Antithrombotic therapy for stable coronary artery disease and atrial fibrillation in patients with and without revascularisation: the AFIRE trial

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ABSTRACT

BACKGROUND: The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial demonstrated non-inferior efficacy endpoints for rivaroxaban monotherapy versus combination therapy (rivaroxaban plus a single antiplatelet) and superior safety endpoints in patients with atrial fibrillation and stable coronary artery disease.

AIMS: This *post hoc* analysis investigated whether the AFIRE trial results reflected the presence or absence of prior revascularisation.

METHODS: Among 2,215 patients, 1,697 (76.6%) had previously undergone revascularisation, and the remaining 518 (23.4%) had not undergone prior revascularisation. The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation, or death from any cause, while the primary safety endpoint was major bleeding.

RESULTS: In 1,697 patients with prior revascularisation, the efficacy and safety endpoints were superior for monotherapy versus combination therapy (efficacy: hazard ratio [HR] 0.62, 95% confidence interval [CI]: 0.45-0.85; p=0.003; safety: HR 0.62, 95% CI: 0.39-0.98; p=0.042). Among 518 without prior revascularisation, there were no significant differences in endpoints (efficacy: HR 1.19, 95% CI: 0.67-2.12; p=0.554; safety: HR 0.47, 95% CI: 0.18-1.26; p=0.134). There was borderline interaction of the efficacy endpoints (p=0.055) between two treatments. The safety benefit of monotherapy on any bleeding was significant in patients without prior revascularisation (HR 0.59, 95% CI: 0.38-0.93; p=0.022).

CONCLUSIONS: In high-risk thrombosis patients with a history of prior revascularisation, rivaroxaban monotherapy versus combination therapy demonstrated favourable safety and efficacy outcomes.

KEYWORDS: atrial fibrillation, bleeding, death, stable angina, stroke

Oral anticoagulation is considered essential for patients with atrial fibrillation (AF), which is a risk factor for thromboembolic events[1-4], whereas antiplatelet agents are considered the cornerstone of treatment for patients with stable coronary artery disease (CAD)[5-7]. Therefore, patients with AF and CAD often require combination antithrombotic therapy, which increases their risk of fatal and non-fatal bleeding and death. The Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial demonstrated remarkable evidence that rivaroxaban monotherapy was non-inferior to combination therapy with rivaroxaban plus a single antiplatelet agent for composite major adverse cardiovascular and cerebral events. Additionally, rivaroxaban monotherapy was superior for major bleeding in patients with AF and stable CAD at 1 year after revascularisation (prior percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) and in those with angiographically confirmed CAD not requiring revascularisation[8].

However, it is unclear whether the results of the AFIRE trial would remain consistent regardless of whether a patient has had a prior revascularisation procedure (PCI or CABG) or not.

Methods

STUDY POPULATION AND TRIAL DESIGN

The AFIRE trial was a multicentre, randomised, open-label, parallel-group trial[9]. Full details, including the trial design and results of the primary analysis, have been described previously[8]. In brief, men and women who were ≥20 years of age and had received a diagnosis of AF with a CHADS$_2$ score ≥1 and stable CAD were enrolled. The eligible patients fulfilled one of the following criteria: (i) angioplasty with or without stenting at least 1 year before enrolment; (ii) evidence of ≥50% coronary stenosis, as detected by coronary computed tomography or coronary angiography; or (iii) a history of undergoing CABG at least 1 year before enrolment. The main exclusion criteria were a history of stent thrombosis, coexistent active tumours, and poorly controlled hypertension. The trial was designed and conducted by an executive steering committee[9]. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Japan, as well as the institutional review boards of all participating institutions. An independent data and safety monitoring committee reviewed all data, and all participating patients provided written informed consent. Under the guidance of the authors, Mebix, a contract research organisation, assisted in the selection, supervision, and monitoring of the participating centres; the collection, storage, and analysis of the trial data; the interpretation of trial results; and preparation of the manuscript.

Impact on daily practice

This *post hoc* subgroup analysis of high-risk thrombosis patients with a history of prior revascularisation with percutaneous coronary intervention or coronary artery bypass grafting demonstrated that rivaroxaban monotherapy consistently resulted in favourable safety and efficacy outcomes versus combination therapy. Further clinical trials are needed to determine whether anticoagulant monotherapy could be applicable to patients who are at particularly high risk of thrombosis, including those with previous stent thrombosis, severe diffuse coronary artery disease, or extensive complex coronary stenting.

A total of 2,240 patients were enrolled; 2,236 were randomly assigned in a 1:1 ratio to receive monotherapy with rivaroxaban (10 mg once daily for patients with a creatinine clearance of 15-49 ml/min or 15 mg once daily for patients with a creatinine clearance of ≥50 ml/min) or combination therapy with rivaroxaban at the previously stated doses plus an antiplatelet agent (aspirin or a P2Y$_{12}$ inhibitor) according to the treating physician's discretion.

In the present *post hoc* subanalysis of 2,215 patients (1,697 who had undergone prior revascularisation, 518 who had not undergone prior revascularisation) in the modified intention-to-treat population in the AFIRE trial, we analysed the outcomes according to the presence or absence of prior revascularisation (Figure 1).

OUTCOMES

The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation, or death from any cause. The primary safety endpoint was major bleeding, as defined by the International Society on Thrombosis and Haemostasis criteria. The individual components of the efficacy and safety endpoints were analysed as secondary endpoints. Net adverse clinical events (NACE) were defined as a composite of death from any cause, myocardial infarction, stroke, or major bleeding.

STATISTICAL ANALYSIS

Continuous variables are presented as a mean±standard deviation or median (interquartile range) as appropriate, while categorical variables are presented as count (percentage). Cumulative event rates were estimated using the Kaplan-Meier method, with incidence rates in each treatment arm shown as percentages per patient-year. A Cox proportional hazards model was used to compare the outcomes between monotherapy with rivaroxaban and combination therapy with rivaroxaban and an antiplatelet agent, with the results

Abbreviations

AF	atrial fibrillation	**CABG**	coronary artery bypass grafting	**HR**	hazard ratio
AFIRE	Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease	**CAD**	coronary artery disease	**NACE**	net adverse clinical events
		CI	confidence interval	**PCI**	percutaneous coronary intervention
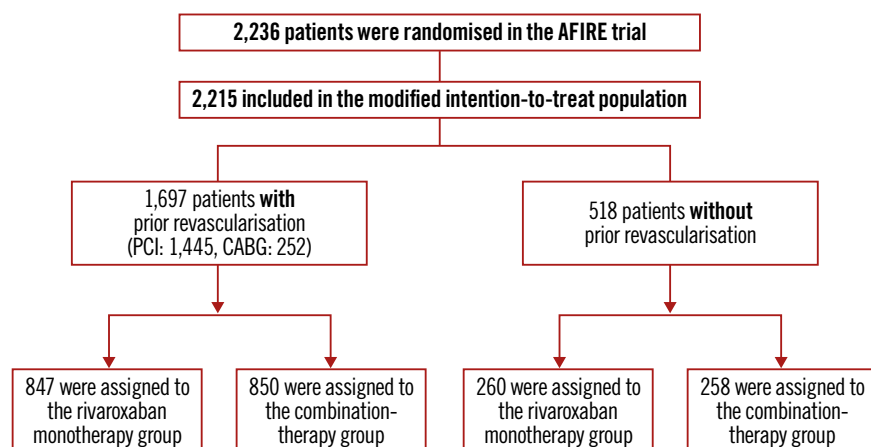
Figure 1. *Patient flow of the subanalysis population. AFIRE: Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

expressed as hazard ratios (HR) and 95% confidence intervals (CI). The latter were not adjusted for multiple comparisons; therefore, the inferences drawn from these intervals may not be reproducible. Randomisation in the AFIRE trial was adjusted using a minimisation method for age, sex, history of PCI, cardiac insufficiency, heart failure, hypertension, diabetes mellitus, and stroke. All statistical analyses were performed using SAS software version 9.4 for Windows (SAS Institute). All reported p-values were 2-tailed, and those <0.05 were considered statistically significant.

