risk reduction of stroke/systemic embolism and more favorable risk reduction of major bleeding. Another meta-analysis of three RCTs (ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48) compared full and reduced doses, as specified in previous important trials [19]. The annual rates of stroke/systemic embolism and major bleeding in patients receiving reduced-dose therapy (2.70% and 4.35%, respectively) were higher than those in patients receiving full-dose therapy (1.60% and 2.87%, respectively). Nonetheless, reduced-dose NOAC therapy and warfarin showed clinical outcomes similar to those of full-dose NOAC therapy and warfarin (Table 3).

COMPARISON BETWEEN ASIAN AND NON-ASIAN PATIENTS IN RCTs

In a RE-LY trial subgroup analysis, hemorrhagic stroke in patients treated with warfarin occurred more often among Asian than non-Asian patients [20]. In ROCKET-AF, both stroke/systemic embolism and major bleeding or non-major clinically relevant bleeding were significantly more common in East Asian than non-East Asian patients, irrespective of rivaroxaban or warfarin treatment [21]. High adverse event rates in Asian patients treated with OACs might affect the efficacy and safety of NOACs compared with warfarin [22]. Explanations for these ethnic differences can be obtained from RCT subgroup analyses comparing Asians and non-Asians.

The RE-LY trial involved 2,782 (15%) Asian patients and 15,331 (85%) non-Asian patients. Dabigatran at 150 mg significantly reduced the risk of stroke/systemic embolism compared with warfarin in both Asians and non-Asians [20]. There was no significant treatment-by-region interaction (Table 4). Dabigatran at 150 mg also significantly reduced the risk of major bleeding in Asians, but not in non-Asians (Table 5). Dabigatran at 110 mg showed similar results in

Table 3. Comparison of clinical outcomes among any-/full-dose NOACs, reduced-dose NOACs, and warfarin in RCTs

Clinical outcome	Any dose NOACs [7]	Reduced dose NOACs [7]	Full dose NOACs [19]	Reduced dose NOACs [19]	Interaction *p* value[a] [19]
Stroke/systemic embolism	0.81 (0.73–0.91)	1.03 (0.84–1.27)	0.86 (0.77–0.96)	0.84 (0.69–1.03)	0.89
Ischemic stroke	0.92 (0.83–1.02)	1.28 (1.02–1.60)	0.92 (0.80–1.07)	0.95 (0.72–1.26)	0.84
Hemorrhagic stroke	0.49 (0.38–0.64)	0.33 (0.23–0.46)	0.54 (0.42–0.70)	0.55 (0.34–0.89)	0.92
Major bleeding	0.86 (0.73–1.00)	0.65 (0.43–1.00)	0.87 (0.70–1.08)	0.70 (0.50–0.97)	0.26
Intracranial hemorrhage	0.48 (0.39–0.59)	0.31 (0.24–0.41)	0.53 (0.40–0.69)	0.58 (0.34–0.98)	0.78
Gastrointestinal bleeding	1.25 (1.01–1.55)	0.89 (0.57–1.37)	1.42 (1.19–1.70)	1.24 (0.78–1.98)	0.60
All cause death	0.90 (0.85–0.95)	0.89 (0.83–0.96)	0.88 (0.81–0.97)	0.89 (0.75–1.06)	0.93

Values are presented as relative risk (95% confidence interval).
NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial.
[a]Interaction *p* value between full dose NOACs relative to warfarin and reduced dose NOACs relative to warfarin.

https://doi.org/10.3904/kjim.2023.035

Table 4. Comparison of risk of stroke/systemic embolism between Asians and non-Asians in RCTs

Variable	Asian					Non-Asian					Interaction *p* value
	Number of patients		Event rate (%/yr)		HR (95% CI)	Number of patients		Event rate (%/yr)		HR (95% CI)	
	NOACs	Warfarin	NOACs	Warfarin		NOACs	Warfarin	NOACs	Warfarin		
Dabigatran 150 mg [20]	933	926	1.39	3.06	0.45 (0.28–0.72)	5,143	5,096	1.06	1.48	0.72 (0.56–0.92)	0.09
Dabigatran 110 mg [20]	923	926	2.50	3.06	0.81 (0.54–1.21)	5,092	5,096	1.37	1.48	0.93 (0.74–1.17)	0.56
Rivaroxaban [21]	468	464	2.6	3.4	0.78 (0.44–1.39)	6,663	6,669	2.1	2.4	0.89 (0.75–1.05)	0.666
Apixaban [23]	988	1,005	2.52	3.39	0.74 (0.50–1.10)	8,132	8,076	1.12	1.38	0.81 (0.66–0.99)	0.698
Edoxaban 60 mg [24]	642	641	1.34	2.62	0.53 (0.31–0.90)	6,370	6,371	1.16	1.38	0.84 (0.68–1.01)	0.64
Edoxaban 30 mg [24]	652	641	2.52	2.62	0.98 (0.63–1.54)	6,350	6,371	1.51	1.38	1.09 (0.90–1.33)	0.11

CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial.

