Terapia antitrombotica nei pazienti con coronaropatia cronica e fibrillazione atriale in base alla storia di rivascolarizzazione

Analisi post-hoc del trial AFIRE

Background

- Oral anticoagulation is considered essential for patients with atrial fibrillation (AF), which is a risk factor for thromboembolic events, whereas antiplatelet agents are considered the cornerstone of treatment for patients with stable coronary artery disease (CAD).
- Therefore, patients with AF and CAD often require combination antithrombotic therapy, which increases their risk of fatal and non-fatal bleeding and death.

EuroIntervention 434 2023;19:e425-e435

2019

AFIRE TRIAL

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

Multicenter, open-label trial conducted in Japan

Objective: To evaluate the use of antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease.

2236 patients

Inclusion criteria: patients with atrial fibrillation who had undergone PCI or CABG more than 1 year earlier or who had angiographically confirmed coronary artery disease not requiring revascularization were included.

Rivaroxaban monotherapy (N = 1107)	VS	Rivaroxaban + one antiplatelet agent (N = 1108)

PRIMARY OUTCOME

Rivaroxaban monotherapy	Stroke, embolism, MI, UA requiring revascularization, or death %	Rivaroxaban + one antiplatelet agent
4.14	HR 0.72; 95% CI, 0.55 to 0.95; P<0.001 for noninferiority	5.75

SECONDARY OUTCOME

Rivaroxaban monotherapy		Rivaroxaban + one antiplatelet agent
31.3	Ischemic stroke % HR 0.73; 95% CI, 0.42 to 1.29	24.9
1.62	Major bleeding % HR 0.59; 95% CI, 0.39 to 0.89, P = 0.01	2.76

Conclusion: The trial was stopped early because of increased mortality in the combination-therapy group. As antithrombotic therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in patients with atrial fibrillation and stable coronary artery disease.

Satoshi Yasuda, et al. NEJM, 2019; 381:1103-1113

CardioTrials

Background

- Rivaroxaban monotherapy was superior to combined antithrombotic therapy for major bleeding in patients with AF and stable CAD at 1 year after revascularisation (prior PCI or CABG) and in those with angiographically confirmed CAD not requiring revascularisation.
- 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.

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

Takashi Noda[1], MD, PhD; Kotaro Nochioka[1], MD, PhD; Koichi Kaikita[2], MD, PhD; Masaharu Akao[3], MD, PhD; Junya Ako[4], MD, PhD; Tetsuya Matoba[5], MD, PhD; Masato Nakamura[6], MD, PhD; Katsumi Miyauchi[7], MD, PhD; Nobuhisa Hagiwara[8], MD, PhD; Kazuo Kimura[9], MD, PhD; Atsushi Hirayama[10], MD, PhD; Kunihiko Matsui[11], MD, MPH; Hisao Ogawa[12], MD, PhD; Satoshi Yasuda[1]*, MD, PhD; on behalf of the AFIRE investigators