Results

BASELINE CHARACTERISTICS

Among the 2,215 patients in the modified intention-to-treat population, 1,697 had a history of revascularisation (1,445 with PCI, 252 with CABG). The remaining 518 patients had no history of revascularisation. **Table 1** shows the patient baseline characteristics by treatment groups (rivaroxaban monotherapy and combination therapy) and the presence or absence of a history of revascularisation. There were no significant intergroup differences in the baseline characteristics of patients with a history of previous revascularisation. The mean $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were 2.5, 4.1, and 2.2, respectively. The prevalence of previous myocardial infarction was approximately 40%. In the combination therapy group, 68.8% of patients were treated with aspirin. There were no intergroup differences in the baseline characteristics of the patients without a history of prior revascularisation. The mean $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were 2.4, 3.7, and 1.7, respectively. The prevalence of previous myocardial infarction was approximately 10%. In the combination therapy group, 81.8% of patients were treated with aspirin. Compared to patients without a history of prior revascularisation, the CHA_2DS_2-VASc and the HAS-BLED scores were significantly higher in patients with prior revascularisation **(Supplementary Table 1)**.

PRIMARY EFFICACY AND SAFETY ENDPOINTS

Figure 2A and **Figure 2B** show the primary efficacy endpoints of the monotherapy (rivaroxaban only) and combination

therapy (rivaroxaban plus a single antiplatelet agent) groups. Among the 1,697 patients with a history of prior revascularisation, rivaroxaban monotherapy was superior to combination therapy. Primary efficacy endpoint events were observed in 63 of 847 patients and 100 of 850 patients receiving rivaroxaban monotherapy and combination therapy, respectively, corresponding to incidence rates of 3.83% and 6.18% per patient-year, respectively (HR 0.62, 95% CI: 0.45-0.85; p=0.003), whereas no significant differences were noted in the primary efficacy endpoints among the 518 patients without a history of prior revascularisation. Primary efficacy endpoint events occurred in 26 of 260 patients and 21 of 258 patients receiving rivaroxaban monotherapy and combination therapy, respectively, corresponding to incidence rates of 5.14% and 4.34% per patient-year, respectively (HR 1.19, 95% CI: 0.67-2.12; p=0.554). There was borderline interaction for the primary efficacy outcome between prior revascularisation and antithrombotic therapy (p=0.055) depending on the randomised treatment allocations.

As for the primary safety endpoint **(Figure 3A, Figure 3B)**, rivaroxaban monotherapy was superior to combination therapy in the 1,684 patients with a history of prior revascularisation. Primary safety endpoint events were observed in 29 of 841 patients and 46 of 843 patients receiving rivaroxaban monotherapy and combination therapy, respectively, corresponding to incidence rates of 1.76% and 2.85% per patient-year, respectively (HR 0.62, 95% CI: 0.39-0.98; p=0.042), while no significant intergroup difference was noted among the 518 patients without a history of prior revascularisation. Primary safety endpoint events were observed in 6 of 258 patients and 12 of 256 patients receiving rivaroxaban monotherapy and combination therapy, respectively, corresponding to incidence rates of 1.17% and 2.48% per patient-year, respectively (HR 0.47, 95% CI: 0.18-1.26; p=0.134). There was no interaction in the primary safety outcomes between prior revascularisation and antithrombotic therapy (p=0.633).

In relation to the treatment effect based on the type of revascularisation, we observed a significant difference in the primary efficacy endpoint among a subgroup of 1,445 patients
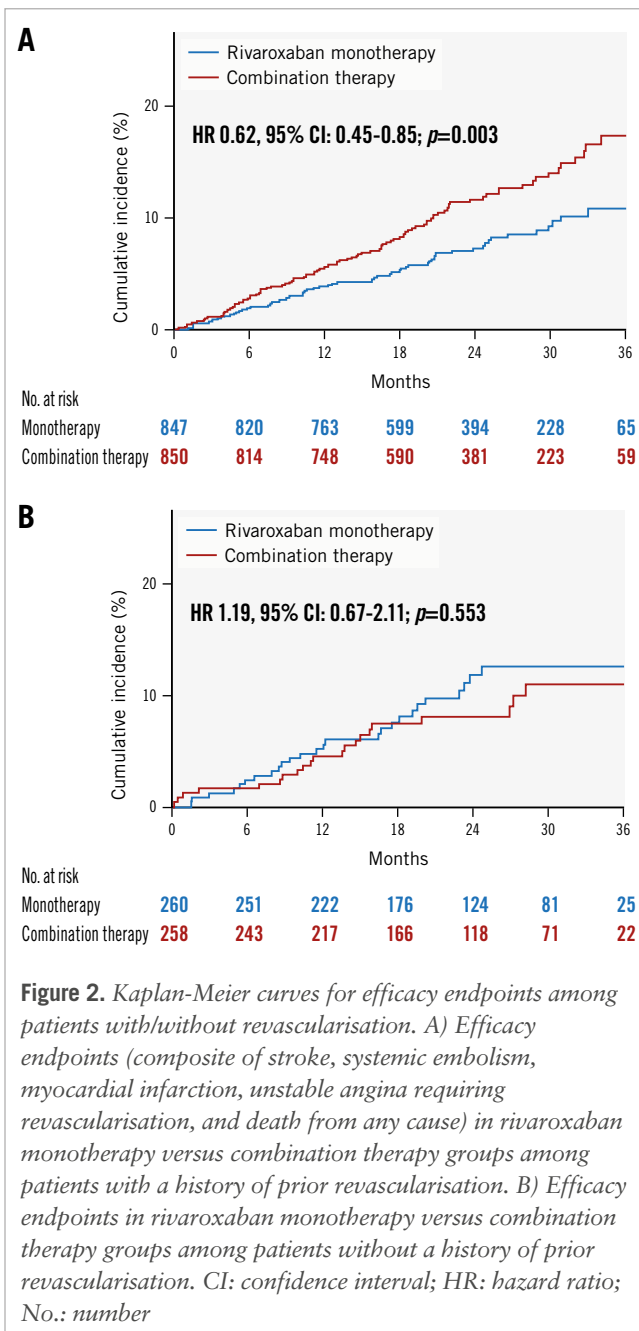
Table 1. Patient clinical characteristics by study group.