Table 5. Comparison of risk of major bleeding between Asians and non-Asians in RCTs

Variable	Asian					Non-Asian					Interaction *p* value
	Number of patients		Event rate (%/yr)		HR (95% CI)	Number of patients		Event rate (%/yr)		HR (95% CI)	
	NOACs	Warfarin	NOACs	Warfarin		NOACs	Warfarin	NOACs	Warfarin		
Dabigatran 150 mg [20]	933	926	2.17	3.82	0.57 (0.38–0.84)	5,143	5,096	3.52	3.53	1.00 (0.87–1.16)	0.008
Dabigatran 110 mg [20]	923	926	2.22	3.82	0.57 (0.39–0.85)	5,092	5,096	2.99	3.53	0.85 (0.73–0.99)	0.07
Rivaroxaban[a] [21]	468	464	20.9	20.7	1.01 (0.79–1.30)	6,663	6,669	14.5	14.1	1.03 (0.96–1.11)	0.867
Apixaban [23]	988	1,005	2.02	3.84	0.53 (0.35–0.80)	8,132	8,076	2.15	3.00	0.72 (0.62–0.83)	0.174
Edoxaban 60 mg [24]	642	641	2.86	4.80	0.61 (0.41–0.89)	6,370	6,371	2.74	3.29	0.83 (0.73–0.96)	0.12
Edoxaban 30 mg [24]	652	641	1.59	4.80	0.34 (0.21–0.54)	6,350	6,371	1.62	3.29	0.49 (0.42–0.58)	0.12

CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial.
[a]Bleeding events in rivaroxaban defined as major and nonmajor clinically relevant bleeding.

https://doi.org/10.3904/kjim.2023.035

terms of the prevention of stroke/systemic embolism compared with warfarin in both Asians and non-Asians. There was no significant treatment-by-region interaction. Furthermore, 110 mg dabigatran significantly reduced the risk of major bleeding compared with warfarin in both Asians and non-Asians. There was no significant treatment-by-region interaction (Table 5).

In ROCKET-AF, 932 (6.5%) East Asian patients were compared with 13,222 non-East Asian patients [21]. In terms of prevention of stroke/systemic embolism, rivaroxaban was superior to warfarin in both East Asian and non-East Asian patients (Table 4). Superiority of rivaroxaban over warfarin in terms of risk of major bleeding and non-major clinically relevant bleeding was also seen in both East Asians and non-East Asians (Table 5).

In the ARISTOTLE trial, 1,993 (11.1%) East Asian patients were compared with 16,028 non-East Asian patients [23]. Apixaban resulted in a consistent reduction in stroke/systemic embolism in both East Asians and non-East Asians (Table 4). Apixaban also significantly reduced the risk of major bleeding compared with warfarin in both Asians and non-Asians (Table 5).

In the ENGAGE AF-TIMI 48 trial, 1,943 (9.2%) East Asian patients were compared with 19,162 non-East Asian patients [24]. In terms of prevention of stroke/systemic embolism, 60 mg edoxaban was superior to warfarin in both East Asians and non-East Asians (Table 4). Edoxaban at 60 mg significantly reduced the risk of major bleeding in both East Asians and non-East Asians. There was no significant treatment-by-region interaction (Table 5). In terms of prevention of stroke/systemic embolism, 30 mg edoxaban was also superior to warfarin in both East Asians and non-East Asians (Table 4). Finally, 30 mg edoxaban significantly reduced the risk of major bleeding in both East Asians and non-East Asians. There was no significant treatment-by-region interaction (Table 5).

REAL-WORLD EVIDENCE OF LOW-DOSE NOACs

Low-dose NOACs, as well as dabigatran, which is not defined as a low-dose NOAC, are used more frequently in real-world practice than in RCTs. [25-28].

