Rivaroxaban Underdose for Atrial Fibrillation with Stable Coronary Disease: The AFIRE Trial Findings

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Abstract

Background Rivaroxaban monotherapy was noninferior to combination therapy (rivaroxaban plus antiplatelet therapy) in efficacy but superior in safety in the Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial. Among 2,215 patients with atrial fibrillation (AF) and stable coronary artery disease (CAD), 1,378 had baseline creatinine clearance (CrCl) ≥ 50 mL/min and received 10 (underdose) or 15 mg/d (standard-dose) rivaroxaban. We aimed to assess the effects of rivaroxaban underdose on clinical outcomes.

Methods We assessed efficacy endpoint (a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, and death from any cause) and major bleeding in the subgroup of patients with preserved renal function in the AFIRE trial.

Results Age ≥ 75 years, female sex, lower CrCl, heart failure, and percutaneous coronary intervention history were associated with the underdose prescription. The underdose

Keywords
► coronary disease
► direct oral anticoagulant
► percutaneous coronary intervention
► stent

group had a similar incidence of the efficacy endpoint (3.62 vs. 3.51% per patient-year; $p = 0.871$) and significantly lower incidence of major bleeding (0.82 vs. 2.17% per patient-year; $p = 0.022$) than the standard-dose group. In patients receiving monotherapy, the incidences of efficacy endpoint and major bleeding were similar between the groups, whereas in those receiving combination therapy, the incidence of major bleeding was significantly lower in the underdose group than that in the standard-dose group.

Conclusion   In patients with AF, stable CAD, and preserved renal function, rivaroxaban underdose was associated with similar rates of thrombotic events but a lower incidence of hemorrhagic events than the standard dose.

Clinical Trial Registration   AFIRE UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr/), number UMIN000016612, and ClinicalTrials.gov, number NCT02642419.

Introduction

Direct oral anticoagulant (DOAC) therapy is a standard antithrombotic treatment in patients with atrial fibrillation (AF).[1] Regarding antithrombotic therapy for patients with AF and indication for concomitant antiplatelet therapy, DOAC is the first recommended anticoagulation therapy, and single antiplatelet therapy (P_2Y_{12} inhibitor) is superior to dual antiplatelet therapy (P_2Y_{12} inhibitor and aspirin) in terms of safety.[2] The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial was a randomized controlled trial that aimed to determine whether monotherapy with rivaroxaban is non-inferior to combination therapy with rivaroxaban plus an antiplatelet agent for cardiovascular events and death from any cause and superior for major bleeding in patients with AF and stable coronary artery disease (CAD).[3,4] The trial showed that rivaroxaban monotherapy is noninferior to the combination therapy in terms of efficacy and superior in terms of safety. These results suggest that the antithrombotic regimen for patients with both AF and stable CAD could be revised in a specific setting to be less intensive than the combination of DOAC and antiplatelet therapy.

DOAC therapy is the standard therapeutic strategy for patients with AF, with dosage reduction recommended mainly depending on renal function and age. In real-world clinical practice, some patients with AF and preserved renal function are treated with nonrecommended low doses of DOACs, depending on their weight, age, or concomitant medications.[5–7] A previous study reported that the non-recommended underdose of DOAC is associated with a lower risk of bleeding but a higher risk of all-cause mortality or thrombotic events.[5,8–11] The less intensive antithrombotic therapy seems to reduce the bleeding risk, whereas it increases the thrombotic risk.[2,12] Thus, it is important to weigh the risks of bleeding and thrombosis in individual patients for optimization of the antithrombotic therapy. A recent randomized controlled trial suggested a favorable effect of low-dose DOAC in patients with a very high bleeding risk, although it was not a study that approved the strategy of low dose compared with standard-dose DOAC in clinical practice.[13] To date, the treatment of patients with AF, stable CAD, and preserved renal function with an underdose DOAC has not been fully assessed for the frequency of thrombotic and hemorrhagic events.

Accordingly, the aims of the present subgroup analysis of the AFIRE trial were to examine the following: (1) the proportion of patients who received rivaroxaban underdose therapy; (2) factors associated with the underdose prescription of rivaroxaban; (3) effect of the rivaroxaban underdose therapy on thrombotic and hemorrhagic events in patients with AF, stable CAD, and preserved renal function; and (4) effects of the treatments administered—rivaroxaban monotherapy and combination therapy—on the underdose treatment outcomes.

Methods

Study Design and Patient Population

The design, methods, and primary results of the AFIRE trial have been reported previously.[3,4] Briefly, the AFIRE trial was a multicenter, randomized, open-label, parallel-group trial conducted in Japan. The inclusion criteria for the study were men and women aged 20 years or older with a $CHADS_2$ score of at least 1 and diagnosed with stable CAD and AF. In the AFIRE trial, patients were randomly assigned in a 1:1 ratio to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus an antiplatelet agent. The treating physician determined the dose of rivaroxaban and the type of the antiplatelet agent. Patients were assessed at baseline, 6 months after the initiation of the medications, and at the end of the trial, with additional assessments conducted for routine clinical care as needed.