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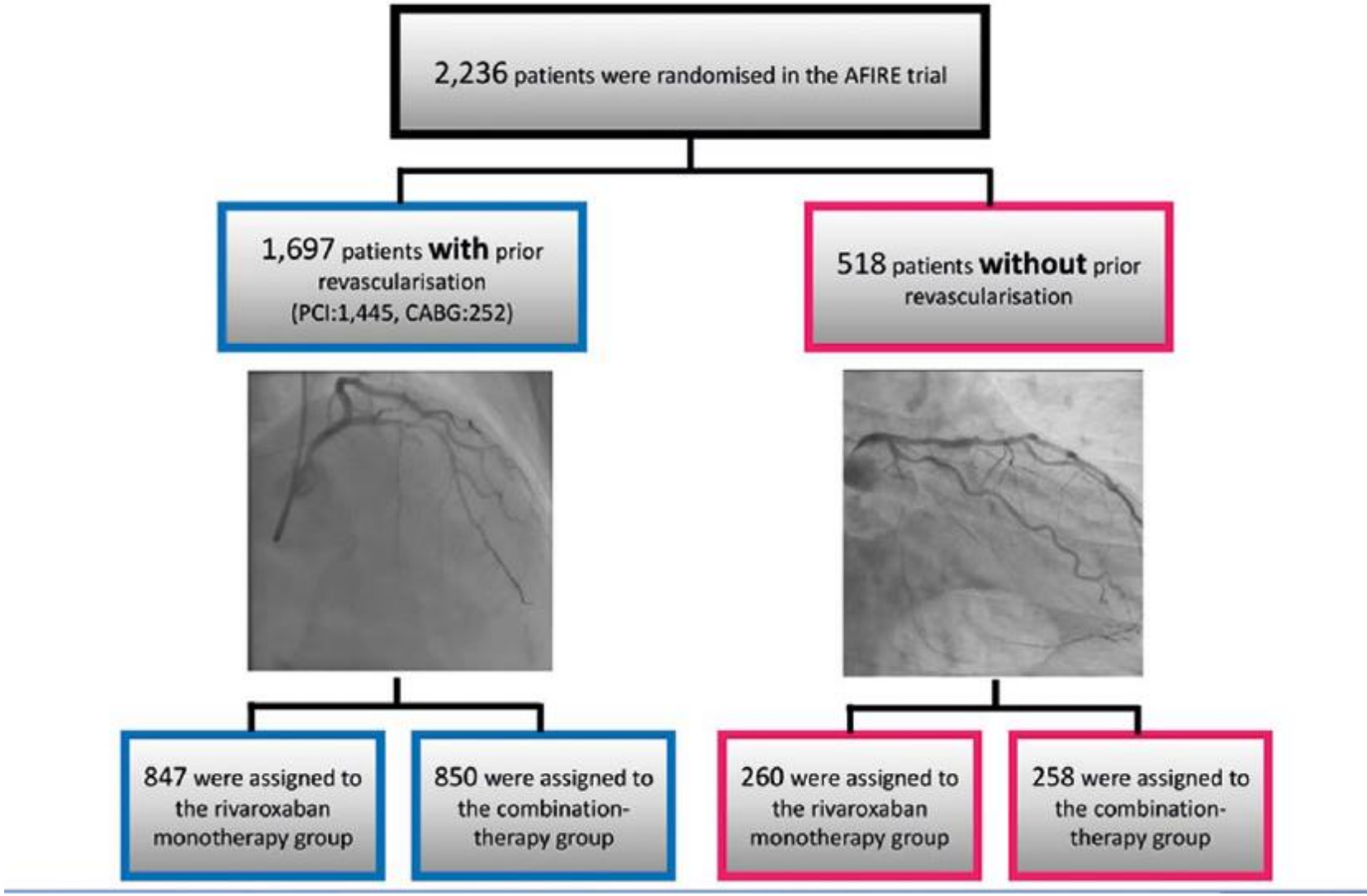
Methods

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

Patient flow of the subanalysis population



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Patient clinical characteristics by study group

No significant intergroup differences in the baseline characteristics

	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/m^2	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)	

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Patient clinical characteristics by study group

- CHA2DS2-VASc and the HAS-BLED scores were significantly higher in patients with prior revascularisation

	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
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)	
$CHADS_2$ 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)	
CHA_2DS_2-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)	-
$P2Y_{12}$ inhibitor	5 (0.6)	265 (31.2)		0 (0)	42 (16.3)	