Rivaroxaban

In ROCKET-AF, 20.7% of the enrolled patients received low-dose rivaroxaban [11,29]. According to a Korean database, low-dose rivaroxaban was prescribed in 51.5–59.7% of all patients treated with rivaroxaban [30,31], whereas it was prescribed in 17.3–21.7% of patients in the United States [29,32].

Table 6. Comparison of clinical outcomes between low-dose NOACs and warfarin according to real-world evidence

Variable	Stroke/systemic embolism	Major bleeding	All-cause death
Rivaroxaban			
KNHIS [30]	0.72 (0.62–0.82)	0.99 (0.85–1.15)	0.74 (0.65–0.83)
Jeong et al. [31]	0.95 (0.45–1.97)	0.47 (0.22–1.01)	0.56 (0.26–1.21)
Apixaban in KNHIS [30]			
All-population	0.76 (0.68–0.89)	0.70 (0.58–0.85)	0.78 (0.69–0.89)
< 75-yr without chronic kidney disease	0.99 (0.76–1.28)	0.72 (0.51–1.02)	0.85 (0.62–1.16)
Dabigatran			
KNHIS [30]	0.80 (0.70–0.93)	0.85 (0.71–1.00)	0.75 (0.66–0.85)
Lee et al. [35]	0.46 (0.19–1.12)	0.19 (0.07–0.55)	0.46 (0.19–1.10)
TNHIRD [36]	0.62[a] (0.52–0.75)	0.61 (0.47–0.78)	0.46 (0.38–0.84)
Edoxaban			
KNHIS [37]	0.73[a] (0.48–1.08)	0.69 (0.43–1.06)	0.76 (0.58–1.00)

Values are presented as hazard ratio (95% confidence interval).
CI, confidence interval; HR, hazard ratio; KNHIS, Korean National Health Insurance Service; NOAC, non-vitamin K antagonist oral anticoagulant; TNHIRD, Taiwan National Health Insurance Research Database.
[a]Hazard ratio for ischemic stroke.

https://doi.org/10.3904/kjim.2023.035

According to the Korean National Health Insurance Service database, low-dose rivaroxaban was associated with a lower risk of ischemic stroke/systemic embolism and all-cause death, without a benefit for major bleeding [30]. In a retrospective Korean study, low-dose rivaroxaban was associated with a risk of TE and major bleeding comparable with that for warfarin (Table 6) [31]. In a retrospective Taiwanese study, 384 patients treated according to the ROCKET-AF dosing criteria (20 vs. 15 mg) were compared with 1,936 patients treated according to the J-ROCKET-AF dosing criteria (15 vs. 10 mg) [33]. Compared with warfarin-treated patients, patients following the ROCKET-AF or J-ROCKET-AF dosing criteria had a significantly lower risk of major bleeding and a comparable risk of TE. Among patients without chronic kidney disease, the risks of TE and major bleeding were not different between the two dosing groups. Among patients with chronic kidney disease, however, the ROCKET-AF dosing group had a higher risk of major bleeding and a comparable risk of TE compared with the J-ROCKET-AF dosing group.

Apixaban

In the ARISTOLE trial, 4.6% of the enrolled patients received low-dose apixaban [12,25,29,34]. According to the Korean National Health Insurance Service database, 7,839 (62.7%) of 12,502 patients treated with apixaban took low-dose apixaban [30]. According to the IMS LifeLink dataset from the United States, 20.8% of patients treated with apixaban took low-dose apixaban [29].

The Korean National Health Insurance Service database showed that compared with warfarin, low-dose apixaban was associated with a lower risk of ischemic stroke or systemic embolism, all-cause death, and major bleeding [30]. However, in patients aged < 75 years without chronic kidney disease, low-dose apixaban lost its ability to prevent ischemic stroke/systemic embolism and all-cause death (Table 6).

Dabigatran

According to the Korean National Health Insurance Service database, 9,458 (75.1%) of 12,593 patients treated with dabigatran took low-dose dabigatran (110 mg) twice a day [30]. Compared with warfarin, low-dose dabigatran was associated with a lower risk of ischemic stroke/systemic embolism, all-cause death, and major bleeding. In a Korean retrospective study, 550 (65%) of 844 patients treated with dabigatran took low-dose dabigatran [35]. Compared with warfarin, low-dose dabigatran was associated with a lower risk of major bleeding and a comparable risk of TE. According to the Taiwan National Health Insurance Research Database, 8,772 (88%) of 9,940 patients treated with dabigatran took low-dose dabigatran [36]. Compared with warfarin, low-dose dabigatran was associated with a lower risk of ischemic stroke, all-cause death, and major bleeding (Table 6).