In the present subgroup analysis of the AFIRE trial, 1,378 patients with a baseline creatinine clearance (CrCl) of ≥50 mL/min were enrolled. Based on the Japanese package insert, the recommended dose of rivaroxaban is 15 mg/d for patients with CrCl ≥50 mL/min, although the dose of rivaroxaban was chosen at the discretion of the investigators. Thus, patients treated with 10 mg/d rivaroxaban were categorized into the underdose group, and those treated with 15 mg/d rivaroxaban were categorized into the standard-dose group in this study. The efficacy and safety endpoints were compared between the groups.

All participants provided written informed consent before enrolment. The trial was conducted in accordance with the principles outlined in the Declaration of Helsinki. The institutional review boards of the National Cerebral and Cardiovascular Center, Japan, and the institutional review board of all the participating institutions approved the study. An independent data and safety monitoring committee reviewed the data collected in the AFIRE trial. The study was designed and led by an executive steering committee. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Endpoints

The primary efficacy endpoint of this study was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. The primary safety endpoint was major bleeding, which was defined according to the criteria published by the International Society on Thrombosis and Haemostasis.[14] The secondary efficacy endpoints were the individual components of the primary efficacy endpoint, including ischemic stroke, hemorrhagic stroke, myocardial infarction, unstable angina, systemic embolism, cardiovascular death, and noncardiovascular death. The secondary safety endpoints were any bleeding and nonmajor bleeding.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD); they were compared using the Wilcoxon rank-sum test. Categorical variables are presented as number and percentage; they were compared using the chi-squared test or Fisher's exact test.

A multivariable logistic regression model analysis was performed to investigate the predictors associated with the rivaroxaban underdose therapy in the entire cohort. The covariates included the following variables collected at baseline: age, sex, body weight, CrCl, heart failure, diabetes, current smoker, previous percutaneous coronary intervention (PCI), and treatment group.

Cumulative event rates were estimated using the Kaplan–Meier method, with incidence rates in each group expressed as a percentage per patient-year. A Cox proportional hazards model was used to compare outcomes between the groups. The results are expressed as hazard ratio (HR) with 95% confidence interval (CI). A multivariable Cox hazard model analysis was performed to investigate the major determinants of the primary efficacy or safety endpoints in the entire cohort. The covariates included the following variables collected at baseline: age, sex, CrCl, type of AF, heart failure, diabetes, rivaroxaban dose, and treatment group for efficacy and age, sex, bleeding diathesis, previous stroke, rivaroxaban dose, and treatment group for safety. Variables included in the multivariable analyses were selected based on the results of the univariate analyses ($p < 0.10$ by an unpaired test) and clinical meaningfulness.

Propensity score matching was performed to investigate the association between the rivaroxaban dose and the occurrence of the primary efficacy and safety endpoints. The following baseline data were included as covariates to calculate the propensity score: age, sex, treatment group, body weight, CrCl, type of AF, hypertension, diabetes, angina, previous stroke, and previous myocardial infarction. Matching was achieved using a 1:1 nearest neighbor approach (without replacement) within a caliper of 0.2 of the SD.

All statistical analyses were performed using SAS software version 9.4 for Windows (SAS Institute, Cary, North Carolina, United States). Statistical significance was set at $p < 0.05$.

