Rivaroxaban monotherapy versus combination therapy according to patient risk of stroke and bleeding in atrial fibrillation and stable coronary disease: AFIRE trial subanalysis

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Background In the AFIRE trial, rivaroxaban monotherapy was noninferior to combination therapy with rivaroxaban and an antiplatelet agent for thromboembolic events or death, and superior for major bleeding in patients with atrial fibrillation (AF) and stable coronary artery disease. Little is known about impacts of stroke and bleeding risks on the efficacy and safety of rivaroxaban monotherapy.

Methods In this subanalysis of the AFIRE trial, we assessed the risk of stroke and bleeding by the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction (MI), unstable angina requiring revascularization, or death from any cause. The primary safety end point was major bleeding defined by the International Society on Thrombosis and Haemostasis.

Results Rivaroxaban monotherapy significantly reduced the primary efficacy and safety end points with no evidence of differential effects by stroke risk ($CHADS_2$, p for interaction = 0.727 for efficacy, 0.395 for safety; CHA_2DS_2-VASc, p for interaction = 0.740 for efficacy, 0.265 for safety) or bleeding risk (HAS-BLED, p for interaction = 0.581 for efficacy, 0.225 for safety). There was also no evidence of statistical heterogeneity across patient risk categories for other end points; stroke or systemic embolism, ischemic stroke, hemorrhagic stroke, MI, MI or unstable angina, death from any cause, any bleeding, or net adverse clinical events.

Conclusions The advantages of rivaroxaban monotherapy compared with those of combination therapy with respect to all prespecified end points, including thromboembolism, bleeding, and mortality were similar across patients with AF and stable coronary artery disease, irrespective of their risk for stroke and bleeding.

Clinical Trial Registration UMIN Clinical Trials Registry number, UMIN000016612, and ClinicalTrials.gov number, NCT02642419. (Am Heart J 2021;236:59–68.)

The optimal antithrombotic strategy, either anticoagulant monotherapy or combination therapy of an anticoagulant plus antiplatelet therapy, for patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) is an important issue in current clinical practice. The Atrial Fibrillation and Ischemic Events with Rivaroxaban

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in Patients with Stable Coronary Artery Disease (AFIRE) trial[1] demonstrated that monotherapy with rivaroxaban, a non-vitamin K antagonist oral anticoagulant, was noninferior to combination therapy with rivaroxaban and an antiplatelet agent, either aspirin or a $P2Y_{12}$ inhibitor, with respect to thromboembolic events or death from any cause and was superior with respect to major bleeding in patients with AF and stable CAD more than 1 year after revascularization or with angiographically confirmed CAD not requiring revascularization.

There are some risk stratification schemes for predicting thromboembolism and bleeding in patients with AF to help inform the treatment decision. The $CHADS_2$ score,[2] which assigns one point each for congestive heart failure, hypertension, age 75 years or older, and diabetes and two points for a previous stroke or transient ischemic attack, and the CHA_2DS_2-VASc score,[3] which assigns points to additional risk factors, such as vascular disease, age 65 to 75 years, and female sex, are the most widely used for the risk assessment of thromboembolism. The HAS-BLED score[4] is used to quantify the risk of bleeding associated with anticoagulant use in patients with AF. Among a number of risk scores developed for AF patients, these have been well-validated worldwide and are implemented in the current clinical guidelines for the management of AF,[5,6] and therefore we prespecified the analysis stratified by these scores.

In this pre-specified subgroup analysis of the AFIRE trial, we assessed the efficacy and safety of rivaroxaban monotherapy versus combination therapy according to patient risk categories, as determined by the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores in patients with AF and stable CAD.

Methods

Trial design and oversight

The AFIRE trial was a randomized, multicenter, open-label, parallel-group trial conducted in Japan. Details of the trial design and results of the primary analysis have been previously described.[1,7] In brief, the inclusion criteria of the trial were men and women aged ≥20 years diagnosed with AF and stable CAD, patients with a baseline $CHADS_2$ score ≥1, and patients who met at least one of the following criteria: history of percutaneous coronary intervention (PCI), including angioplasty with or without stenting, at least 1 year prior to enrollment; history of angiographically confirmed CAD (stenosis of 50% or greater) not requiring revascularization; or history of coronary artery bypass grafting at least 1 year prior to enrollment. Key exclusion criteria were history of stent thrombosis, a coexisting active tumor, or poorly controlled hypertension. All patients provided written informed consent before enrollment. The trial was conducted according to the Declaration of Helsinki and was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Japan, and the institutional review boards of all participating institutions. Data were reviewed by an independent data and safety monitoring committee. Funding was provided by the Japan Cardiovascular Research Foundation under a contract with Bayer Yakuhin. The company had no role in the design of the trial, in the collection or analysis of the data, in the interpretation of the trial results, or in the writing of the manuscript.

Randomization and treatment

Patients were randomly assigned in equal numbers to either the group receiving monotherapy with rivaroxaban (10 mg once daily for patients with a creatinine clearance [CrCl] of 15–49 mL/min or 15 mg once daily for patients with a CrCl ≥50 mL/min) or combination therapy with rivaroxaban and an antiplatelet agent (aspirin or a $P2Y_{12}$ inhibitor, according to the discretion of the treating physician).

End points

The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction (MI), unstable angina requiring revascularization, or death from any cause. The primary safety end point was major bleeding, as defined according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH).

Other end points were stroke or systemic embolism; ischemic stroke; hemorrhagic stroke; MI; MI or unstable angina; death from any cause; any bleeding; or net adverse clinical events (composite of death from any cause, MI, stroke, or major bleeding). Any bleeding was defined as major or nonmajor bleeding, according to the criteria of ISTH. Blinded adjudication of the end points was conducted by an independent clinical events committee.