Edoxaban

In the ENGAGE AF-TMI 48 trial, 25.4% of the high-dose (60-mg) edoxaban group received low-dose (reduced-dose) edoxaban [13]. The Korean National Health Insurance Service database showed that 2,371 (58.4%) of 4,061 patients treated with edoxaban took low-dose edoxaban (30 mg) [37]. Compared with warfarin, low-dose edoxaban had a comparable risk of ischemic stroke and major bleeding, with a significantly lower risk of all-cause death (Table 6).

REAL-WORLD EVIDENCE OF UNDERDOSING

No RCT to date has compared NOACs with warfarin in terms of underdosing or overdosing. Therefore, evidence of the clinical outcomes of underdosing and overdosing must be obtained from real-world retrospective or prospective registry studies. Underdosing is more common than overdosing in real-world studies. The prevalence of underdosing in real-world studies ranges from 8% to 52% [38]. Underdosing of NOACs more commonly occurs in studies of Asian patients (20–50%) than in studies of non-Asian patients (8–20%). This high rate of NOAC underdosing in Asian patients reflects concern regarding bleeding complications. Comparisons between underdosing of NOACs and either standard-dose NOACs or warfarin have produced inconsistent results, as described below.

Underdosing of NOACs resulted in superior or similar outcomes

Lee et al. [35] compared 294 patients treated with on-label dabigatran to 183 patients treated with underdosed dabigatran. There were no differences in terms of the prevention of stroke/TE or major bleeding between the two groups. Cho et al. [39] compared 8,549 patients treated with underdosed rivaroxaban or apixaban versus 4,536 patients treat-

ed with warfarin. Rivaroxaban underdosing was associated with a lower risk of thromboembolic events and all-cause death and a similar risk of major bleeding. Apixaban underdosing was not associated with any differences in the risk of thromboembolic events, all-cause death, or major bleeding. Lee et al. [40] compared 5,777 patients treated with underdosed rivaroxaban to 5,777 patients treated with warfarin. Rivaroxaban underdosing was associated with a lower risk of ischemic stroke, hospitalization for major bleeding, and all-cause death. However, rivaroxaban underdosing was not associated with any differences in the prevention of ischemic stroke, major bleeding, or all-cause death compared with on-label rivaroxaban. In the Japan SAKURA AF Registry, 369 (22.2%) patients underdosed with NOACs were compared with 746 (45.0%) patients treated with standard-dose NOACs [41]. NOAC underdosing was associated with a lower risk of major bleeding and similar risks of stroke/systemic embolism and all-cause death. Briasoulis et al. [42] analyzed a retrospective cohort using Medicare data. They identified 8,035 and 19,712 patients who initiated treatment with dabigatran and rivaroxaban, respectively. Overall, 1,401 (17.4%) and 7,820 (39.7%) patients who received dabigatran and rivaroxaban, respectively, met the criteria for low-dose therapy. Of these patients, 959 (68.5%) and 3,904 (49.9%) received standard-dose therapy. By contrast, 1,013 (15.3%) and 2,551 (21.5%) patients who were eligi-

Table 7. Comparison of clinical outcomes among off-label low-dose NOACs, standard-dose NOACs, and warfarin according to real-world evidence

Variable	Stroke/systemic embolism	Major bleeding	All-cause death	CV hospitalization
Similar clinical outcomes				
Overall NOACs				
SAKURA AF registry [41]	1.16[a] (0.39–1.89)	0.47[a] (0.19–1.07)	1.78[a] (0.81–3.92)	
Rivaroxaban				
KNHIS [39]	0.53[b] (0.41–0.69)	1.10[b] (0.82–1.46)	0.57[b] (0.41–0.82)	
KNHIS [40]	0.86[a,c] (0.66–1.13)	0.86[a] (0.66–1.11)	0.84[a] (0.69–1.03)	
US administrative database [43]	0.71[a] (0.45–2.09)	1.09[a] (0.63–1.87)		
US Medicare data [42]	1.13[a,c] (0.83–1.56)	1.20[a] (0.93–1.53)		
Apixaban				
KNHIS [39]	0.90[b] (0.70–1.16)	0.84[b] (0.61–1.17)	0.94[b] (0.71–1.24)	
Dabigatran				
Lee et al. [35]	1.03[a] (0.30–3.56)	0.36[a] (0.04–3.49)	1.33[a] (0.05–5.47)	
US administrative database [43]	0.92[a] (0.30–2.87)	0.91[a] (0.45–1.85)		
US Medicare data [42]	0.74[a,c] (0.53–1.04)	1.01[a] (0.74–1.37)		
Inferior clinical outcomes				
Overall NOACs				
Lee et al. [44]	2.51[b] (1.28–4.93)	0.73[b] (0.31–1.71)		
ORBIT-AF II [46]	1.17[a] (0.61–2.26)	0.80[a] (0.52–1.23)	1.25[a] (0.89–1.76)	1.26[a] (1.07–1.50)
Clalit Healthcare Service [47]	1.02[a] (0.71–1.46)	1.53[a] (1.14–2.34)	1.72[a] (1.45–2.03)	
Apixaban				
US administrative database [43]	4.87[a] (1.30–18.26)	1.29[a] (0.48–3.42)		