Results

Patients

Among the 1,378 patients included in this subgroup analysis, 356 (25.8%) were treated with the underdose of rivaroxaban and 1,022 (74.2%) with the standard dose of rivaroxaban (►**Fig. 1**). The patient baseline characteristics are shown in ►**Table 1**. The mean age of the patients was 71 years, 86% of the patients were males, the mean CrCl was 74.3 mL/min, and the mean body weight was 68.6 kg. The underdose group included more patients who were ≥75 years old, more females, and fewer current smokers than the standard-dose group. The underdose group was also associated with a lower mean body weight and a lower CrCl, a higher prevalence of heart failure, a lower prevalence of diabetes mellitus, and a higher mean $CHADS_2$ and CHA_2DS_2-VASc scores than the standard-dose group (►**Table 1**). The multivariable logistic regression analysis revealed that age ≥75 years, female sex, lower CrCl, heart failure, and PCI history were associated with the rivaroxaban underdose therapy (►**Supplementary Table S1**, available in the online version).
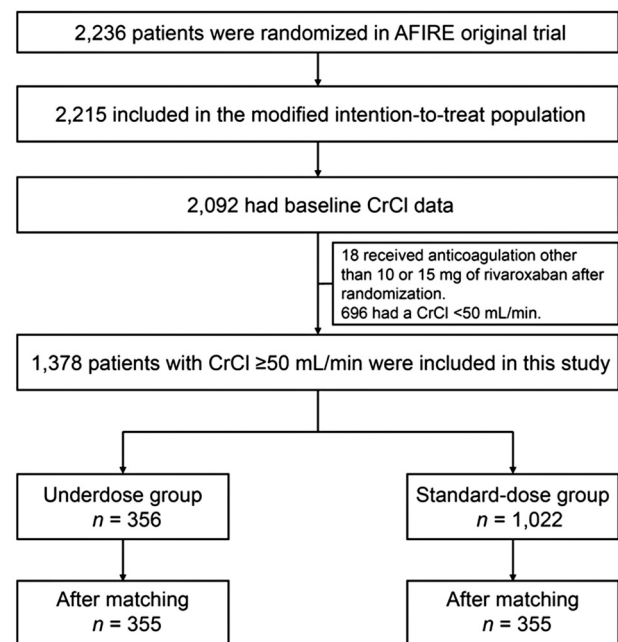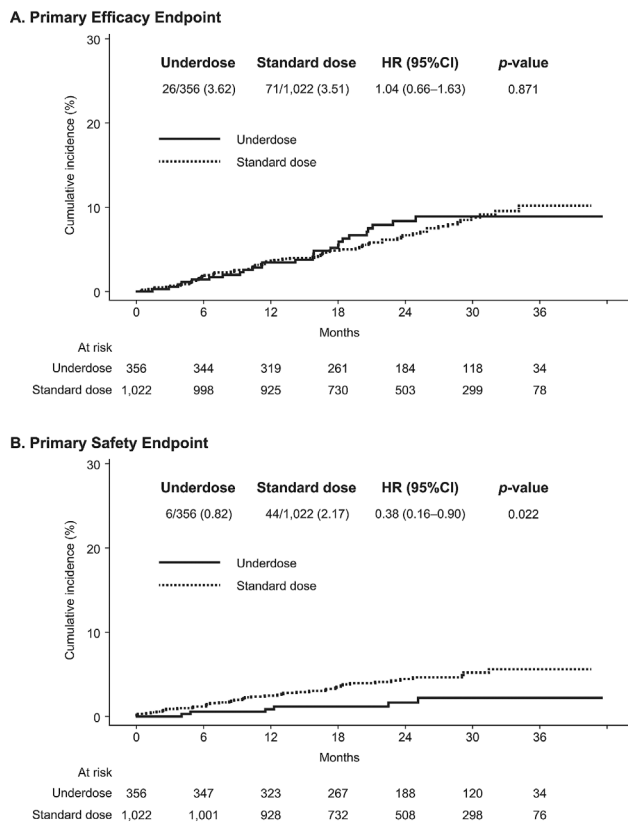

Fig. 1 Flow chart. We included 1,378 patients from the AFIRE trial who had baseline creatinine clearance of ≥50 mL/min and categorized them into two groups based on the administered dose of rivaroxaban: 10 mg/d (the underdose group, $n = 356$ [25.8%]) and 15 mg/d (the standard-dose group, $n = 1,022$ [74.2%]). CrCl, creatinine clearance.