Risk scores

To compare efficacy, safety, and balance of efficacy and safety of rivaroxaban monotherapy versus combination therapy across patient risk categories, we calculated the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores for every patient at randomization. The $CHADS_2$ score[2] ranges from 0 to 6, with higher scores indicating a greater risk of stroke. The CHA_2DS_2-VASc score[3] ranges from 0 to 9, with higher scores indicating a greater risk of stroke. "C" of the CHA_2DS_2-VASc score was counted when congestive heart failure was present; left ventricular dysfunction was not included, since echocardiographic data were not available in all trial patients. "V" of the CHA_2DS_2-VASc score was counted when prior myocardial infarction or peripheral artery disease was present; aortic plaque was not included. The HAS-BLED score[4] ranges from 0 to 9, with higher scores indicating a greater risk of bleeding. The "L," or the labile international normalized ratio of prothrombin time, was not included.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are presented as counts and percentages. Annualized event rates of end points are expressed as percentage per patient-year. A Cox proportional-hazards model was used to compare outcomes between the groups, with the results expressed as a hazard ratio (HR) with a 95% confidence interval (CI). Interactions between the effects of rivaroxaban monotherapy versus combination therapy and patient risk categories were assessed. The performance of $CHADS_2$ and CHA_2DS_2-VASc scores for stroke or systemic embolism and that of the HAS-BLED score for major bleeding were evaluated using receiver operating characteristic analysis. The data were expressed as C-statistics with a 95% CI.

All statistical analyses were performed using SAS software, version 9.4 for Windows (SAS Institute, Cary, NC).

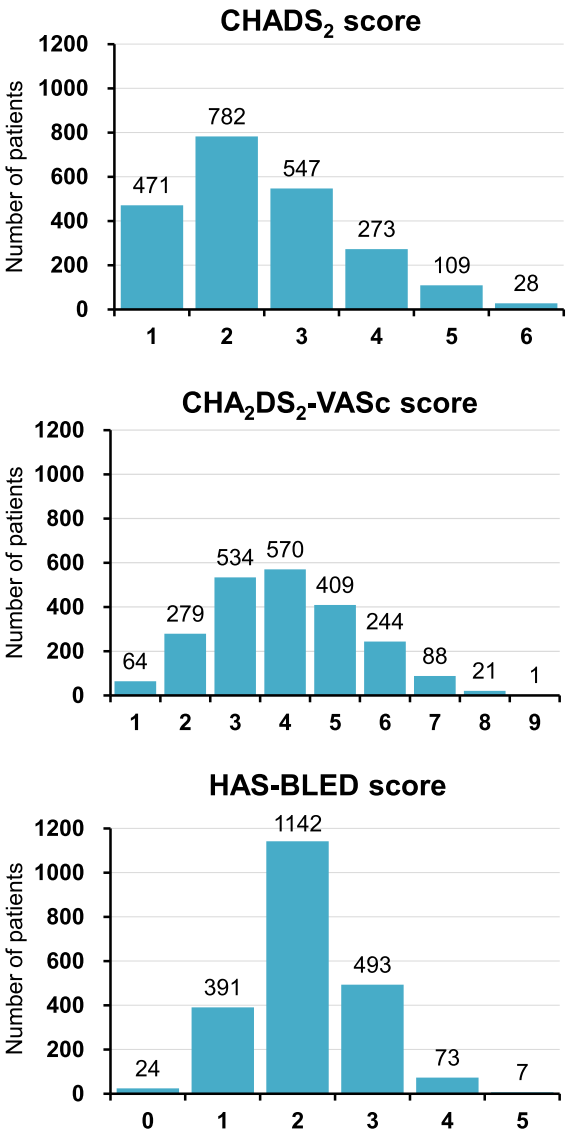
Results

Baseline characteristics

In this sub-analysis, of the 2215 patients included in the AFIRE trial, 2210 were analyzed for the $CHADS_2$ and CHA_2DS_2-VASc scores and 2130 for the HAS-BLED score, due to incomplete data entry. The median follow-up period was 24.1 months (interquartile range, 17.3-31.5). The mean age was 74 years and 79% of patients were men. The distribution of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores is shown in Figure 1.

Table 1 shows the baseline characteristics of patients according to the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores (1, 2, or ≥3 for $CHADS_2$ and CHA_2DS_2-VASc; 0-1, 2, or ≥3 for HAS-BLED). With increasing $CHADS_2$ scores, patients were more likely to be older, have more comorbidities included in the score components such as heart failure, hypertension, diabetes, and previous stroke, have a higher HAS-BLED score, and receive the reduced dose of rivaroxaban (10 mg once daily) and less likely to have paroxysmal-type AF. The proportions of patients who underwent PCI and the type of coronary stent placed were not different among the groups. The majority of patients were categorized as CHA_2DS_2-VASc ≥3 ($n = 1867$, 84.5%), were older with more comorbidities, and had higher HAS-BLED scores than those with CHA_2DS_2-VASc scores of 1 ($n = 64$, 3.0%) and 2 ($n = 279$, 12.6%). With increasing HAS-BLED scores, patients were likely to be older, have a history of stroke or bleeding, have lower CrCl, receive a reduced dose of rivaroxaban (10 mg once daily) more frequently, and have higher $CHADS_2$ and CHA_2DS_2-VASc scores. The proportion of patients who underwent PCI was higher as the HAS-BLED score increased, but the type of coronary stents was not different among the groups.

Figure 1



Distribution of $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores.