Values are presented as hazard ratio (95% confidence interval).
CV, cardiovascular; KNHIS, Korean National Health Insurance Service; NOAC, non-vitamin K-dependent antagonist oral anticoagulant; ORBIT-AF II, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II.
[a]Comparison between off-label reduced dose NOACs and standard dose NOACs.
[b]Comparison between off-label reduced dose NOACs and warfarin.
[c]Hazard ratio for ischemic stroke.

https://doi.org/10.3904/kjim.2023.035

ble for standard-dose dabigatran and rivaroxaban received low-dose therapy. After propensity score matching, NOAC underdosing was not associated with any differences in the risk of stroke or major, gastrointestinal, or intracranial bleeding compared with standard-dose NOACs, including both dabigatran and rivaroxaban. Yao et al. [43] analyzed 14,865 AF patients treated with apixaban, dabigatran, and rivaroxaban using a large administrative database from the United States. Among the 13,392 patients without renal indications for dose reduction, 13.3% were underdosed. Patients underdosed with dabigatran and rivaroxaban showed no differences in stroke/systemic embolism or major bleeding compared with those treated with standard-dose NOACs. However, patients treated with underdosed apixaban had a significantly higher risk of stroke/systemic embolism, and a similar risk of major bleeding, compared with patients who received standard-dose NOACs (Table 7).

Underdosing of NOACs resulted in inferior outcomes

Lee et al. [44] retrospectively compared 3,733 patients treated with NOACs and 2,659 patients treated with warfarin. Off-label use of NOACs was applied in 27.0% of patients. Among them, 20.3% of patients treated with NOACs were underdosed. Compared with warfarin, NOAC underdosing increased the risk of TE and had a similar risk of major bleeding. In a Korean retrospective study, both on-label and underdosed rivaroxaban were associated with a comparable risk of TE and a significant reduction in major bleeding compared with warfarin. On-label use of rivaroxaban significantly reduced the incidence of the composite clinical outcome of stroke, systemic embolism, major bleeding, and all-cause death. However, rivaroxaban underdosing attenuated this benefit [45]. In the ORBIT-AF II registry, 541 (9.4%) patients underdosed with NOACs were compared with 5,000 (87.0%) patients treated with standard-dose NOACs [46]. NOAC underdosing significantly increased the rate of first cardiovascular hospitalization; however, it was not associated with any differences in the risk of first stroke, non-central nervous system embolism, transient ischemic attack, first bleeding hospitalization, or all-cause death compared with standard doses of NOACs. Arbel et al. [47] compared 3,285 (39%) patients treated with underdosed NOACs and 5,140 (61%) patients treated with on-label NOACs using data from Clalit Health Services (Tel Aviv, Israel). Compared with standard-dose NOAC therapy, NOAC underdosing was associated with a significantly higher rate of bleeding and the composite clinical outcome of death, stroke, and myocardial infarction, without a difference in the risk of stroke (Table 7).

DISCUSSION

NOACs account for most OACs used to prevent TE in patients with AF because of their benefits and convenience relative to warfarin. The latest guidelines also suggest preferential use of NOACs over warfarin in patients with AF who have high thromboembolic risk [1-4].