Table 1 Baseline characteristics according to the initial dose of rivaroxaban

Characteristic	Overall (n = 1,378)	Underdose (n = 356)	Standard dose (n = 1,022)	p-Value[a]
Age, mean (SD), y	71.4 (7.6)	74.0 (7.1)	70.5 (7.5)	<0.001
≥ 75 y, N (%)	512 (37.2)	192 (53.9)	320 (31.3)	<0.001
Male sex, N (%)	1,178 (85.5)	279 (78.4)	899 (88.0)	<0.001
CrCl, mean (SD), mL/min	74.3 (21.8)	66.7 (16.5)	77.0 (22.8)	<0.001
Body weight, mean (SD), kg	68.6 (11.7)	66.5 (11.3)	69.3 (11.8)	<0.001
BMI, mean (SD), kg/m^2	25.4 (3.6)	25.2 (3.4)	25.5 (3.6)	0.196
Current smoker, N (%)	205 (14.9)	37 (10.4)	168 (16.4)	0.006
Type of AF, N (%)				
Paroxysmal	725 (52.6)	194 (54.5)	531 (52.0)	0.423
Persistent or permanent	653 (47.4)	162 (45.5)	491 (48.0)	
Hypertension, N (%)	1,194 (86.6)	306 (86.0)	888 (86.9)	0.652
Diabetes, N (%)	624 (45.3)	144 (40.4)	480 (47.0)	0.036
Dyslipidemia, N (%)	978 (71.0)	250 (70.2)	728 (71.2)	0.735
Heart failure, N (%)	417 (30.3)	134 (37.6)	283 (27.7)	<0.001
Angina, N (%)	853 (61.9)	228 (64.0)	625 (61.2)	0.343
Bleeding diathesis, N (%)	14 (1.0)	4 (1.1)	10 (1.0)	0.765
Previous stroke, N (%)	178 (12.9)	49 (13.8)	129 (12.6)	0.583
Previous myocardial infarction, N (%)	464 (33.7)	127 (35.7)	337 (33.0)	0.362
Previous peripheral arterial disease, N (%)	64 (4.6)	12 (3.4)	52 (5.1)	0.241
Previous CABG, N (%)	125 (9.1)	29 (8.1)	96 (9.4)	0.522
Previous PCI, N (%)	975 (70.8)	265 (74.4)	710 (69.5)	0.079
Prior use of an antiplatelet agent, N (%)				
Aspirin	797 (57.8)	219 (61.5)	578 (56.6)	0.101
P2Y$_{12}$ inhibitor	365 (26.5)	87 (24.4)	278 (27.2)	0.063
Clopidogrel	314 (22.8)	73 (20.5)	241 (23.6)	
Prasugrel	38 (2.8)	9 (2.5)	29 (2.8)	
Ticagrelor	1 (0.1)	0 (0.0)	1 (0.1)	
Ticlopidine	13 (0.9)	5 (1.4)	8 (0.8)	
Use of an antiplatelet agent at baseline, N (%)				
Aspirin	490 (35.6)	133 (37.4)	357 (34.9)	0.441
P2Y$_{12}$ inhibitor	182 (13.2)	47 (13.2)	135 (13.2)	1
Clopidogrel	167 (12.1)	41 (11.5)	126 (12.3)	
Prasugrel	13 (0.9)	4 (1.1)	9 (0.9)	
Ticagrelor	0 (0.0)	0 (0.0)	0 (0.0)	
Ticlopidine	2 (0.1)	2 (0.6)	0 (0.0)	
Concomitant medication, N (%)				
NSAIDs	33 (2.4)	11 (3.1)	22 (2.2)	0.318
PPI	844 (61.2)	231 (64.9)	613 (60.0)	0.114
CHADS$_2$, mean (SD)	2.3 (1.1)	2.5 (1.1)	2.2 (1.1)	<0.001
CHA$_2$DS$_2$-VASC, mean (SD)	3.7 (1.4)	4.0 (1.4)	3.6 (1.4)	<0.001
HAS-BLED, mean (SD)	2.1 (0.8)	2.1 (0.7)	2.0 (0.8)	0.519

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CI, confidence interval; CrCl, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; SD, standard deviation.
[a]Comparisons between the underdose and standard-dose groups using the Wilcoxon rank-sum test, Fisher's exact test, or chi-squared test.

A. Primary Efficacy Endpoint

	Underdose	Standard dose	HR (95%CI)	p-value
	26/356 (3.62)	71/1,022 (3.51)	1.04 (0.66–1.63)	0.871

Cumulative incidence (%)

—— Underdose
········· Standard dose

Months

At risk
	0	6	12	18	24	30	36
Underdose	356	344	319	261	184	118	34
Standard dose	1,022	998	925	730	503	299	78

B. Primary Safety Endpoint

	Underdose	Standard dose	HR (95%CI)	p-value
	6/356 (0.82)	44/1,022 (2.17)	0.38 (0.16–0.90)	0.022

Cumulative incidence (%)

—— Underdose
········· Standard dose

Months

At risk
	0	6	12	18	24	30	36
Underdose	356	347	323	267	188	120	34
Standard dose	1,022	1,001	928	732	508	298	76

Fig. 2 Primary efficacy and safety endpoints. Cumulative incidences of (**A**) the primary efficacy endpoint, which included stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause, and (**B**) the primary safety endpoint, which included major bleeding. Incidence rates per patient-year are provided in parentheses. CI, confidence interval; HR, hazard ratio.

Primary Efficacy and Safety Endpoints

The primary efficacy endpoint occurred in 26 patients in the underdose group, and it occurred in 71 patients in the standard-dose group, which corresponded to the incidence rates of 3.62% and 3.51% per patient-year, respectively (HR: 1.04; 95% CI: 0.66–1.63; $p = 0.871$) (►Figs. 2A and 3). The incidence of the primary safety endpoint was lower in the underdose group than in the standard-dose group (0.82% vs. 2.17% per patient-year, respectively; HR: 0.38; 95% CI: 0.16–0.90; $p = 0.022$) (►Figs. 2B and 3). These trends in the primary efficacy and safety endpoints did not change when the multivariable Cox hazard model was used to adjust for patient characteristics and treatment group (monotherapy or combination therapy) (underdose group vs. standard-dose group: HR: 0.83; 95% CI: 0.52–1.32; $p = 0.433$ for the primary efficacy endpoint; HR: 0.35; 95% CI: 0.15–0.82; $p = 0.016$ for the primary safety endpoint) (►Tables 2 and 3). The incidences of the secondary endpoints are shown in ►Fig. 3.