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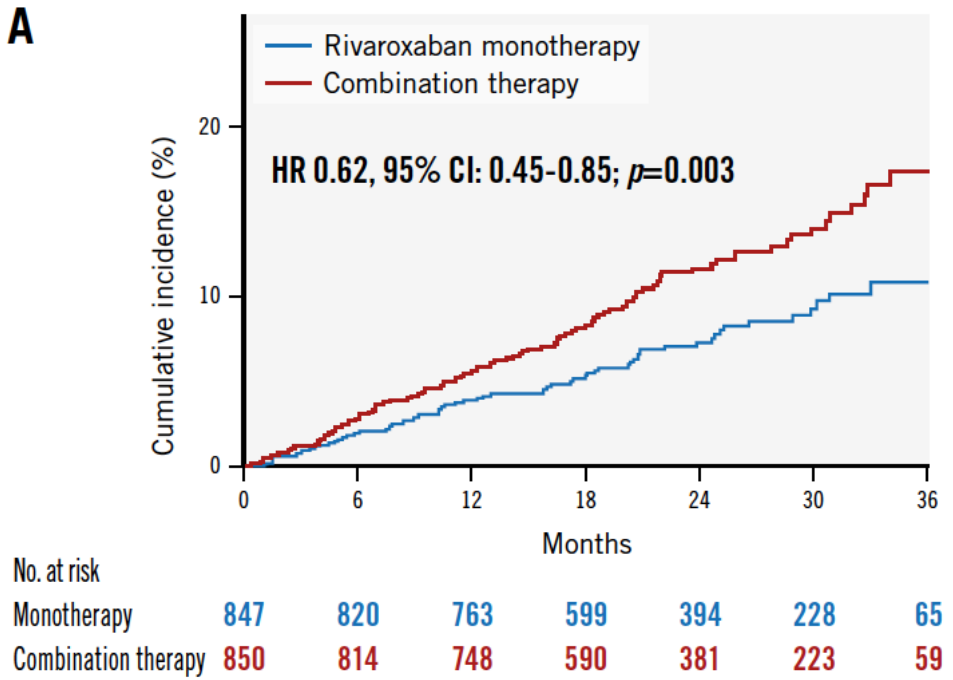
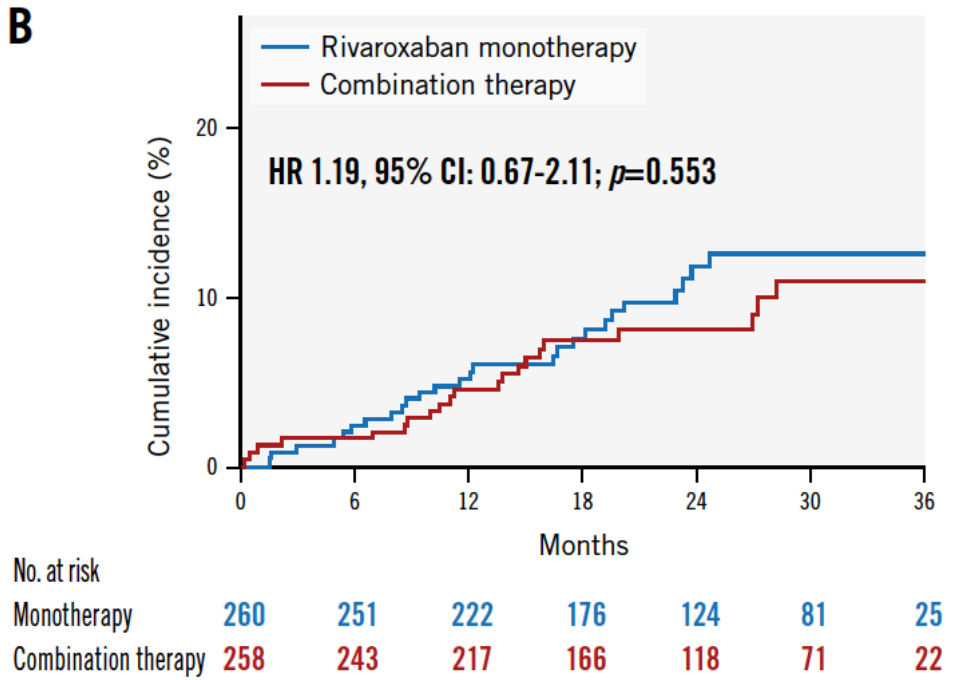
Kaplan-Meier curves for **efficacy endpoints** among patients with/without revascularisation

A) Patients **with a history of prior revascularization:** **rivaroxaban monotherapy was superior to combination therapy.**

B) Patients **without a history of prior revascularization:** **no significant differences**

There was borderline interaction for the primary efficacy outcome between prior revascularization and antithrombotic therapy (p=0.055) depending on the randomised treatment allocations.