The benefits of NOACs have been demonstrated in four RCTs [10-13]. For the prevention of stroke/systemic embolism, 150 mg dabigatran twice a day and 5 mg apixaban twice a day were superior to warfarin. For the prevention of hemorrhagic stroke, all four NOACs evaluated were superior to warfarin: 150 or 110 mg dabigatran twice a day, 20 or 15 mg rivaroxaban once a day, 5 or 2.5 mg apixaban twice a day, and 60 or 30 mg edoxaban once a day. Moreover, 110 mg dabigatran twice a day, apixaban, and edoxaban were associated with a significantly lower risk of major bleeding. Therefore, 150 mg dabigatran twice a day and 5 mg apixaban twice a day are recommended for patients with a high risk of stroke/systemic embolism, and 100 mg dabigatran, apixaban, and edoxaban are recommended for patients with a high risk of bleeding.

Asian patients are more prone to bleeding events with OACs than are non-Asian patients [15,16]. Because pooled analyses of NOACs in RCTs have demonstrated an improved safety profile, NOACs might be more beneficial in Asians than in non-Asians [7]. Benefits were revealed in subgroup analyses of Asian and non-Asian patients in several RCTs [20,21,23,24]. Although 150 mg dabigatran significantly reduced the risk of stroke/systemic embolism in both Asians and non-Asians, it reduced the risk of major bleeding only in Asians. Therefore, 150 mg dabigatran is preferable in Asian patients with high risks of both stroke/systemic embolism and major bleeding. At a dose of 110 mg, no differences in dabigatran, rivaroxaban, apixaban, and edoxaban were found between Asians and non-Asians in terms of the prevention of stroke/systemic embolism and major bleeding. Therefore, although NOACs achieve better outcomes than warfarin in Asians, the efficacy and safety of NOACs are generally similar between Asians and non-Asians; the ex-

ception is 150 mg dabigatran twice a day, which has a better safety profile and similar efficacy between Asians and non-Asians.

Appropriate doses of NOACs have demonstrated similar or superior clinical outcomes compared with warfarin in both RCTs and real-world studies [4,10-13,35,39-43]. Furthermore, low-dose on-label NOACs have shown clinical outcomes comparable to those of standard-dose NOACs in RCTs [7,19]. However, no prospective or randomized study has demonstrated better outcomes with low-dose off-label NOACs. Nonetheless, low-dose NOACs are frequently prescribed in real-world clinical practice. Furthermore, the frequency of prescription of low-dose NOACs is higher in Asian patients than in non-Asian patients.

Physicians might expect fewer bleeding complications with similar or fewer thromboembolic events when using underdosed NOACs. This preference for underdosing reflects a concern regarding bleeding complications rather than thromboembolic events [48]. Some real-world studies have shown benefits of underdosing with NOACs with respect to bleeding complications compared with warfarin [40,41]. However, most of those studies did not demonstrate benefits in terms of bleeding complications [35,39,42-44,46]. Additionally, most real-world studies of underdosed NOACs have demonstrated a similar or reduced risk of stroke compared with standard-dose NOACs or warfarin [35,39-43,46]. By contrast, Lee et al. [44] revealed an increased thromboembolic risk in association with underdosing of NOACs. With regard to the individual classes of NOACs, low doses of apixaban should be reconsidered. According to the Korean National Health Insurance Service database, low-dose apixaban lost its beneficial effects with respect to the prevention of ischemic stroke or systemic embolism and all-cause death compared with warfarin [30]. Furthermore, apixaban underdosing was associated with a 4.87-times higher risk of stroke/systemic embolism than standard dosing in a US study based on an administrative database [43].

In summary, the efficacy and safety of low-dose NOACs administered as on-label therapy were comparable to those of standard-dose NOACs. However, NOAC underdosing did not demonstrate superiority to standard dosing in either RCTs or real-world studies. Therefore, there is no reason to underdose with NOACs, even in Asian patients or patients with a high risk of bleeding. Further RCTs comparing underdosing with NOACs and standard-dose NOACs or warfarin are warranted to more clearly demonstrate the issues associated with NOAC underdosing.

CONCLUSION

Low-dose NOACs are frequently used in real-world clinical practice despite strict dose reduction criteria. The efficacy and safety of low-dose NOACs administered as on-label therapy based on RCTs and real-world evidence are consistent with those of standard-dose NOACs and warfarin. However, NOAC underdosing has produced inconsistent results. Therefore, underdosed NOACs should not be recommended even in patients with a high bleeding risk. NOAC dosing should follow strict dose reduction criteria until the results of RCTs comparing underdosing with NOACs and standard-dose NOACs or warfarin clearly demonstrate the issues associated with NOAC underdosing.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140:e125-e151.
3. Ono K, Iwasaki YK, Akao M, et al.; Japanese Circulation Society and Japanese Heart Rhythm Society Joint Working Group. JCS/JHRS 2020 guideline on pharmacotherapy of cardiac arrhythmias. Circ J 2022 Oct;86:1790-1924.
4. Joung B, Lee JM, Lee KH, et al.; KHRS Atrial Fibrillation Guideline Working Group. 2018 Korean guideline of atrial fibrillation management. Korean Circ J 2018;48:1033-1080.
5. Lee KH, Cho JG, Lee N, et al. Impact of anticoagulation intensity in Korean patients with atrial fibrillation: is it different