End points

Irrespective of the $CHADS_2$ categories ($CHADS_2$ 1, 2, or ≥3), lower proportions of patients assigned to rivaroxaban monotherapy than those assigned to combination therapy reached the primary efficacy (HR 0.72, 95% CI 0.55-0.95) and safety (HR 0.59, 95% CI 0.39-0.89) end points with no evidence of statistical heterogeneity ($CHADS_2$ 1, 2, or ≥3, p for interaction = 0.727 for efficacy, 0.395 for safety) (Figure 2). Rivaroxaban monotherapy was also favored when considering other end points, such as stroke or systemic embolism (HR 0.66, 95% CI

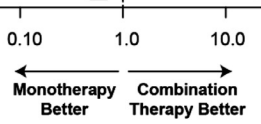
Table 1. Baseline characteristics according to $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores.

	$CHADS_2$ score			CHA_2DS_2-VASc score			HAS-BLED score		
	1 (n = 471)	2 (n = 782)	≥3 (n = 957)	1 (n = 64)	2 (n = 279)	≥3 (n = 1867)	0-1 (n = 415)	2 (n = 1142)	≥3 (n = 573)
Age, mean (SD), y	69.4 (7.0)	74.2 (8.2)	76.9 (7.7)	59.2 (5.0)	68.9 (6.9)	75.6 (7.6)	70.1 (10.6)	75.6 (7.3)	75.1 (6.9)
<75, No. (%), y	409 (86.8)	374 (47.8)	264 (27.6)	64 (100)	246 (88.2)	737 (39.5)	259 (62.4)	481 (42.1)	261 (45.5)
≥75, No. (%), y	62 (13.2)	408 (52.2)	693 (72.4)	0 (0)	33 (11.8)	1,130 (60.5)	156 (37.6)	661 (57.9)	312 (54.5)
Men, No. (%)	411 (87.3)	611 (78.1)	724 (75.7)	64 (100)	278 (99.6)	1,404 (75.2)	307 (74.0)	874 (76.5)	500 (87.3)
Body mass index, mean (SD), kg/m^2	24.3 (3.4)	24.5 (3.8)	24.5 (3.7)	24.4 (3.3)	24.7 (3.6)	24.5 (3.7)	24.9 (4.0)	24.5 (3.7)	24.3 (3.5)
Type of AF, No. (%)									
Paroxysmal	299 (63.5)	422 (54.0)	452 (47.2)	43 (67.2)	163 (58.4)	967 (51.8)	212 (51.1)	628 (55.0)	290 (50.6)
Persistent	69 (14.6)	111 (14.2)	158 (16.5)	11 (17.2)	42 (15.1)	282 (15.3)	72 (17.3)	166 (14.5)	86 (15.0)
Permanent	103 (21.9)	249 (31.8)	347 (36.3)	10 (15.6)	74 (26.5)	615 (32.9)	131 (31.6)	348 (30.5)	197 (34.4)
Hypertension, No. (%)	333 (70.7)	673 (86.1)	885 (92.5)	57 (89.1)	205 (73.5)	1629 (87.3)	357 (86.0)	965 (84.5)	501 (87.4)
Diabetes, No. (%)	37 (7.9)	290 (37.1)	600 (62.7)	3 (4.7)	50 (17.9)	874 (46.8)	174 (41.9)	465 (40.7)	251 (43.8)
Dyslipidemia, No. (%)	311 (66.0)	547 (69.9)	677 (70.7)	42 (65.6)	184 (65.9)	1309 (70.1)	258 (62.2)	816 (71.5)	404 (70.5)
Heart failure, No. (%)	39 (8.3)	173 (22.1)	576 (60.2)	4 (6.3)	27 (9.7)	757 (40.5)	153 (36.9)	406 (35.6)	195 (34.0)
Bleeding predisposition, No. (%)	6 (1.3)	6 (0.8)	20 (2.1)	1 (1.6)	4 (1.4)	27 (1.4)	0 (0)	4 (0.4)	27 (4.7)
Bleeding history, No. (%)	10 (2.1)	19 (2.4)	30 (3.1)	0 (0)	8 (2.9)	51 (2.7)	0 (0)	8 (0.7)	49 (8.6)