Primary Efficacy and Safety Endpoints According to the Treatment Group and Rivaroxaban Dose

►Fig. 4 shows the incidences of the primary efficacy and safety endpoints in patients according to the dose of rivarox-

aban and the treatment group (monotherapy or combination therapy) assigned during the AFIRE trial. There was no difference in the incidence of efficacy events according to the dose of rivaroxaban within the treatment groups. A comparison of the underdose and standard-dose groups revealed a significant decrease in the incidence of the primary safety endpoint in patients on combination therapy (HR: 0.27; 95% CI: 0.08–0.88; $p = 0.002$) but not in those on monotherapy (HR: 0.61; 95% CI: 0.18–2.12; $p = 0.434$). Rivaroxaban monotherapy was associated with a lower incidence of the primary and safety endpoints in the underdose and standard-dose groups (►Supplementary Table S2, available in the online version).
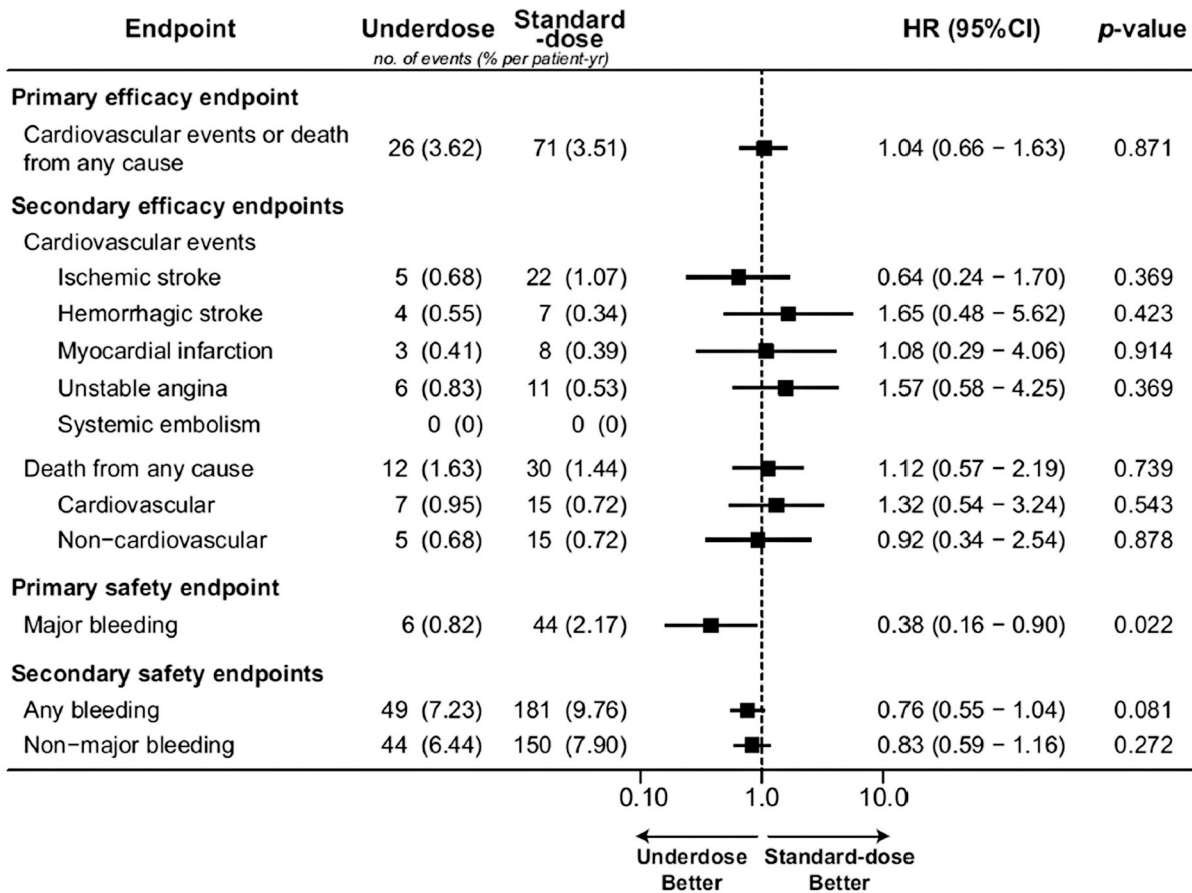
Propensity Score Matching Analyses of the Primary Efficacy and Safety Endpoints

Propensity score matching was performed to ensure baseline similarity between the underdose and standard-dose groups. Propensity score matching resulted in a population of 355 patients in the underdose group and 355 patients in the standard-dose group (►Supplementary Table S3, available in the online version). Consistent with the results before matching, the incidences of the primary efficacy endpoint were similar between the underdose and standard-dose groups after matching (3.63% vs. 3.27% per patient-year, respectively; HR: 1.10; 95% CI: 0.63–1.94; $p = 0.718$; ►Supplementary Fig. S1A, available in the online version). The incidence of the primary safety endpoint was lower in the underdose group than that in the standard-dose group (0.83% vs. 2.13% per patient-year, respectively; HR: 0.39; 95% CI: 0.15–1.00; $p = 0.041$; ►Supplementary Fig. S1B, available in the online version), and this was also consistent with the results before matching.