https://doi.org/10.3904/kjim.2023.035

from western population? Korean Circ J 2020;50:163-175.
6. Cho JG, Lee KH, Kim YR, et al. Standard-intensity versus low-intensity anticoagulation with warfarin in Asian patients with atrial fibrillation: a multi-center, randomized controlled trial. Clin Appl Thromb Hemost 2023;29:10760296231171081.
7. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-962.
8. Lip GY, Wang KL, Chiang CE. Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in Asian patients with atrial fibrillation: time for a reappraisal. Int J Cardiol 2015;180:246-254.
9. Cabral KP, Ansell J, Hylek EM. Future directions of stroke prevention in atrial fibrillation: the potential impact of novel anticoagulants and stroke risk stratification. J Thromb Haemost 2011;9:441-449.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.
11. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-891.
12. Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.
13. Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-2104.
14. Steffel J, Collins R, Antz M, et al.; External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23:1612-1676.
15. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010;9:167-176.
16. Capodanno D, Angiolillo DJ. Impact of race and gender on antithrombotic therapy. Thromb Haemost 2010;104:471-484.
17. Marín F, González-Conejero R, Capranzano P, Bass TA, Roldán V, Angiolillo DJ. Pharmacogenetics in cardiovascular antithrombotic therapy. J Am Coll Cardiol 2009;54:1041-1057.
18. Gan GG, Teh A, Goh KY, Chong HT, Pang KW. Racial background is a determinant factor in the maintenance dosage of warfarin. Int J Hematol 2003;78:84-86.
19. Wang KL, Lopes RD, Patel MR, et al. Efficacy and safety of reduced-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. Eur Heart J 2019;40:1492-1500.
20. Hori M, Connolly SJ, Zhu J, et al.; RE-LY Investigators. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke. 2013;44:1891-1896.
21. Wong KS, Hu DY, Oomman A, et al.; Executive Steering Committee and the ROCKET AF Study Investigators. Rivaroxaban for stroke prevention in East Asian patients from the ROCKET AF trial. Stroke 2014;45:1739-1747.
22. Ma C. Current antithrombotic treatment in East Asia: some perspectives on anticoagulation and antiplatelet therapy. Thromb Haemost 2012;107:1014-1018.
23. Goto S, Zhu J, Liu L, et al.; ARISTOTLE Investigators. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Am Heart J 2014;168:303-309.
24. Yamashita T, Koretsune Y, Yang Y, et al. Edoxaban vs. warfarin in East Asian patients with atrial fibrillation - an ENGAGE AF-TIMI 48 subanalysis. Circ J 2016;80:860-869.
25. Gibson CM, Smith CB, Davis S, Scalese MJ. Assessment of apixaban prescribing patterns for nonvalvular atrial fibrillation in hospitalized patients. Ann Pharmacother 2018;52:54-59.
26. Camm AJ, Amarenco P, Haas S, et al.; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145-1153.
27. Lee KH, Park HW, Cho JG, et al. Comparison of non-vitamin K antagonist oral anticoagulants and warfarin on clinical outcomes in atrial fibrillation patients with renal dysfunction. Europace 2015;17 Suppl 2:ii69-ii75.
28. Lee SR, Lee YS, Park JS, et al. Label adherence for non-vitamin K antagonist oral anticoagulants in a prospective cohort of Asian patients with atrial fibrillation. Yonsei Med J 2019;60:277-284.
29. Nguyen E, White CM, Patel MR, et al. Doses of apixaban and rivaroxaban prescribed in real-world United States cardiology practices compared to registration trials. Curr Med Res Opin 2016;32:1277-1279.
30. Cho MS, Yun JE, Park JJ, et al. Outcomes after use of stan-