Previous stroke, No. (%)	0 (0)	10 (1.3)	313 (32.7)	0 (0)	2 (0.7)	321 (17.2)	1 (0.2)	57 (5.0)	258 (45.0)
Previous transient ischemic attack, No. (%)	0 (0)	0 (0)	48 (5.0)	0 (0)	0 (0)	48 (2.6)	5 (1.2)	26 (2.3)	17 (3.0)
Previous systemic embolism, No. (%)	1 (0.2)	3 (0.4)	7 (0.7)	0 (0)	0 (0)	11 (0.6)	3 (0.7)	4 (0.4)	4 (0.7)
Previous MI, No. (%)	138 (29.3)	278 (35.5)	360 (37.6)	0 (0)	23 (8.2)	753 (40.3)	118 (28.4)	412 (36.1)	211 (36.8)
Peripheral arterial disease, No. (%)	8 (1.7)	35 (4.5)	96 (10.0)	0 (0)	1 (0.4)	138 (7.4)	16 (3.9)	64 (5.6)	52 (9.1)
Previous PCI, No. (%)	319 (67.7)	576 (73.7)	665 (69.5)	34 (53.1)	172 (61.6)	1354 (72.5)	197 (47.5)	862 (75.5)	452 (78.9)
Type of stent, No./Total No. (%)									
Bare-metal	72/294 (24.5)	143/531 (26.9)	127/616 (20.6)	6/31 (19.4)	32/164 (19.5)	304/1246 (24.4)	47/173 (27.2)	200/802 (24.9)	88/419 (21.0)
Drug-eluting	201/294 (68.4)	348/531 (65.5)	425/616 (69.0)	22/31 (71.0)	123/164 (75.0)	829/1246 (66.5)	111/173 (64.2)	533/802 (66.5)	295/419 (70.4)
Both types	11/294 (3.7)	20/531 (3.8)	24/616 (3.9)	2/31 (6.5)	4/164 (2.4)	49/1246 (3.9)	6/173 (3.5)	30/802 (3.7)	17/419 (4.1)
Previous CABG, No. (%)	36 (7.6)	78 (10.0)	138 (14.4)	0 (0)	25 (9.0)	227 (12.2)	31 (7.5)	132 (11.6)	75 (13.1)
Initial dose of rivaroxaban, No. (%)									
10 mg/day	132 (28.0)	345 (44.1)	533 (55.7)	5 (7.8)	75 (26.9)	930 (49.8)	153 (36.9)	561 (49.1)	263 (45.9)
15 mg/day	333 (70.7)	429 (54.9)	417 (43.6)	59 (92.2)	202 (72.4)	918 (49.2)	258 (62.2)	572 (50.1)	302 (52.7)
$CHADS_2$ score									
Median	1	2	3	1	1	3	2	2	3
Mean (SD)	1.0 (0)	2.0 (0)	3.6 (0.8)	1.0 (0)	1.1 (0.4)	2.7 (1.1)	2.1 (0.9)	2.3 (1.0)	3.1 (1.4)
CHA_2DS_2-VASc score									
Median	2	3	5	1	2	4	3	4	5
Mean (SD)	2.2 (0.7)	3.5 (0.7)	5.2 (1.1)	1.0 (0)	2.0 (0)	4.4 (1.2)	3.3 (1.4)	3.9 (1.3)	4.6 (1.6)
HAS-BLED score									
Median	2	2	2	1	2	2	1	2	3
Mean (SD)	1.9 (0.8)	1.9 (0.7)	2.3 (0.8)	1.3 (0.7)	1.9 (0.8)	2.2 (0.8)	0.9 (0.2)	2.0 (0)	3.2 (0.4)
Creatinine clearance, mean (SD), mL/min	72.5 (24.3)	63.9 (25.4)	56.0 (22.8)	92.5 (20.6)	74.6 (23.7)	59.4 (24.0)	72.1 (32.0)	59.4 (21.9)	60.6 (22.8)
<30, No./Total No. (%), mL/min	5/434 (1.2)	28/737 (3.8)	81/916 (8.8)	0/57 (0)	1/265 (0.4)	113/1765 (6.4)	14/394 (3.6)	64/1090 (5.9)	35/545 (6.4)
30 to <50, No./Total No. (%), mL/min	53/434 (12.2)	213/737 (28.9)	327/916 (35.7)	0/57 (0)	26/265 (9.8)	567/1765 (32.1)	82/394 (20.8)	341/1090 (31.3)	154/545 (28.3)
≥50, No./Total No. (%), mL/min	376/434 (86.6)	496/737 (67.3)	508/916 (55.5)	57/57 (100)	238/265 (89.8)	1085/1765 (61.5)	298/394 (75.6)	685/1090 (62.8)	356/545 (65.3)