	Patients with prior revascularisation (n=1,697)			Patients without prior revascularisation (n=518)		
	Rivaroxaban monotherapy (n=847)	Combination therapy (n=850)	*p*-value	Rivaroxaban monotherapy (n=260)	Combination therapy (n=258)	*p*-value
Age, years	74.3±8.3	74.5±8.1	0.8421	74.2±8.3	73.9±8.5	0.8467
Male	683 (80.6)	693 (81.5)	0.6645	192 (73.8)	183 (70.9)	0.4920
BMI, kg/m²	24.57±3.71	24.55±3.74	0.9107	24.12±3.44	24.35±3.60	0.3750
AF type						
Paroxysmal	472 (55.7)	460 (54.1)		124 (47.7)	120 (46.5)	
Persistent	116 (13.7)	129 (15.2)	0.6535	48 (18.5)	46 (17.8)	0.9184
Permanent	259 (30.6)	261 (30.7)		88 (33.8)	92 (35.7)	
Previous PCI	781 (92.2)	783 (92.1)	1.0000	-	-	-
Previous CABG	125 (14.8)	127 (14.9)	0.9456	-	-	-
Hypertension	728 (86.0)	722 (84.9)	0.5821	219 (84.2)	222 (86.0)	0.6217
Diabetes mellitus	363 (42.9)	375 (44.1)	0.6244	98 (37.7)	91 (35.3)	0.5848
Dyslipidaemia	634 (74.9)	615 (72.4)	0.249	147 (56.5)	142 (55.0)	0.7907
Angina	573 (67.7)	604 (71.1)	0.1403	114 (43.8)	119 (46.1)	0.6588
Heart failure	286 (33.8)	305 (35.9)	0.3864	103 (39.6)	94 (36.4)	0.4701
Previous stroke	115 (13.6)	132 (15.5)	0.2709	33 (12.7)	43 (16.7)	0.2159
Previous myocardial infarction	358 (42.3)	369 (43.4)	0.6589	26 (10.0)	24 (9.3)	0.8819
Previous peripheral arterial disease	53 (6.3)	63 (7.4)	0.3868	14 (5.4)	9 (3.5)	0.3942
CrCL	62.9±26.7	61.6±24.6	0.5439	62.5±22.1	62.2±21.9	0.9794
<30 ml/min	44 (5.2)	52 (6.1)		10 (3.8)	8 (3.1)	
≥30 and <50 ml/min	231 (27.3)	229 (26.9)	0.5991	69 (26.5)	64 (24.8)	0.7115
≥50 ml/min	535 (63.2)	511 (60.1)		164 (63.1)	175 (67.8)	
CHADS₂ score	2.5±1.1	2.5±1.2	-	2.4±1.2	2.4±1.2	-
0-2	487 (57.5)	474 (55.8)	0.4715	150 (57.7)	147 (57.0)	0.8692
≥3	360 (42.5)	376 (44.2)		110 (42.3)	111 (43.0)	
CHA₂DS₂-VASc score	4.1±1.4	4.1±1.5	-	3.8±1.4	3.7±1.6	-
0-3	314 (37.1)	316 (37.2)	0.9645	115 (44.2)	120 (46.5)	0.6021
≥4	533 (62.9)	534 (62.8)		145 (55.8)	138 (53.5)	
HAS-BLED score	2.2±0.8	2.2±0.7	-	1.7±0.8	1.8±0.8	-
0-2	574 (67.8)	575 (67.6)	0.9570	212 (81.5)	201 (77.9)	0.3043
3-5	246 (29.0)	245 (28.8)		37 (14.2)	45 (17.4)	
Treatment at baseline						
Dose of rivaroxaban						
10 mg	397 (46.9)	397 (46.7)	0.9805	100 (38.5)	116 (45.0)	0.1527
15 mg	441 (52.1)	445 (52.4)		158 (60.8)	140 (54.3)	
Use of antiplatelet agent						
Aspirin	7 (0.8)	585 (68.8)	-	2 (0.8)	211 (81.8)	-
P2Y₁₂ inhibitor	5 (0.6)	265 (31.2)		0 (0)	42 (16.3)	

Data are expressed as n (%) or mean±standard deviation. AF: atrial fibrillation; BMI: body mass index; CABG: coronary artery bypass grafting; CrCL: creatinine clearance; PCI: percutaneous coronary intervention

with prior PCI. In this subset, patients receiving rivaroxaban monotherapy exhibited lower event rates compared to those on combination therapy (event rates of 3.84% and 6.25% per patient-year, respectively; HR 0.62, 95% CI: 0.44-0.87; p=0.0054) **(Supplementary Figure 1)**. Conversely, among the 252 patients with prior CABG, there was no significant inter-group variation in the primary efficacy endpoint when comparing patients receiving rivaroxaban monotherapy and combination therapy (event rates of 3.76% and 5.76% per patient-year, respectively; HR 0.66, 95% CI: 0.29-1.53;

Figure 2. *Kaplan-Meier curves for efficacy endpoints among patients with/without revascularisation. A) Efficacy endpoints (composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation, and death from any cause) in rivaroxaban monotherapy versus combination therapy groups among patients with a history of prior revascularisation. B) Efficacy endpoints in rivaroxaban monotherapy versus combination therapy groups among patients without a history of prior revascularisation. CI: confidence interval; HR: hazard ratio; No.: number*

Figure 3. *Kaplan-Meier curves for safety endpoints among patients with/without revascularisation. A) Safety endpoints for major bleeding of rivaroxaban monotherapy versus combination therapy groups of patients with a history of prior revascularisation. B) Safety endpoints of rivaroxaban monotherapy and combination therapy groups of patients without a history of prior revascularisation. CI: confidence interval; HR: hazard ratio; No.: number*

p=0.337) **(Supplementary Figure 2)**. Additionally, there was no interaction in the primary efficacy endpoint between the type of revascularisation and the antithrombotic therapy (p=0.158).

Furthermore, our analysis revealed no significant differences concerning the primary safety endpoint. This was observed only in patients with either prior PCI (event rates of 1.70% and 2.77% per patient-year for rivaroxaban monotherapy and combination therapy, respectively; HR 0.62, 95% CI: 0.37-1.03; p=0.064) or prior CABG (event rates of 2.08% and 3.27% per patient-year for rivaroxaban monotherapy and combination therapy, respectively; HR 0.65, 95% CI: 0.21-1.98; p=0.445). In addition, there was no interaction in the primary safety endpoint between the type of revascularisation and the antithrombotic therapy (p=0.891) **(Central illustration)**.
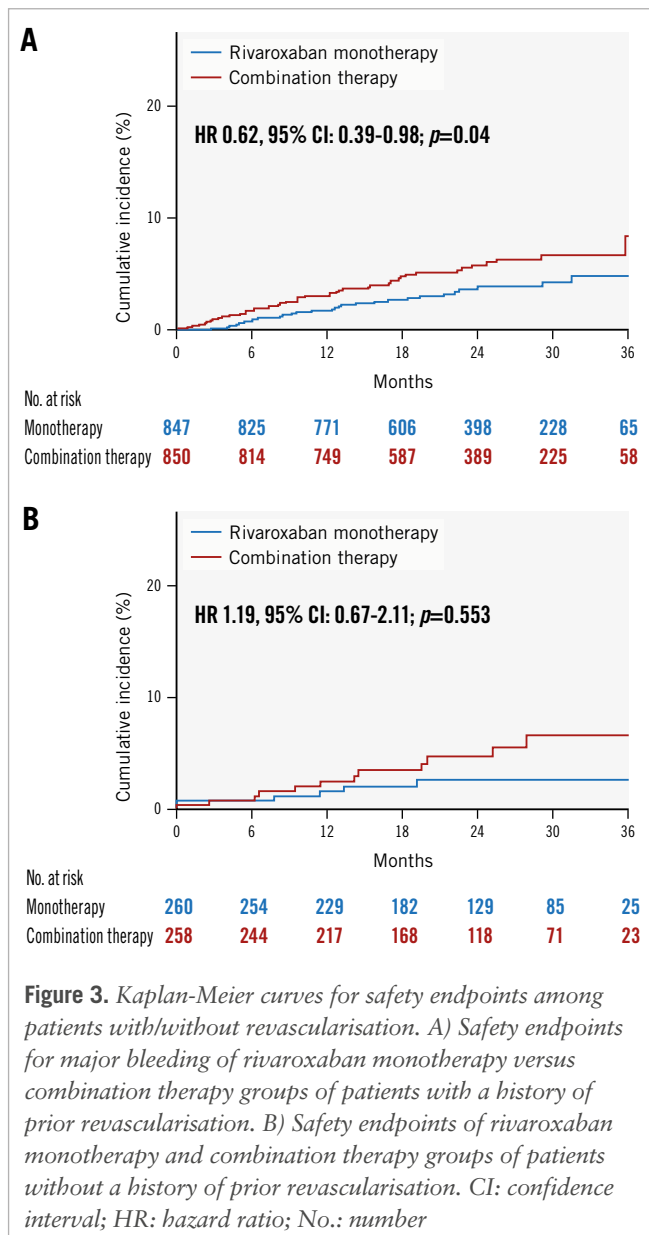
SUBGROUP ANALYSES AMONG PATIENTS WITH PRIOR REVASCULARISATION

As shown in **Figure 4**, the effects of rivaroxaban monotherapy versus combination therapy on the primary efficacy endpoint among patients with a history of prior revascularisation were consistent across subgroups, including sex, age, stroke and bleeding risk scores, renal function, and AF type. With respect to the primary safety endpoint, there was similar consistency in the effect of rivaroxaban monotherapy in patients with a history of prior revascularisation **(Figure 5)**. However, there was a statistically significant interaction for the primary safety endpoint between patients with versus without previous myocardial infarction (HR 0.31 vs 0.89; p for interaction=0.046).