Discussion

The primary findings in the present study were as follows: (1) approximately one-fourth of the patients in the AFIRE trial received the rivaroxaban underdose therapy at the discretion of their physicians, even with preserved renal function; (2) older patients, females, and patients with lower CrCl, heart failure, or PCI history were more likely to be prescribed an underdose of rivaroxaban than other patients; (3) the rivaroxaban underdose therapy was associated with a significantly lower incidence of bleeding events than the standard-dose therapy; however, there was no significant effect on the incidence of thrombotic events; (4) a significant decrease in the incidence of the primary safety endpoint in the underdose group was observed in patients on combination therapy with rivaroxaban and an antiplatelet agent but not in those on monotherapy with rivaroxaban.

In the present study, 25.8% of the patients with AF, stable CAD, and preserved renal function were treated with an underdose of rivaroxaban, even when a standard dose was recommended. From the guideline, only patients with a CrCl of less than 50 mL/min are eligible for the lower dose of rivaroxaban for AF.[15,16] However, patients who were ≥75 years old, females, and those with heart failure or a prior PCI were associated with an underdose of rivaroxaban in the

Endpoint	Underdose	Standard-dose	HR (95%CI)	p-value
	no. of events (% per patient-yr)			
Primary efficacy endpoint				
Cardiovascular events or death from any cause	26 (3.62)	71 (3.51)	1.04 (0.66 − 1.63)	0.871
Secondary efficacy endpoints				
Cardiovascular events				
Ischemic stroke	5 (0.68)	22 (1.07)	0.64 (0.24 − 1.70)	0.369
Hemorrhagic stroke	4 (0.55)	7 (0.34)	1.65 (0.48 − 5.62)	0.423
Myocardial infarction	3 (0.41)	8 (0.39)	1.08 (0.29 − 4.06)	0.914
Unstable angina	6 (0.83)	11 (0.53)	1.57 (0.58 − 4.25)	0.369
Systemic embolism	0 (0)	0 (0)		
Death from any cause	12 (1.63)	30 (1.44)	1.12 (0.57 − 2.19)	0.739
Cardiovascular	7 (0.95)	15 (0.72)	1.32 (0.54 − 3.24)	0.543
Non-cardiovascular	5 (0.68)	15 (0.72)	0.92 (0.34 − 2.54)	0.878
Primary safety endpoint				
Major bleeding	6 (0.82)	44 (2.17)	0.38 (0.16 − 0.90)	0.022
Secondary safety endpoints				
Any bleeding	49 (7.23)	181 (9.76)	0.76 (0.55 − 1.04)	0.081
Non−major bleeding	44 (6.44)	150 (7.90)	0.83 (0.59 − 1.16)	0.272

0.10   1.0   10.0

← Underdose Better   Standard-dose Better →

Fig. 3 Primary and secondary efficacy and safety endpoints. Hazard ratios for the primary and secondary endpoints per initial dose of rivaroxaban. CI, confidence interval; HR, hazard ratio.

current study. A previous multicenter study demonstrated that the predictors for prescribing an underdose of a DOAC were female sex, older age, lower weight, moderate-to-severe chronic kidney disease, non-European ethnicity, acute coronary syndrome, vascular disease, a history of stroke or diabetes mellitus, and a concomitant antiplatelet agent.[5] Another observational study with a large number of patients reported the relationships between similar factors and DOAC underdosing, wherein the most common reasons

for underdosing were a high bleeding risk, older age, and renal impairment.[7] Similarly, in the present study, the condition of individual patients, including older age, female sex, lower CrCl, heart failure, and PCI history, seemed to affect a physician's decision to alter the DOAC dose, which was probably due to bleeding concerns.