AF, atrial fibrillation; *PCI,* percutaneous coronary intervention; *CABG,* coronary artery bypass grafting; *MI,* myocardial infarction; *SD,* standard deviation.

Figure 2

Subgroup	Rivaroxaban Monotherapy *no. of events/total no. (% per patient-yr)*	Combination Therapy *no. of events/total no. (% per patient-yr)*	Hazard Ratio (95%CI)	P Value	P for Interaction
Primary efficacy endpoint	89 / 1104 (4.15)	121 / 1106 (5.76)	0.72 (0.55 – 0.95)	0.020	0.727
1	9 / 230 (1.98)	13 / 241 (2.76)	0.72 (0.31 – 1.68)	0.442	
2	24 / 404 (2.97)	36 / 378 (4.85)	0.61 (0.37 – 1.03)	0.062	
≥3	56 / 470 (6.35)	72 / 487 (8.12)	0.79 (0.55 – 1.11)	0.174	
Stroke/systemic embolism	27 / 1104 (1.24)	40 / 1106 (1.87)	0.66 (0.41 – 1.08)	0.095	0.408
1	1 / 230 (0.22)	5 / 241 (1.04)	0.21 (0.03 – 1.83)	0.121	
2	5 / 404 (0.60)	9 / 378 (1.19)	0.51 (0.17 – 1.51)	0.214	
≥3	21 / 470 (2.35)	26 / 487 (2.89)	0.81 (0.46 – 1.45)	0.483	
Ischemic stroke	21 / 1104 (0.96)	28 / 1106 (1.31)	0.73 (0.42 – 1.29)	0.284	0.437
1	1 / 230 (0.22)	4 / 241 (0.83)	0.27 (0.03 – 2.38)	0.204	
2	4 / 404 (0.48)	7 / 378 (0.93)	0.52 (0.15 – 1.78)	0.289	
≥3	16 / 470 (1.78)	17 / 487 (1.88)	0.95 (0.48 – 1.88)	0.880	
Hemorrhagic stroke	4 / 1104 (0.18)	13 / 1106 (0.60)	0.30 (0.10 – 0.92)	0.026	0.956
1	0 / 230 (–)	1 / 241 (0.21)	–	0.345	
2	1 / 404 (0.12)	2 / 378 (0.26)	0.46 (0.04 – 5.04)	0.512	
≥3	3 / 470 (0.33)	10 / 487 (1.09)	0.30 (0.08 – 1.08)	0.051	
MI/unstable angina	26 / 1104 (1.20)	26 / 1106 (1.22)	0.98 (0.57 – 1.70)	0.956	0.890
1	5 / 230 (1.10)	5 / 241 (1.05)	1.04 (0.30 – 3.60)	0.947	
2	10 / 404 (1.23)	8 / 378 (1.07)	1.14 (0.45 – 2.90)	0.776	
≥3	11 / 470 (1.22)	13 / 487 (1.44)	0.86 (0.38 – 1.91)	0.707	
MI	13 / 1104 (0.59)	8 / 1106 (0.37)	1.61 (0.67 – 3.87)	0.287	0.781
1	3 / 230 (0.66)	2 / 241 (0.42)	1.55 (0.26 – 9.30)	0.627	
2	7 / 404 (0.86)	3 / 378 (0.40)	2.16 (0.56 – 8.34)	0.254	
≥3	3 / 470 (0.33)	3 / 487 (0.33)	1.01 (0.20 – 5.03)	0.986	
Death from any cause	41 / 1104 (1.86)	73 / 1106 (3.38)	0.55 (0.38 – 0.81)	0.002	0.670
1	3 / 230 (0.65)	5 / 241 (1.03)	0.64 (0.15 – 2.68)	0.539	
2	10 / 404 (1.20)	22 / 378 (2.90)	0.42 (0.20 – 0.88)	0.018	
≥3	28 / 470 (3.05)	46 / 487 (5.01)	0.61 (0.38 – 0.97)	0.036	
Primary safety endpoint	35 / 1104 (1.61)	58 / 1106 (2.76)	0.59 (0.39 – 0.89)	0.012	0.395
1	6 / 230 (1.32)	7 / 241 (1.47)	0.90 (0.30 – 2.68)	0.852	
2	15 / 404 (1.85)	19 / 378 (2.59)	0.72 (0.36 – 1.41)	0.333	
≥3	14 / 470 (1.55)	32 / 487 (3.60)	0.43 (0.23 – 0.81)	0.007	
Any bleeding	146 / 1104 (7.21)	239 / 1106 (12.75)	0.57 (0.47 – 0.70)	<0.001	0.249
1	30 / 230 (7.12)	54 / 241 (12.91)	0.55 (0.36 – 0.87)	0.009	
2	58 / 404 (7.71)	72 / 378 (10.80)	0.72 (0.51 – 1.02)	0.066	
≥3	58 / 470 (6.82)	113 / 487 (14.31)	0.48 (0.35 – 0.66)	<0.001	
Net adverse clinical events	84 / 1104 (3.91)	131 / 1106 (6.29)	0.62 (0.47 – 0.82)	<0.001	0.791
1	10 / 230 (2.21)	13 / 241 (2.75)	0.81 (0.35 – 1.84)	0.609	
2	30 / 404 (3.76)	44 / 378 (6.04)	0.62 (0.39 – 0.99)	0.044	
≥3	44 / 470 (4.91)	74 / 487 (8.39)	0.58 (0.40 – 0.85)	0.004	



End points by $CHADS_2$ score. *MI,*myocardial infarction.

0.41-1.08), ischemic stroke (HR 0.73, 95% CI 0.42-1.29), hemorrhagic stroke (HR 0.30, 95% CI 0.10-0.92), death from any cause (HR 0.55, 95% CI 0.38-0.81), any bleeding (HR 0.57, 95% CI 0.47-0.70), and net adverse clinical events (HR 0.62, 95% CI 0.47-0.82). Statistical tests for interaction were not significant for the $CHADS_2$ categories in all end points (Figure 2). The HRs for the incidence of ischemic stroke were numerically lower in the lower $CHADS_2$ categories (score 1: 0.27, score 2: 0.52, score ≥3: 0.95), but the p-value for interaction was not significant (P= .437). In contrast, the HRs for the incidence of the primary safety end point were numerically lower in the higher $CHADS_2$ categories (score 1: 0.90, score 2: 0.72, score ≥3: 0.43), but the p-value for interaction was not significant (P= .395). MI was nonsignificantly higher in the monotherapy group (HR 1.61, 95% CI 0.67-3.87) without subgroup heterogeneity, but the combined MI and unstable angina was neutral between the treatment arms (HR 0.98, 95% CI 0.57-1.70).

The benefits of rivaroxaban monotherapy compared with those of combination therapy for all end points across the CHA_2DS_2-VASc categories were similar to those seen across the $CHADS_2$ categories (CHA_2DS_2-VASc 1, 2, or ≥3, p for interaction = 0.740 for efficacy, 0.265 for safety) (Figure 3).

Irrespective of the HAS-BLED categories (HAS-BLED 0-1, 2, or ≥3), lower rates of patients assigned to rivaroxaban monotherapy reached the primary efficacy safety end points with no evidence of statistical heterogeneity (HAS-BLED 0-1, 2, or ≥3, p for interaction = 0.581 for efficacy, 0.225 for safety) (Figure 4). For all other end points, statistical tests for interaction were not significant for the HAS-BLED categories.

The incidences of stroke or systemic embolism and major bleeding according to the risk score categories are shown in Figure 5. There was a modest increase in the incidence of stroke or systemic embolism as the $CHADS_2$ score increased, but the association between the incidence of bleeding and the HAS-BLED score was poor. Receiver operating characteristic analysis demonstrated that the C-statistics of the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke or systemic embolism were 0.6480 (95% CI: 0.5863-0.7097) and 0.6373 (95% CI: 0.5728-0.7018), respectively, and that of the HAS-BLED score for major bleeding was 0.5329 (95% CI: 0.4742-0.5916).