INDIVIDUAL COMPONENTS OF EFFICACY AND SAFETY ENDPOINTS

Table 2 shows the incidence of the individual components of the efficacy and safety endpoints among patients with

Relative risk of efficacy and safety endpoints, secondary efficacy and safety endpoints, and net adverse clinical events in patients with and without prior revascularisation.
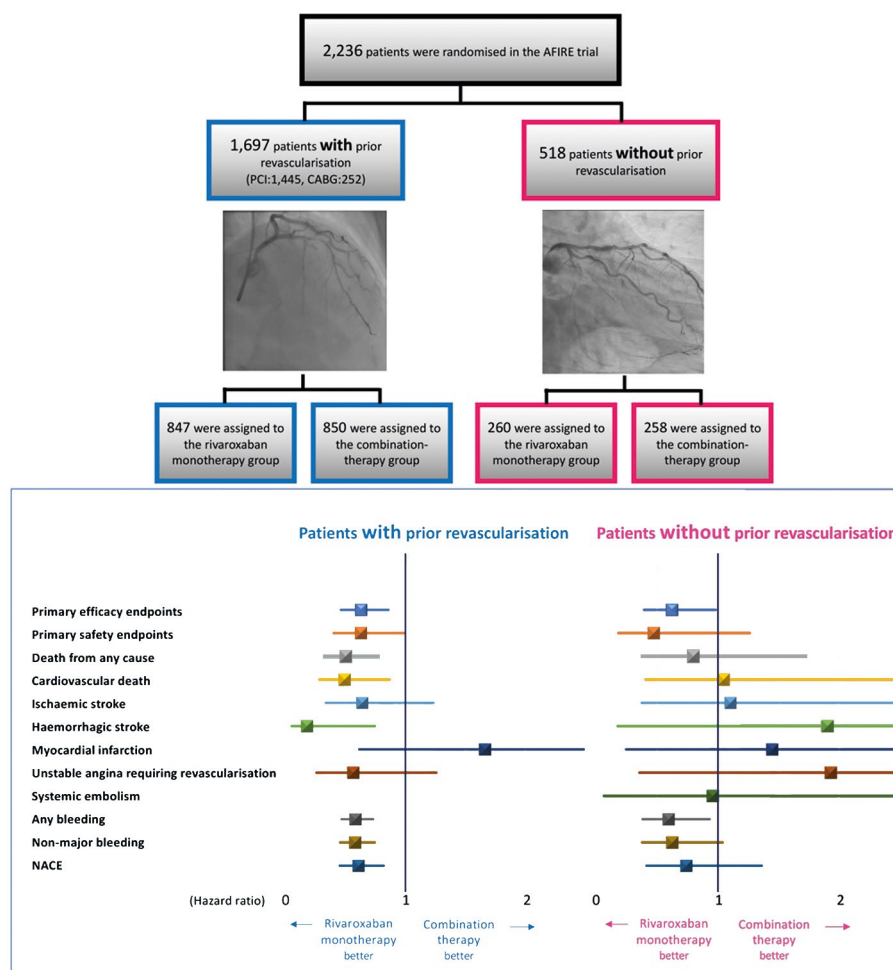
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In the subgroup of patients who had undergone prior revascularisation, rivaroxaban monotherapy demonstrated superiority over combination therapy with respect to the primary efficacy and safety endpoints. Conversely, for patients without a history of prior revascularisation, no statistically significant disparities were observed in the primary efficacy and safety endpoints.
AFIRE: Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease;
CABG: coronary artery bypass grafting; NACE: net adverse clinical events; PCI: percutaneous coronary intervention

versus without prior revascularisation as secondary endpoints. Among the patients with prior revascularisation, all-cause mortality was significantly lower in patients receiving rivaroxaban monotherapy versus combination therapy (event rates of 1.72% and 3.53%, respectively; HR 0.49, 95% CI: 0.31-0.77; p=0.0013). As for cardiovascular death, this occurred in 1.01% of the patients receiving rivaroxaban monotherapy and in 2.10% of those receiving combination therapy per patient-year (HR 0.48, 95% CI: 0.27-0.86; p=0.011). The event rate for any bleeding was significantly lower in the rivaroxaban monotherapy versus combination therapy group (7.5% vs 13.2% per patient-year, respectively; HR 0.57, 95% CI: 0.46-0.72; p<0.0001).

Regarding the incidence of the individual components of the efficacy and safety endpoints among patients without prior revascularisation, there were no significant differences in any parameters of the efficacy endpoints, including death from any cause and cardiovascular death. However, the incidence of any bleeding was significantly lower in the rivaroxaban monotherapy versus the combination therapy group among the patients without a history of prior revascularisation (6.4% vs 11.1% per patient-year, respectively; HR 0.59, 95% CI: 0.38-0.93; p=0.022).

Rivaroxaban monotherapy was superior to combination therapy regarding NACE among patients with a history of prior revascularisation (event rates of 3.96% and 6.67%

Subgroup	Monotherapy no. of events/total no. (% patient-year)	Combination therapy no. of events/total no. (% patient-year)	HR (95% CI)	p-value	p for interaction
Overall	63/847 (3.83)	100/850 (6.18)	0.62 (0.45 to 0.85)	0.003	
Sex					0.677
Male	49/683 (3.71)	81/693 (6.16)	0.60 (0.42 to 0.86)	0.005	
Female	14/164 (4.33)	19/157 (6.24)	0.74 (0.37 to 1.48)	0.392	
Age					0.101
<75 years	27/396 (3.50)	31/399 (3.97)	0.88 (0.53 to 1.48)	0.628	
≥75 years	36/451 (4.13)	69/451 (8.23)	0.51 (0.34 to 0.76)	0.001	
CHADS$_2$					0.489
1	9/169 (2.73)	11/172 (3.29)	0.83 (0.34 to 1.99)	0.669	
2-6	54/675 (4.13)	89/677 (6.93)	0.60 (0.43 to 0.84)	0.002	
CHA$_2$DS$_2$-VASc					0.529
0-3	19/314 (3.07)	26/316 (4.20)	0.73 (0.40 to 1.32)	0.293	
≥4	44/533 (4.29)	74/534 (7.40)	0.58 (0.40 to 0.85)	0.004	
HAS-BLED					0.913
0-1	8/111 (3.84)	12/104 (5.94)	0.64 (0.26 to 1.58)	0.332	
2	32/463 (3.51)	58/471 (6.29)	0.56 (0.36 to 0.87)	0.008	
3-5	20/246 (4.24)	29/245 (6.53)	0.65 (0.37 to 1.15)	0.133	
Diabetes mellitus					0.638
Yes	30/363 (4.31)	53/375 (7.50)	0.58 (0.37 to 0.91)	0.016	
No	33/484 (3.48)	47/475 (5.15)	0.67 (0.43 to 1.05)	0.080	
Creatinine clearance					0.344
<30 ml/min	7/44 (9.13)	12/52 (13.96)	0.69 (0.27 to 1.77)	0.432	
30 to <50 ml/min	28/231 (6.53)	34/229 (8.38)	0.77 (0.47 to 1.27)	0.301	
≥50 ml/min	25/535 (2.34)	51/511 (5.00)	0.47 (0.29 to 0.75)	0.001	
Rivaroxaban dose					0.741
10 mg once daily	37/397 (4.87)	61/397 (8.27)	0.59 (0.39 to 0.89)	0.010	
15 mg once daily	25/441 (2.86)	38/445 (4.34)	0.66 (0.40 to 1.09)	0.101	
Use of PPI					0.468
Yes	39/530 (3.78)	69/559 (6.64)	0.58 (0.39 to 0.86)	0.006	
No	24/317 (3.91)	31/291 (5.35)	0.73 (0.43 to 1.25)	0.253	
Type of atrial fibrillation					0.300
Paroxysmal	23/472 (2.49)	42/460 (4.73)	0.53 (0.32 to 0.88)	0.012	
Persistent	10/116 (4.74)	22/129 (9.89)	0.48 (0.23 to 1.02)	0.050	
Permanent	30/259 (5.88)	36/261 (7.07)	0.86 (0.53 to 1.41)	0.554	
Previous myocardial infarction					0.444
Yes	31/358 (4.49)	43/369 (6.26)	0.72 (0.45 to 1.14)	0.164	
No	32/489 (3.35)	57/481 (6.12)	0.56 (0.36 to 0.86)	0.008	