Bleeding events were less common in patients treated with an underdose of DOAC than in those treated with a standard dose; however, thrombotic events were more

Table 2 Multivariable Cox hazard analysis of indicators in the incidence of primary efficacy endpoint

	Adjusted hazard ratio (95% CI)	p-Value
Age ≥75 y	1.39 (0.90–2.15)	0.137
Female sex	1.03 (0.59–1.80)	0.928
CrCl[a] mL/min	0.99 (0.98–1.00)	0.133
Paroxysmal AF	0.60 (0.40–0.92)	0.019
Heart failure	1.64 (1.09–2.48)	0.019
Diabetes	1.70 (1.13–2.55)	0.010
Rivaroxaban underdose	0.83 (0.52–1.32)	0.433
Rivaroxaban monotherapy	0.57 (0.38–0.86)	0.008

Abbreviation: AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; PCI percutaneous coronary intervention.
[a]Per 1 increase.

Table 3 Multivariable Cox hazard analysis of indicators in the incidence of primary safety endpoint

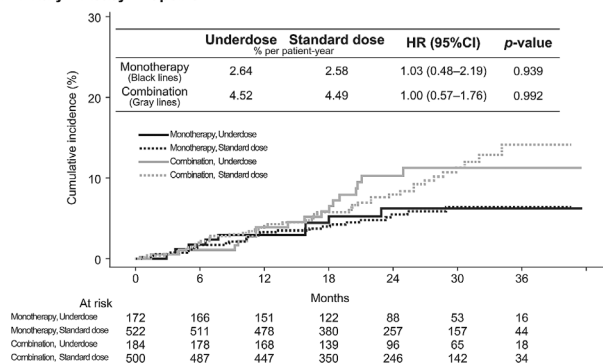|	Adjusted hazard ratio (95% CI)	*p*-Value
Age ≥ 75 y	1.55 (0.87–2.75)	0.136
Female sex	0.65 (0.25–1.65)	0.362
Bleeding diathesis	2.87 (0.66–12.42)	0.159
Previous stroke	2.42 (1.26–4.65)	0.008
Rivaroxaban underdose	0.35 (0.15–0.82)	0.016
Rivaroxaban monotherapy	0.52 (0.29–0.93)	0.027

Abbreviation: CI, confidence interval.

common in the former group in previous studies.[5,8–11] Similarly, in the present study, there were fewer bleeding events in the underdose group than in the standard-dose group, whereas mortality and incidence of cardiovascular events were not different between the groups. These results remained consistent between the groups even after adjusting for baseline characteristics. The present results might be attributed to a possible variation in the risks of adverse events among different races. Previous studies have reported that the frequencies of thrombotic and hemorrhagic events differ between Asian and non-Asian patients with AF on anticoagulant therapy.[17–19] Accordingly, the optimal DOAC dose to prevent adverse events may be different in Asian and non-Asian patients with AF. Lee et al[11] reported the efficacy and safety of the anticoagulation therapy with nonrecommended underdosed DOAC in Asian patients. In this retrospective observational study, nonrecommended underdosed DOAC was associated with a higher risk of thromboembolism compared with warfarin. Although this finding seems to be in contrast with our result, the case cannot be considered equivalent because it was a comparison of anticoagulant therapy with warfarin. In addition to racial differences, it has been reported that thrombotic events are more likely to occur after the onset of bleeding events.[20,21] Given this, the underdose group had less bleeding events than the standard-dose group, which may have resulted in less thrombotic events after the bleeding events in the underdose group. Another possible reason for the equivalent frequencies of thrombotic events with both underdose and standard-dose rivaroxaban therapies is a concomitant optimal medical treatment in the present study. All patients in the AFIRE trial had stable CAD and were likely to receive a relatively long-term medical treatment for secondary prevention, yet detailed data on concomitant therapy were not collected in this study. Newby et al[22] suggested that the long-term use of optimal medical therapy is associated with lower mortality. The optimal medical treatment for the secondary prevention of stable CAD might weaken the effect of standard-dose rivaroxaban therapy. Although patients with stable CAD are thought to be at high risk for thromboembolism or cardiovascular events, bleeding events are a major problem in patients receiving DOAC therapy. Therefore, a balance between the risks of ischemia and hemorrhage should be carefully considered in this population. A previous study demonstrated that physician-guided discontinuation of dual antiplatelet therapy, with careful consideration of the risk of bleeding in individual patients, was associated with a lower risk of cardiovascular events after PCI.[23] The results of our study suggested that physician-guided DOAC underdosing might be a possible treatment option to reduce bleeding events in patients with stable CAD and AF.