Discussion

The major findings of this subanalysis were as follows: (1) the baseline clinical characteristics of patients with different risk categories were distinctive; (2) the advantages of rivaroxaban monotherapy compared with those of combination therapy with regard to pre-specified primary end points as well as various secondary end points including thromboembolism, bleeding, and mortality were consistent across patients with different risk categories assessed by the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores; and (3) the C-statistics of the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke or systemic embolism were 0.6480 and 0.6373, respectively, and that of the HAS-BLED score for major bleeding was 0.5329 in AF patients with CAD taking rivaroxaban.

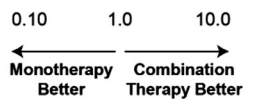
A substantial proportion of patients with AF also have CAD; the estimated prevalence of CAD was reportedly 19.2% in the international cohort,[8] 23.4% in the European cohort,[9] and 15.0% in the Japanese cohort.[10] Patients with both AF and CAD are at an increased risk for ischemic events and cardiovascular death than those with AF and without CAD.[11,12] These patients are likely to be administered an oral anticoagulant and an antiplatelet agent, further placing them at a high risk of bleeding.[13,14] Thus, the selection of the most effective antithrombotic regimen for patients with AF and CAD is challenging, requiring careful assessment of risk of thromboembolism and bleeding in each patient.

For assessing the risk of stroke, numerous risk scores have been postulated. The most widely used stroke risk scores are the $CHADS_2$ and CHA_2DS_2-VASc scores, which have been implemented in the current AF treatment guidelines.[5,6] Despite their widespread use, these scores are, at best, only modestly good at predicting an individual's risk of thromboembolism, with a C-statistics of around 0.6.[15] Furthermore, it has not been well-validated whether these scores can be applied to patients with both AF and CAD. The present subanalysis showed that high $CHADS_2$ or CHA_2DS_2-VASc scores identified patients at a high risk of stroke during treatment with rivaroxaban monotherapy or combination therapy, but the performance of these scores was suboptimal. However, it should be noted that the distribution of patients, especially in the application of the CHA_2DS_2-VASc score, is very skewed with very few patients in the low score groups, thereby minimizing the power of to detect differences between scores.

Similarly, several bleeding risk scores have been proposed; guidelines have recommended the HAS-BLED score to help guide decisions about anticoagulation therapy. A score of 3 or higher suggests a high risk of bleeding that merits some caution or regular clinical review of the patient.[5,6] In our analysis, we showed that a higher HAS-BLED score was poorly associated with increased bleeding risk during treatment with rivaroxaban monotherapy or combination therapy. In addition, rivaroxaban monotherapy was better than combination therapy in reducing bleeding across all HAS-BLED score categories. The performance of the HAS-BLED score, originally developed to assess bleeding risk of patients receiving warfarin, was poor in stratifying bleeding risk in the AFIRE trial participants, suggesting the difficulty in bleeding risk assessment in patients with AF and CAD taking a non-vitamin K antagonist oral anticoagulant. Despite the limitation of our observation from a relatively small

Figure 3

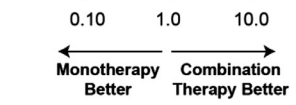
Subgroup	Rivaroxaban Monotherapy *no. of events/total no. (% per patient-yr)*	Combination Therapy *no. of events/total no. (% per patient-yr)*	Hazard Ratio (95%CI)	P Value	P for Interaction
Primary efficacy endpoint	89 / 1104 (4.15)	121 / 1106 (5.76)	0.72 (0.55 – 0.95)	0.020	0.740
1	1 / 30 (1.74)	2 / 34 (3.19)	0.65 (0.06 – 7.37)	0.730	
2	4 / 131 (1.59)	10 / 148 (3.42)	0.46 (0.14 – 1.47)	0.180	
≥3	84 / 943 (4.58)	109 / 924 (6.25)	0.73 (0.55 – 0.98)	0.033	
Stroke/systemic embolism	27 / 1104 (1.24)	40 / 1106 (1.87)	0.66 (0.41 – 1.08)	0.095	1.000
1	0 / 30 (–)	1 / 34 (1.60)	–	0.333	
2	0 / 131 (–)	2 / 148 (0.66)	–	0.182	
≥3	27 / 943 (1.45)	37 / 924 (2.09)	0.69 (0.42 – 1.14)	0.144	
Ischemic stroke	21 / 1104 (0.96)	28 / 1106 (1.31)	0.73 (0.42 – 1.29)	0.284	1.000
1	0 / 30 (–)	1 / 34 (1.60)	–	0.333	
2	0 / 131 (–)	2 / 148 (0.66)	–	0.182	
≥3	21 / 943 (1.12)	25 / 924 (1.41)	0.80 (0.45 – 1.42)	0.441	
Hemorrhagic stroke	4 / 1104 (0.18)	13 / 1106 (0.60)	0.30 (0.10 – 0.92)	0.026	1.000
1	0 / 30 (–)	0 / 34 (–)	–	–	
2	0 / 131 (–)	0 / 148 (–)	–	–	
≥3	4 / 943 (0.21)	13 / 924 (0.73)	0.29 (0.09 – 0.89)	0.021	
MI/unstable angina	26 / 1104 (1.20)	26 / 1106 (1.22)	0.98 (0.57 – 1.70)	0.956	0.916
1	0 / 30 (–)	0 / 34 (–)	–	–	
2	4 / 131 (1.59)	6 / 148 (2.02)	0.79 (0.22 – 2.80)	0.714	
≥3	22 / 943 (1.18)	20 / 924 (1.13)	1.05 (0.58 – 1.93)	0.865	
MI	13 / 1104 (0.59)	8 / 1106 (0.37)	1.61 (0.67 – 3.87)	0.287	0.997
1	0 / 30 (–)	0 / 34 (–)	–	–	
2	3 / 131 (1.19)	2 / 148 (0.66)	1.76 (0.29 – 10.51)	0.533	
≥3	10 / 943 (0.53)	6 / 924 (0.34)	1.61 (0.58 – 4.42)	0.355	
Death from any cause	41 / 1104 (1.86)	73 / 1106 (3.38)	0.55 (0.38 – 0.81)	0.002	0.880
1	1 / 30 (1.74)	1 / 34 (1.57)	1.48 (0.09 – 24.46)	0.782	
2	0 / 131 (–)	2 / 148 (0.65)	–	0.186	
≥3	40 / 943 (2.11)	70 / 924 (3.91)	0.54 (0.37 – 0.80)	0.002	
Primary safety endpoint	35 / 1104 (1.61)	58 / 1106 (2.76)	0.59 (0.39 – 0.89)	0.012	0.265
1	0 / 30 (–)	3 / 34 (4.96)	–	0.094	
2	4 / 131 (1.58)	2 / 148 (0.66)	2.39 (0.44 – 13.07)	0.299	
≥3	31 / 943 (1.67)	53 / 924 (3.05)	0.55 (0.35 – 0.86)	0.007	
Any bleeding	146 / 1104 (7.21)	239 / 1106 (12.75)	0.57 (0.47 – 0.70)	<0.001	0.356
1	2 / 30 (3.59)	8 / 34 (14.82)	0.25 (0.05 – 1.19)	0.059	
2	20 / 131 (8.65)	30 / 148 (11.37)	0.75 (0.43 – 1.32)	0.322	
≥3	124 / 943 (7.14)	201 / 924 (12.91)	0.56 (0.45 – 0.70)	<0.001	
Net adverse clinical events	84 / 1104 (3.91)	131 / 1106 (6.29)	0.62 (0.47 – 0.82)	<0.001	0.439
1	1 / 30 (1.74)	3 / 34 (4.96)	0.40 (0.04 – 3.86)	0.410	
2	6 / 131 (2.40)	6 / 148 (2.01)	1.19 (0.38 – 3.68)	0.766	
≥3	77 / 943 (4.19)	122 / 924 (7.08)	0.59 (0.45 – 0.79)	<0.001	