0.1   1   10

← Monotherapy better   Combination therapy better →

Figure 4. *Primary efficacy endpoint according to subgroup based on revascularisation history. Hazard ratios for the primary efficacy endpoint (composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularisation, or death from any cause) in the two trial groups among patients with a history of prior revascularisation. CI: confidence interval; HR: hazard ratio; PPI: proton pump inhibitor*
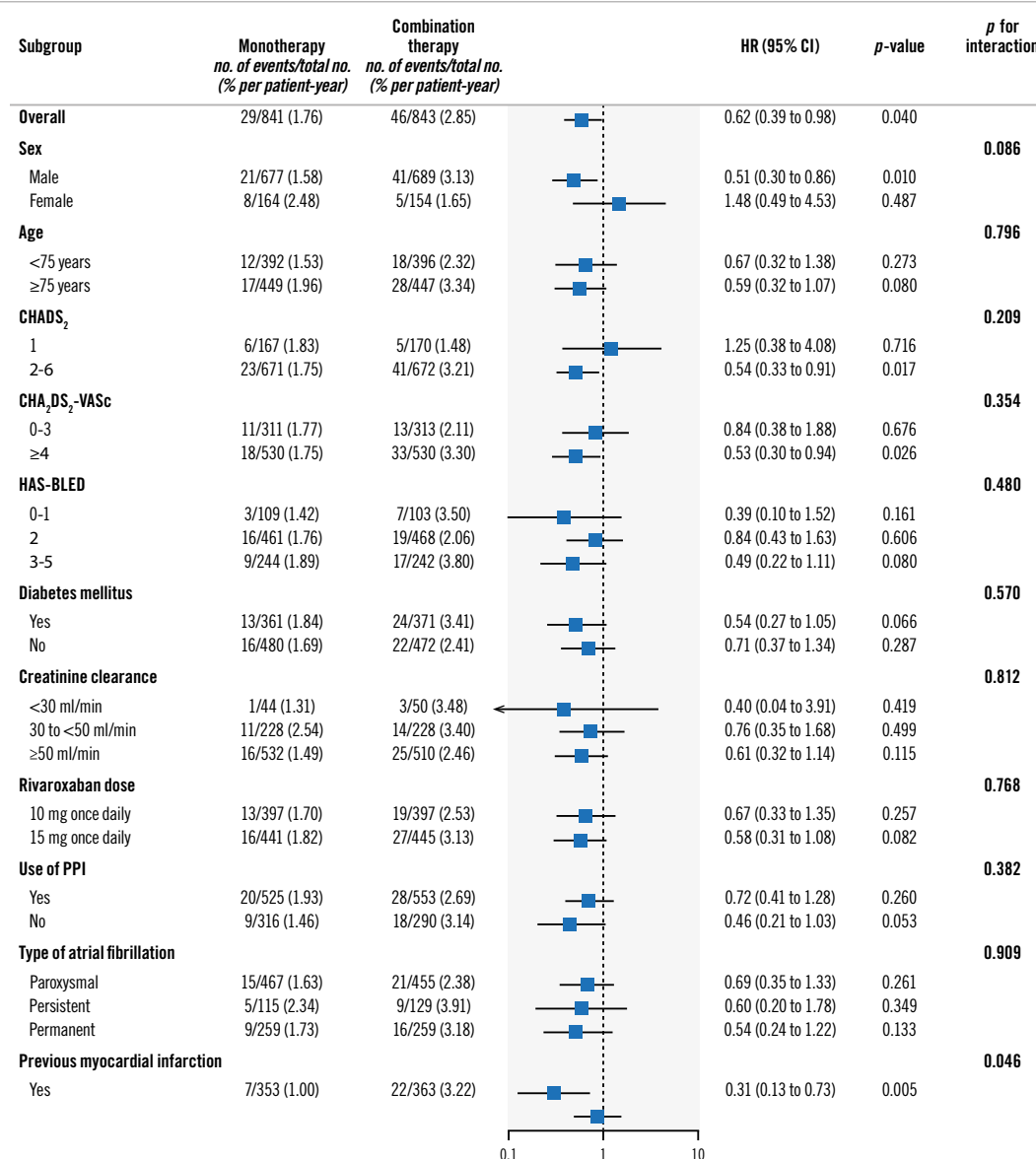
per patient-year, respectively; HR 0.60, 95% CI: 0.44-0.81; p=0.0009), whereas no significant difference was noted regarding NACE in patients receiving rivaroxaban monotherapy versus combination therapy among the 518 patients without a history of prior revascularisation (event rates of 3.70% and 4.99% per patient-year, respectively; HR 0.74, 95% CI: 0.41-1.36; p=0.336). There was no interaction in NACE between prior revascularisation and antithrombotic therapy (p=0.535).

Discussion

In this *post hoc* analysis of the AFIRE trial, the major findings were as follows: 1) rivaroxaban monotherapy had a greater impact on efficacy and safety endpoints in patients with versus without a history of prior revascularisation; 2) there was borderline interaction between the primary efficacy outcomes of prior revascularisation and antithrombotic therapy depending on the randomised treatment assignment; and 3) the incidence of any bleeding was significantly lower in the monotherapy versus the combination therapy group among patients without a history of prior revascularisation.