The AFIRE trial was a randomized controlled trial that compared rivaroxaban monotherapy and combination therapy of rivaroxaban and an antiplatelet agent. Therefore, it

A. Primary Efficacy Endpoint

	Underdose	Standard dose	HR (95%CI)	*p*-value
	% per patient-year			
Monotherapy (Black lines)	2.64	2.58	1.03 (0.48–2.19)	0.939
Combination (Gray lines)	4.52	4.49	1.00 (0.57–1.76)	0.992

At risk

Monotherapy, Underdose	172	166	151	122	88	53	16
Monotherapy, Standard dose	522	511	478	380	257	157	44
Combination, Underdose	184	178	168	139	96	65	18
Combination, Standard dose	500	487	447	350	246	142	34

B. Primary Safety Endpoint

	Underdose	Standard dose	HR (95%CI)	*p*-value
	% per patient-year			
Monotherapy (Black lines)	0.86	1.42	0.61 (0.18–2.12)	0.434
Combination (Gray lines)	0.79	2.98	0.27 (0.08–0.88)	0.002

At risk

Monotherapy, Underdose	172	167	154	126	89	54	16
Monotherapy, Standard dose	522	516	486	385	261	157	40
Combination, Underdose	184	180	169	141	99	66	18
Combination, Standard dose	500	485	442	347	247	141	36

Fig. 4 Primary efficacy and safety endpoints according to the treatment group and dose of rivaroxaban. Cumulative incidences of (**A**) the primary efficacy endpoint, which included stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause, and (**B**) the primary safety endpoint, which included major bleeding. The doses of rivaroxaban and the treatment group (monotherapy [*solid line*] or combination therapy [*dotted line*]) were assigned during the AFIRE trial. CI, confidence interval; HR, hazard ratio.

should be noted that both monotherapy and combination therapy were included in the present subgroup analysis. Regardless of the standard-dose group and underdose group, DOAC monotherapy was associated with a lower incidence of thrombotic events compared with combination therapy, and this tendency was similar to that in the AFIRE trial. This result emphasizes the main results of the AFIRE trial. The current guidelines recommend a DOAC mono-therapy for the clinical treatment of patients with AF and stable CAD.[24–26] In the present study, a significant decrease in the incidence of the primary safety endpoint in the underdose group was observed in patients on combination therapy but not in those on monotherapy. However, the multivariable Cox hazard model analysis, which adjusted for the treatment group (monotherapy or combination therapy), showed independent superiority of rivaroxaban underdose therapy for the primary safety endpoint. The results of the present study may be useful for the application of antithrombotic therapy in patients with AF in various clinical practice situations. Although the current guidelines recommend standard-dose DOAC monotherapy in patients with AF, stable CAD, and preserved renal function, there are situations in which we should consider weakening or strengthening the antithrombotic regimen because of the risk of bleeding or thrombosis. Thus, if a patient with stable CAD and AF has a very high risk of bleeding or if a patient has been recommended a combination therapy with a DOAC and an antiplatelet agent because of a very high risk of stent thrombosis or for other reasons, an underdose DOAC might be a possible treatment option. Future studies aimed to examine the efficacy and safety of less intensive antithrombotic therapy would make an underdose DOAC into an adequately dosed DOAC.

The present study had some important limitations. First, this was a subgroup analysis of a prospective study, and this design resulted in an insufficient sample size and an under-powered study; therefore, further prospective studies are needed to validate our findings. Second, the dose of rivarox-aban was based on the decision of the treating physician and not standardized. Thus, the results of the present study should be interpreted with caution. Third, the results of the AFIRE trial do not include information regarding the patients' medications at baseline; therefore, medication differences between the present study and previous studies could not be investigated. Fourth, our study consisted only of Japanese patients; this may affect the generalizability of our findings to non-Japanese patients. Finally, rivaroxaban was prescribed at the dose approved in Japan[15] rather than the globally approved once-daily dose of 20 mg.

Conclusion

Physician-guided rivaroxaban underdose therapy resulted in a similar rate of thrombotic events to the standard-dose therapy; however, the rivaroxaban underdose was associated with a lower rate of hemorrhagic events than the standard dose in patients with AF, stable CAD, and preserved renal function. Further prospective studies are needed to validate the efficacy and safety in antithrombotic therapy with underdose DOAC compared with standard-dose DOAC in patients with AF and stable CAD.

What is known about this topic?

- Rivaroxaban monotherapy was noninferior to the combination therapy of rivaroxaban and an antiplate-let agent in terms of cardiovascular events and death from any cause but superior in terms of major bleeding in patients with atrial fibrillation (AF) and coronary artery disease (CAD).
- The antithrombotic regimen for patients with both AF and CAD should be less intensive than the combination of antithrombotic drugs required for each condition.
- Direct oral anticoagulant (DOAC) therapy is a standard therapeutic strategy for patients with AF, with dosage reduction recommended mainly depending on renal function and age. However, in real-world clinical prac-tice, some patients with AF and preserved renal func-tion are treated with nonrecommended low doses of DOACs, depending on their weight, age, or concomitant medications.

What does this paper add?

- Rivaroxaban underdose resulted in a similar rate of thrombotic events to the standard-dose rivaroxaban therapy. However, rivaroxaban underdose was associ-ated with a significantly lower rate of hemorrhagic events than the standard dose.
- Physician-guided administration of rivaroxaban underdose may be appropriate for patients with AF, stable CAD, and preserved renal function.

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