End points by CHA_2DS_2-VASc score. *MI*, myocardial infarction.

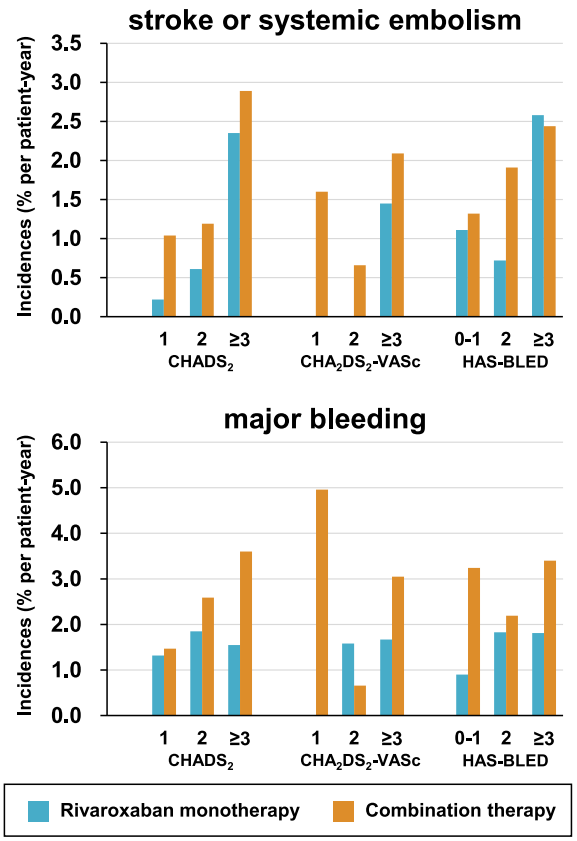
Figure 4

Subgroup	Rivaroxaban Monotherapy *no. of events/total no. (% per patient-yr)*	Combination Therapy *no. of events/total no. (% per patient-yr)*	Hazard Ratio (95%CI)	P Value	P for Interaction
Primary efficacy endpoint	86 / 1066 (4.16)	120 / 1064 (5.90)	0.71 (0.54 – 0.93)	0.013	0.581
0-1	16 / 223 (3.64)	17 / 192 (4.61)	0.79 (0.40 – 1.57)	0.500	
2	42 / 560 (3.84)	71 / 582 (6.22)	0.62 (0.42 – 0.91)	0.013	
≥3	28 / 283 (5.22)	32 / 290 (6.12)	0.86 (0.52 – 1.42)	0.547	
Stroke/systemic embolism	27 / 1066 (1.28)	40 / 1064 (1.93)	0.66 (0.41 – 1.08)	0.097	0.172
0-1	5 / 223 (1.11)	5 / 192 (1.32)	0.85 (0.25 – 2.94)	0.798	
2	8 / 560 (0.72)	22 / 582 (1.91)	0.38 (0.17 – 0.85)	0.014	
≥3	14 / 283 (2.58)	13 / 290 (2.44)	1.06 (0.50 – 2.26)	0.876	
Ischemic stroke	21 / 1066 (1.00)	28 / 1064 (1.35)	0.74 (0.42 – 1.30)	0.288	0.381
0-1	3 / 223 (0.67)	3 / 192 (0.79)	0.85 (0.17 – 4.22)	0.845	
2	6 / 560 (0.54)	14 / 582 (1.21)	0.45 (0.17 – 1.16)	0.089	
≥3	12 / 283 (2.20)	11 / 290 (2.06)	1.08 (0.48 – 2.45)	0.850	
Hemorrhagic stroke	4 / 1066 (0.19)	13 / 1064 (0.62)	0.30 (0.10 – 0.93)	0.027	0.337
0-1	1 / 223 (0.22)	2 / 192 (0.52)	0.42 (0.04 – 4.68)	0.471	
2	1 / 560 (0.09)	9 / 582 (0.77)	0.11 (0.01 – 0.90)	0.013	
≥3	2 / 283 (0.36)	2 / 290 (0.37)	0.92 (0.13 – 6.54)	0.932	
MI/unstable angina	24 / 1066 (1.14)	26 / 1064 (1.26)	0.91 (0.52 – 1.58)	0.734	0.902
0-1	6 / 223 (1.36)	7 / 192 (1.88)	0.72 (0.24 – 2.15)	0.556	
2	11 / 560 (1.00)	12 / 582 (1.04)	0.95 (0.42 – 2.15)	0.898	
≥3	7 / 283 (1.27)	7 / 290 (1.31)	0.99 (0.35 – 2.81)	0.978	
MI	12 / 1066 (0.57)	8 / 1064 (0.38)	1.48 (0.61 – 3.63)	0.386	0.674
0-1	4 / 223 (0.90)	3 / 192 (0.80)	1.12 (0.25 – 5.01)	0.880	
2	5 / 560 (0.45)	2 / 582 (0.17)	2.57 (0.50 – 13.26)	0.241	
≥3	3 / 283 (0.54)	3 / 290 (0.56)	0.99 (0.20 – 4.91)	0.990	
Death from any cause	40 / 1066 (1.88)	72 / 1064 (3.44)	0.55 (0.37 – 0.81)	0.002	0.511
0-1	8 / 223 (1.77)	7 / 192 (1.83)	0.97 (0.35 – 2.68)	0.955	
2	23 / 560 (2.06)	49 / 582 (4.20)	0.50 (0.30 – 0.82)	0.005	
≥3	9 / 283 (1.61)	16 / 290 (2.94)	0.54 (0.24 – 1.23)	0.138	
Primary safety endpoint	34 / 1066 (1.63)	55 / 1064 (2.70)	0.60 (0.39 – 0.92)	0.019	0.225
0-1	4 / 223 (0.90)	12 / 192 (3.24)	0.28 (0.09 – 0.87)	0.018	
2	20 / 560 (1.83)	25 / 582 (2.19)	0.82 (0.46 – 1.48)	0.518	
≥3	10 / 283 (1.81)	18 / 290 (3.40)	0.53 (0.24 – 1.15)	0.101	
Any bleeding	142 / 1066 (7.27)	228 / 1064 (12.53)	0.59 (0.48 – 0.72)	<0.001	0.054
0-1	23 / 223 (5.41)	50 / 192 (15.85)	0.35 (0.22 – 0.58)	<0.001	
2	82 / 560 (8.11)	118 / 582 (11.48)	0.70 (0.53 – 0.93)	0.014	
≥3	37 / 283 (7.17)	60 / 290 (12.61)	0.58 (0.39 – 0.88)	0.009	
Net adverse clinical events	81 / 1066 (3.91)	127 / 1064 (6.29)	0.62 (0.47 – 0.82)	<0.001	0.917
0-1	14 / 223 (3.17)	21 / 192 (5.77)	0.55 (0.28 – 1.09)	0.081	