The AFIRE trial findings indicated that rivaroxaban monotherapy was non-inferior to combination therapy with rivaroxaban plus a single antiplatelet agent regarding efficacy and superior for safety endpoints in patients with AF and stable CAD[8]. In this subanalysis of the AFIRE trial, we found that the benefit of rivaroxaban monotherapy regarding primary efficacy and safety endpoints among the patients with

Subgroup	Monotherapy no. of events/total no. (% per patient-year)	Combination therapy no. of events/total no. (% per patient-year)		HR (95% CI)	p-value	p for interaction
Overall	29/841 (1.76)	46/843 (2.85)		0.62 (0.39 to 0.98)	0.040	
Sex						0.086
Male	21/677 (1.58)	41/689 (3.13)		0.51 (0.30 to 0.86)	0.010	
Female	8/164 (2.48)	5/154 (1.65)		1.48 (0.49 to 4.53)	0.487	
Age						0.796
<75 years	12/392 (1.53)	18/396 (2.32)		0.67 (0.32 to 1.38)	0.273	
≥75 years	17/449 (1.96)	28/447 (3.34)		0.59 (0.32 to 1.07)	0.080	
CHADS$_2$						0.209
1	6/167 (1.83)	5/170 (1.48)		1.25 (0.38 to 4.08)	0.716	
2-6	23/671 (1.75)	41/672 (3.21)		0.54 (0.33 to 0.91)	0.017	
CHA$_2$DS$_2$-VASc						0.354
0-3	11/311 (1.77)	13/313 (2.11)		0.84 (0.38 to 1.88)	0.676	
≥4	18/530 (1.75)	33/530 (3.30)		0.53 (0.30 to 0.94)	0.026	
HAS-BLED						0.480
0-1	3/109 (1.42)	7/103 (3.50)		0.39 (0.10 to 1.52)	0.161	
2	16/461 (1.76)	19/468 (2.06)		0.84 (0.43 to 1.63)	0.606	
3-5	9/244 (1.89)	17/242 (3.80)		0.49 (0.22 to 1.11)	0.080	
Diabetes mellitus						0.570
Yes	13/361 (1.84)	24/371 (3.41)		0.54 (0.27 to 1.05)	0.066	
No	16/480 (1.69)	22/472 (2.41)		0.71 (0.37 to 1.34)	0.287	
Creatinine clearance						0.812
<30 ml/min	1/44 (1.31)	3/50 (3.48)		0.40 (0.04 to 3.91)	0.419	
30 to <50 ml/min	11/228 (2.54)	14/228 (3.40)		0.76 (0.35 to 1.68)	0.499	
≥50 ml/min	16/532 (1.49)	25/510 (2.46)		0.61 (0.32 to 1.14)	0.115	
Rivaroxaban dose						0.768
10 mg once daily	13/397 (1.70)	19/397 (2.53)		0.67 (0.33 to 1.35)	0.257	
15 mg once daily	16/441 (1.82)	27/445 (3.13)		0.58 (0.31 to 1.08)	0.082	
Use of PPI						0.382
Yes	20/525 (1.93)	28/553 (2.69)		0.72 (0.41 to 1.28)	0.260	
No	9/316 (1.46)	18/290 (3.14)		0.46 (0.21 to 1.03)	0.053	
Type of atrial fibrillation						0.909
Paroxysmal	15/467 (1.63)	21/455 (2.38)		0.69 (0.35 to 1.33)	0.261	
Persistent	5/115 (2.34)	9/129 (3.91)		0.60 (0.20 to 1.78)	0.349	
Permanent	9/259 (1.73)	16/259 (3.18)		0.54 (0.24 to 1.22)	0.133	
Previous myocardial infarction						0.046
Yes	7/353 (1.00)	22/363 (3.22)		0.31 (0.13 to 0.73)	0.005	

0.1   1   10

Figure 5. *Primary safety endpoint among patients with prior revascularisation history. Hazard ratios for the primary safety endpoint of major bleeding in the two trial groups among patients with a history of prior revascularisation. CI: confidence interval; HR: hazard ratio; PPI: proton pump inhibitor*

a history of prior revascularisation was consistent with that of the whole population of the AFIRE trial. Compared to patients with AF and stable CAD without a history of prior revascularisation, rivaroxaban monotherapy demonstrated more favourable safety and efficacy outcomes than combination therapy. These results may be related to baseline characteristics, especially the higher thrombotic and bleeding risks among patients with AF and stable CAD with a history of prior revascularisation. The HAS-BLED scores were higher in patients with prior revascularisation than in those without. Because bleeding is strongly correlated with subsequent cardiovascular events in patients with CAD[10], it is important to suppress bleeding events in the setting of antithrombotic therapy. An additional analysis of the AFIRE trial results showed that the rate of cardiovascular events was high in patients with major

bleeding and that major bleeding events were associated with high morbidity and mortality rates[11]. A recent subanalysis of the AFIRE trial consistently demonstrated that the safety benefit of monotherapy was even greater in patients receiving PCI for multivessel disease or left main trunk lesions than in those with single-vessel disease[12]. Moreover, there was a statistically significant interaction of the primary safety endpoint between patients with versus without previous myocardial infarction among patients with prior revascularisation, which may indicate that rivaroxaban monotherapy resulted in more favourable safety outcomes than combination therapy in severely high-risk thrombosis patients with a history of previous myocardial infarction. A *post hoc* analysis of the AFIRE trial consistently reported that rivaroxaban monotherapy significantly reduced net adverse events compared to combination therapy

Table 2. Primary and secondary endpoints among patients with versus without prior revascularisation.

Endpoints	Patients with prior revascularisation				Patients without prior revascularisation				p for interaction
	Rivaroxaban monotherapy (n=847) (per patient-year)	Combination therapy (n=850) (per patient-year)	Hazard ratio (95% CI)	p-value	Rivaroxaban monotherapy (n=260) (per patient-year)	Combination therapy (n=258) (per patient-year)	Hazard ratio (95% CI)	p-value	
Efficacy endpoints									
Primary efficacy endpoint	63 (3.83)	100 (6.18)	0.62 (0.45-0.85)	0.003	26 (5.14)	21 (4.34)	1.19 (0.67-2.12)	0.554	0.055
Death from any cause	29 (1.72)	59 (3.53)	0.49 (0.31-0.77)	0.001	12 (2.28)	14 (2.84)	0.80 (0.37-1.73)	0.565	0.289
Cardiovascular death	17 (1.01)	35 (2.10)	0.48 (0.27-0.86)	0.011	9 (1.71)	8 (1.62)	1.05 (0.40-2.71)	0.925	0.172
Ischaemic stroke	14 (0.84)	22 (1.33)	0.63 (0.32-1.23)	0.171	7 (1.35)	6 (1.23)	1.10 (0.37-3.28)	0.860	0.392
Haemorrhagic stroke	2 (0.12)	12 (0.72)	0.17 (0.04-0.74)	0.007	2 (0.38)	1 (0.20)	1.90 (0.17-20.98)	0.593	0.092
Myocardial infarction	10 (0.60)	6 (0.36)	1.66 (0.60-4.57)	0.320	3 (0.58)	2 (0.41)	1.45 (0.24-8.66)	0.684	0.890
Unstable angina requiring revascularisation	9 (0.54)	16 (0.97)	0.55 (0.25-1.25)	0.150	4 (0.77)	2 (0.41)	1.93 (0.35-10.54)	0.440	0.197
Systemic embolism	1 (0.06)	0 (0)	-	-	1 (0.19)	1 (0.20)	0.96 (0.06-15.29)	0.975	0.995
Safety endpoints									
Primary safety endpoint	29 (1.76)	46 (2.85)	0.62 (0.39-0.98)	0.042	6 (1.17)	12 (2.48)	0.47 (0.18-1.26)	0.134	0.633
Any bleeding	116 (7.50)	191 (13.20)	0.57 (0.46-0.72)	<0.001	31 (6.41)	48 (11.14)	0.59 (0.38-0.93)	0.022	0.893
Non-major bleeding	97 (6.17)	162 (10.89)	0.57 (0.44-0.73)	<0.001	25 (5.09)	37 (8.43)	0.62 (0.38-1.04)	0.066	0.760

Data are expressed as n (%). CI: confidence interval

in patients with atrial fibrillation, CAD, and prior athero-thrombotic disease (those with a history of myocardial infarction, stroke, and/or peripheral artery disease)[13].