dard- and low-dose non-vitamin K oral anticoagulants in Asian patients with atrial fibrillation. Stroke 2019;50:110-118.
31. Jeong HK, Lee KH, Park HW, et al. Real world comparison of rivaroxaban and warfarin in Korean patients with atrial fibrillation: propensity matching cohort analysis. Chonnam Med J 2019;55:54-61.
32. Coleman CI, Antz M, Bowrin K, et al. Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the REVISIT-US study. Curr Med Res Opin 2016;32:2047-2053.
33. Chan YH, Lee HF, Wang CL, et al. Comparisons of rivaroxaban following different dosage criteria (ROCKET AF or J-ROCKET AF Trials) in Asian patients with atrial fibrillation. J Am Heart Assoc 2019;8:e013053.
34. Santos J, António N, Rocha M, Fortuna A. Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: a systematic review. Br J Clin Pharmacol 2020;86:533-547.
35. Lee KH, Park HW, Lee N, et al. Optimal dose of dabigatran for the prevention of thromboembolism with minimal bleeding risk in Korean patients with atrial fibrillation. Europace 2017;19(suppl_4):iv1-iv9.
36. Chan YH, Yen KC, See LC, et al. Cardiovascular, bleeding, and mortality risks of dabigatran in Asians with nonvalvular atrial fibrillation. Stroke 2016;47:441-449.
37. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. J Am Coll Cardiol 2018;72:838-853.
38. Vinter N, Linder M, Andersen M, et al. Classification and characteristics of on-label and off-label apixaban use in Denmark and Sweden. Pharmacoepidemiol Drug Saf 2019;28:867-878.
39. Cho MS, Yun JE, Park JJ, et al. Pattern and impact of off-label underdosing of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation who are indicated for standard dosing. Am J Cardiol 2020;125:1332-1338.
40. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Optimal rivaroxaban dose in Asian patients with atrial fibrillation and normal or mildly impaired renal function. Stroke 2019;50:1140-1148.
41. Murata N, Okumura Y, Yokoyama K, et al.; SAKURA AF Registry Investigators. Clinical outcomes of off-label dosing of direct oral anticoagulant therapy among Japanese patients with atrial fibrillation identified from the SAKURA AF registry. Circ J 2019;83:727-735.
42. Briasoulis A, Gao Y, Inampudi C, et al. Characteristics and outcomes in patients with atrial fibrillation receiving direct oral anticoagulants in off-label doses. BMC Cardiovasc Disord 2020;20:42.
43. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol 2017;69:2779-2790.
44. Lee KN, Choi JI, Boo KY, et al. Effectiveness and safety of off-label dosing of non-vitamin K antagonist anticoagulant for atrial fibrillation in Asian patients. Sci Rep 2020;10:1801.
45. Kim SS, Lee KH, Yoon NS, Park HW, Cho JG. What is standard dose of rivaroxaban in elderly Asian patients with atrial fibrillation: 20ms versus. 15mg? Clin Appl Thromb Hemost 2021;27:10760296211061148.
46. Steinberg BA, Shrader P, Thomas L, et al.; ORBIT-AF Investigators and Patients. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. J Am Coll Cardiol 2016;68:2597-2604.
47. Arbel R, Sergienko R, Hammerman A, et al. Effectiveness and safety of off-label dose-reduced direct oral anticoagulants in atrial fibrillation. Am J Med 2019;132:847-855.e3.
48. Carlin S, Pickering J, Schulman S. Appropriateness of apixaban dosing to prevent stroke in patients with atrial fibrillation: a pilot study. Can J Hosp Pharm 2016;69:449-453.

Received : January 24, 2023
Revised : June 14, 2023
Accepted : August 3, 2023

Correspondence to
Hyung Wook Park, M.D., Ph.D.
Department of Cardiovascular Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jaebongro, Dong-gu, Gwangju 61469, Korea
Tel: +82-62-220-6572, Fax: +82-62-223-3105
E-mail: mdhwp@naver.com
https://orcid.org/0000-0002-9630-0467

CRedit authorship contributions
Ki Hong Lee: conceptualization, data curation, formal analysis, funding acquisition, methodology, project administration, visualization, writing - original draft, writing - review & editing; Hyung Wook Park: conceptualization, methodology, data curation, formal analysis, writing - original draft, writing - review & editing, project administration, funding acquisition

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by a grant (2021R1F1A1048115) of the National Research Foundation of Korea (NRF) funded by the Korea government (MSIT) and a grant (BCRI23054) of Chonnam National University Hospital Biomedical Research Institute.

https://doi.org/10.3904/kjim.2023.035