2	44 / 560 (4.05)	72 / 582 (6.35)	0.64 (0.44 – 0.93)	0.020	
≥3	23 / 283 (4.22)	34 / 290 (6.52)	0.64 (0.38 – 1.09)	0.096	



End points by HAS-BLED score. *MI,* myocardial infarction.

Figure 5



Incidences (% per patient-year) of stroke or systemic embolism and major bleeding according to the patient risk categories.

study with a short follow-up period, these scores perform rather poorly in general, but especially here in AF patients with concomitant CAD.

This subanalysis had several limitations. First, the open-label trial design increases the potential to introduce bias. Second, the trial population received the Japan-approved rivaroxaban dose of 10 or 15 mg once daily, according to the patient's CrCl, rather than the globally approved once-daily dose of 20 mg. However, pharmacokinetic modelling has shown that the rivaroxaban blood concentration of Japanese patients taking the rivaroxaban 15 mg once daily dose was similar to Caucasian patients taking the rivaroxaban 20 mg once daily dose.[16] Third, the results of the present study need to be interpreted while considering that only patients who met the eligibility criteria in the AFIRE trial were enrolled. Fourth, the determination of the risk scores was not identical to the original components of the risk scores due to missing data.

Conclusions

In conclusion, the advantages of rivaroxaban monotherapy compared with those of combination therapy with respect to pre-specified primary end points as well as all individual secondary end points including thromboembolism, bleeding, and mortality were similar across patients, irrespective of their risk for stroke and bleeding, assessed by $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, in AF patients with stable CAD more than 1 year after revascularization or with angiographically confirmed CAD not requiring revascularization.

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Disclosures

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CRediT authorship contribution statement

Masaharu Akao: Conceptualization, Methodology, Writing - original draft, Visualization. **Satoshi Yasuda:** Investigation, Project administration, Writing - review & editing. **Koichi Kaikita:** Writing - review & editing. **Junya Ako:** Writing - review & editing. **Tetsuya Matoba:** Writing - review & editing. **Masato Nakamura:** Writing - review & editing. **Katsumi Miyauchi:** Writing - review & editing. **Nobuhisa Hagiwara:** Writing - review & editing. **Kazuo Kimura:** Writing - review & editing. **Atsushi Hirayama:** Writing - review & editing. **Kunihiko Matsui:** Writing - review & editing. **Hisao Ogawa:** Supervision, Investigation, Project administration, Writing - review & editing.

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