Among the patients without a history of prior revascularisation, in whom the median HAS-BLED score was 1.7, there were no significant differences in any parameters of the efficacy endpoints; however, the incidence of any bleeding was significantly lower in the monotherapy group than in the combination therapy group. Despite the relatively lower thrombotic and bleeding risks, anticoagulant monotherapy would be a better choice, as it is associated with less bleeding and offers a potential net clinical benefit.

Limitations

This study had several limitations as previously reported[8]. The *post hoc* design was a limitation of the study. We divided the entire cohort into several groups; therefore, the number of patients in these analyses was relatively small, which may have influenced the results, especially the borderline interaction between the primary outcomes of prior revascularisation and antithrombotic therapy according to the randomised

treatment allocations. Second, the trial participants consisted only of Japanese patients who received the rivaroxaban dose approved in Japan (10 or 15 mg once daily, according to the patient's creatinine clearance) rather than a globally approved once-daily dose of 15 or 20 mg. In addition, the selection of an antiplatelet agent, either aspirin or a $P2Y_{12}$ inhibitor, was made at the discretion of the treating physicians. However, no significant differences were found in efficacy and safety outcomes between the $P2Y_{12}$ inhibitor and aspirin groups in a *post hoc* analysis of the AFIRE trial[14]. With respect to the limited number of patients, further studies of patients with prior CABG, generally characterised as having multivessel or left main trunk lesions, are needed to determine whether oral anticoagulant monotherapy is the preferred treatment strategy.

Conclusions

In this *post hoc* subgroup analysis of the AFIRE trial, among high-risk thrombosis patients with a history of prior PCI or CABG, rivaroxaban monotherapy consistently resulted in favourable safety and efficacy outcomes compared to

combination therapy. Among patients without revascularisation, the incidence of bleeding was significantly lower in the monotherapy versus combination therapy group, indicating a potential net clinical benefit.

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Conflict of interest statement

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References

1. Ono K, Iwasaki YK, Akao M, Ikeda T, Ishii K, Inden Y, Kusano K, Kobayashi Y, Koretsune Y, Sasano T, Sumitomo N, Takahashi N, Niwano S, Hagiwara N, Hisatome I, Furukawa T, Honjo H, Maruyama T, Murakawa Y, Yasaka M, Watanabe E, Aiba T, Amino M, Itoh H, Ogawa H, Okumura Y, Aoki-Kamiya C, Kishihara J, Kodani E, Komatsu T, Sakamoto Y, Satomi K, Shiga T, Shinohara T, Suzuki A, Suzuki S, Sekiguchi Y, Nagase S, Hayami N, Harada M, Fujino T, Makiyama T, Maruyama M, Miake J, Muraji S, Murata H, Morita N, Yokoshiki H, Yoshioka K, Yodogawa K, Inoue H, Okumura K, Kimura T, Tsutsui H, Shimizu W; Japanese Circulation Society and; Japanese Heart Rhythm Society Joint Working Group. JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias. *J Arrhythm*. 2022;38:833-973.

2. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 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. *J Am Coll Cardiol*. 2019;74: 104-32.

3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; 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.

4. Angiolillo DJ, Bhatt DL, Cannon CP, Eikelboom JW, Gibson CM, Goodman SG, Granger CB, Holmes DR, Lopes RD, Mehran R, Moliterno DJ, Price MJ, Saw J, Tanguay JF, Faxon DP. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention: A North American Perspective: 2021 Update. *Circulation*. 2021;143: 583-96.

5. Nakamura M, Kimura K, Kimura T, Ishihara M, Otsuka F, Kozuma K, Kosuge M, Shinke T, Nakagawa Y, Natsuaki M, Yasuda S, Akasaka T, Kohsaka S, Haze K, Hirayama A. JCS 2020 Guideline Focused Update on Antithrombotic Therapy in Patients With Coronary Artery Disease. *Circ J*. 2020;84:831-65.

6. Gallone G, Baldetti L, Pagnesi M, Latib A, Colombo A, Libby P, Giannini F. Medical Therapy for Long-Term Prevention of Atherothrombosis Following an Acute Coronary Syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018;72:2886-903.

7. Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS, Lopez-Jimenez F, McNallan SM, Patel M, Roger VL, Sellke FW, Sica DA, Zimmerman L; American Heart Association Council on Cardiovascular Surgery and Anesthesia. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. *Circulation*. 2015;131:927-64.

8. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med*. 2019;381:1103-13.

9. Yasuda S, Kaikita K, Ogawa H, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K. Atrial fibrillation and ischemic events with rivaroxaban in patients with stable coronary artery disease (AFIRE): Protocol for a multicenter, prospective, randomized, open-label, parallel group study. *Int J Cardiol*. 2018;265:108-12.

10. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, Messenger JC, Marso SP; National Cardiovascular Data Registry. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. *JAMA*. 2013;309:1022-9.

11. Yasuda S, Ogawa H; AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. Reply. *N Engl J Med*. 2019;381:2481.

12. Ishii M, Akao M, Yasuda S, Kaikita K, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Rivaroxaban Monotherapy in Patients With Atrial Fibrillation and Coronary Stenting at Multiple Vessels or the Left Main Trunk: The AFIRE Trial Subanalysis. *J Am Heart Assoc*. 2022;11:e027107.

13. Matsuzawa Y, Kimura K, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Antithrombotic Therapy for Atrial Fibrillation and Coronary Artery Disease in Patients With Prior Atherothrombotic Disease: A Post Hoc Analysis of the AFIRE Trial. *J Am Heart Assoc*. 2021;10:e020907.

14. Fukaya H, Ako J, Yasuda S, Kaikita K, Akao M, Matoba T, Nakamra M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H. Aspirin versus $P2Y_{12}$ inhibitors with anticoagulation therapy for atrial fibrillation. *Heart*. 2021;107:1731-8.

Supplementary data

Supplementary Table 1. Patients' clinical characteristics for patients with prior revascularisation and those without prior revascularisation.

Supplementary Figure 1. Kaplan-Meier curves for efficacy and safety endpoints among patients with prior percutaneous coronary intervention only.

Supplementary Figure 2. Kaplan-Meier curves for efficacy and safety endpoints among patients with prior coronary artery bypass grafting only.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00396

Supplementary data

Supplementary Table 1. Patients' clinical characteristics for patients with prior revascularisation and those without prior revascularisation.

	Patients with prior revascularisation (n =1,697)	Patients without prior revascularisation (n = 518)	P value
Age, years	74.4 ± 8.2	74.0 ± 8.4	0.3551
Male, n (%)	1376 (81.1%)	375 (72.4%)	<0.0001
BMI (kg/m^2)	24.56 ± 3.73	24.24 ± 3.52	0.2094
AF type			
Paroxysmal, n (%)	932 (54.9%)	244 (47.1%)	
Persistent, n (%)	245 (14.4%)	94 (18.1%)	0.0058
Permanent, n (%)	520 (30.6%)	180 (34.7%)	
Hypertension, n (%)	1450 (85.4%)	441 (85.1%)	0.8871

Diabetes mellitus, n (%)	738 (43.5%)	189 (36.5%)	0.0051
Dyslipidemia, n (%)	1249 (73.6%)	289 (55.8%)	<0.0001
Angina, n (%)	1177 (69.4%)	233 (45%)	<0.0001
Heart failure, n (%)	591 (34.8%)	197 (38.0%)	0.1901
Previous stroke, n (%)	247 (14.6%)	76 (14.7%)	0.9434
Previous myocardial infarction, n (%)	727 (42.8%)	50 (9.7%)	<0.0001
Previous peripheral arterial disease, n (%)	116 (6.8%)	23 (4.4%)	0.00495
CrCL	62.2 ± 25.7	62.4 ± 22.0	0.2257
<30 mL/min, n (%)	96 (5.7%)	18 (3.5%)	
≥30 and <50 mL/min, n (%)	460 (27.1%)	133 (25.7%)	0.0853
≥50 mL/min, n (%)	1046 (61.6%)	339 (65.4%)	

CHADS2 score	2.5 ± 1.2	2.4 ± 1.2	0.2552
0-2	961 (56.6%)	297 (57.3%)	
			0.7763
≥3	736 (43.4%)	221 (42.7%)	
CHA2DS2-VASc score	4.1 ± 1.5	3.7 ± 1.5	<0.0001
0-3	630 (37.1%)	235 (45.4%)	
			0.0008
≥4	1067 (62.9%)	283 (54.6%)	
HAS-BLED score	2.2 ± 0.7	1.7 ± 0.8	<0.0001
0-2	1149 (67.7%)	413 (79.7%)	
			<0.0001
3-5	491 (28.9%)	82 (15.8%)	
Treatment at baseline			
Dose of rivaroxaban			

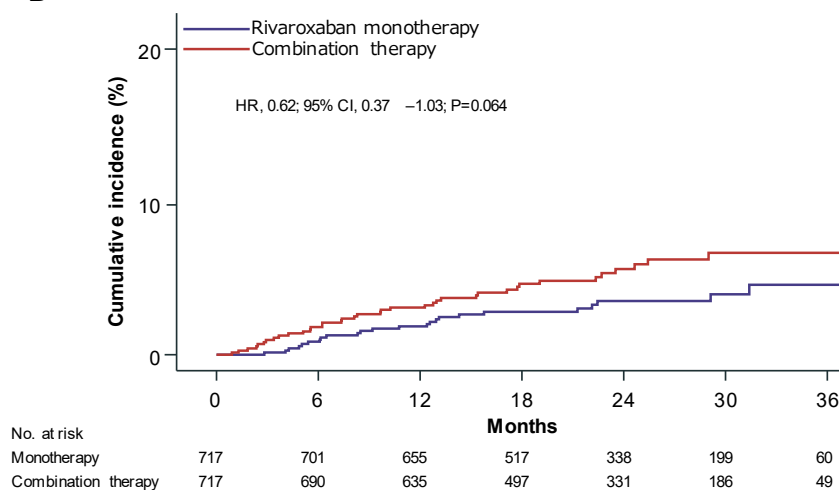|			
10 mg, n (%)	794 (46.8%)	216 (41.7%)	
			0.1017
15 mg, n (%)	886 (52.2%)	298 (57.5%)	
Use of antiplatelet agent			
Aspirin, n (%)	592 (34.9%)	213 (41.1%)	
			-
P2Y12 inhibitor, n (%)	270 (15.9%)	42 (8.1%)	

AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CrCL, creatinine clearance; PCI, percutaneous coronary intervention
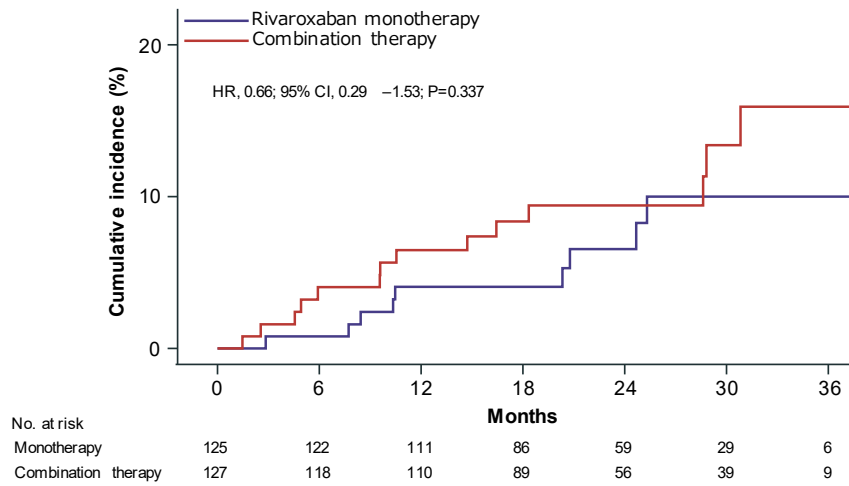
Supplementary Figure 1

A
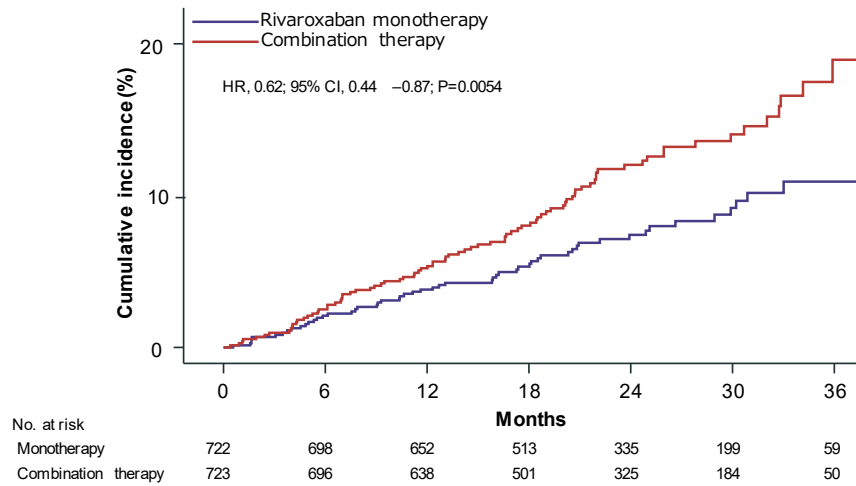
B

Supplementary Figure 1. Kaplan-Meier curves for efficacy and safety endpoints among patients with prior percutaneous coronary intervention only.

Panel A shows the efficacy endpoints of rivaroxaban monotherapy versus combination therapy groups of patients with prior percutaneous coronary intervention. Panel B shows the safety endpoints of rivaroxaban monotherapy and combination therapy groups of patients with prior percutaneous coronary intervention.
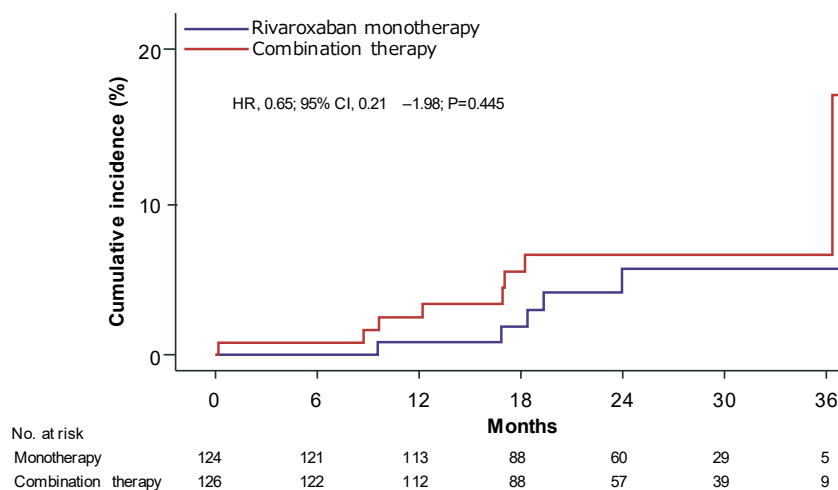
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Supplementary Figure 2

A

B

Supplementary Figure 2. Kaplan-Meier curves for efficacy and safety endpoints among patients with prior coronary artery bypass grafting only.

Panel A shows the efficacy endpoints of rivaroxaban monotherapy versus combination therapy groups of patients with prior coronary artery bypass grafting. Panel B shows the safety endpoints of rivaroxaban monotherapy and combination therapy groups of patients with prior coronary artery bypass grafting.

No: number