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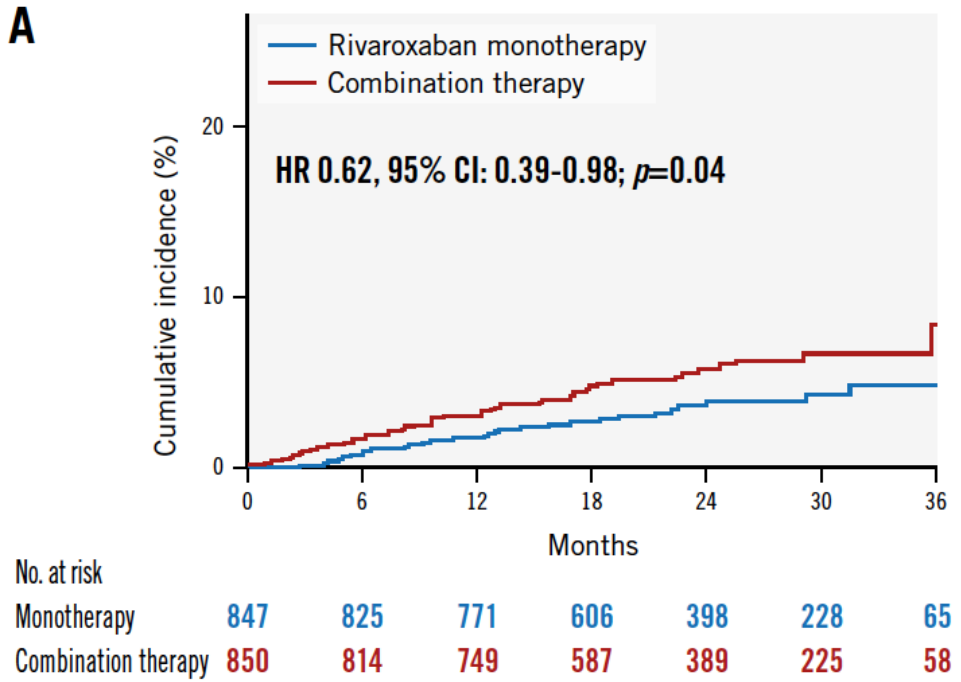
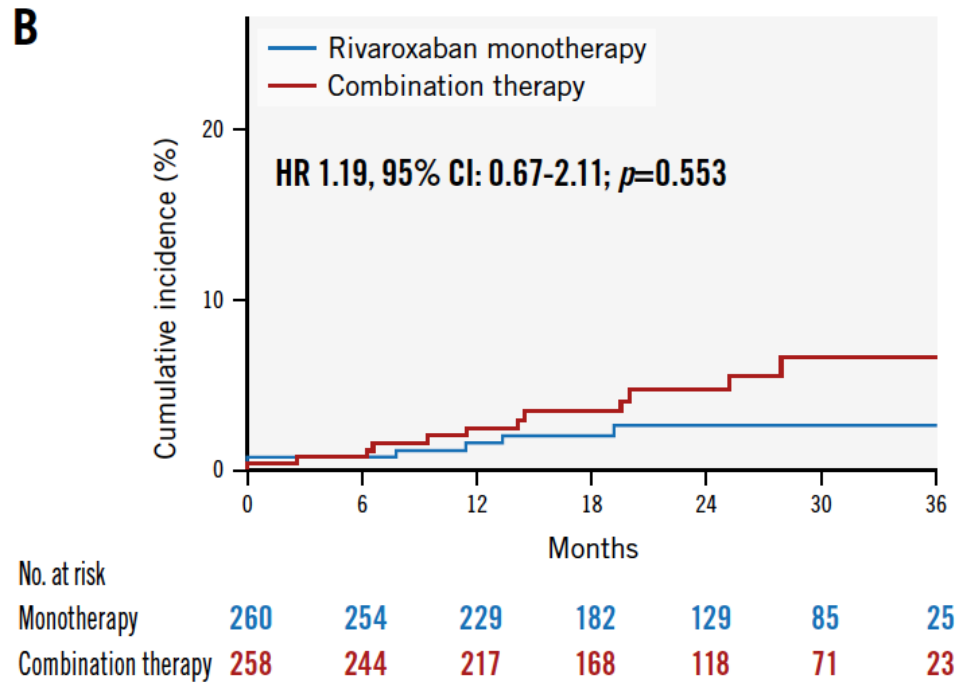
Kaplan-Meier curves for **safety endpoints** among patients with/without revascularisation

A) Patients **with a history of prior revascularization:** rivaroxaban monotherapy was superior to combination therapy

B) Patients **without a history of prior revascularization:** no significant intergroup difference

There was no interaction in the primary safety outcome between prior revascularisation and antithrombotic therapy (p=0.633).





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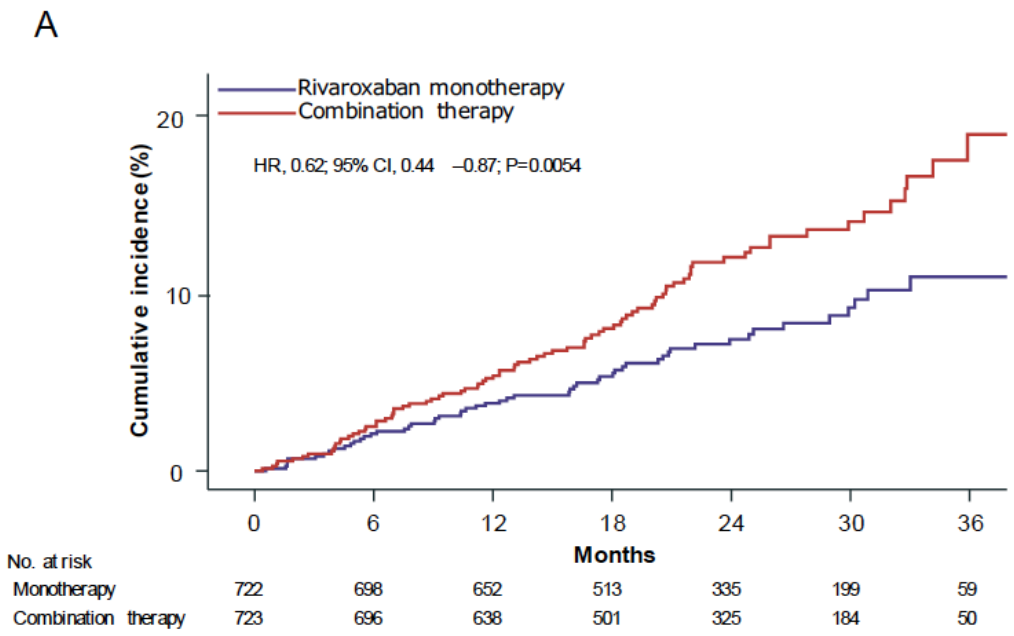
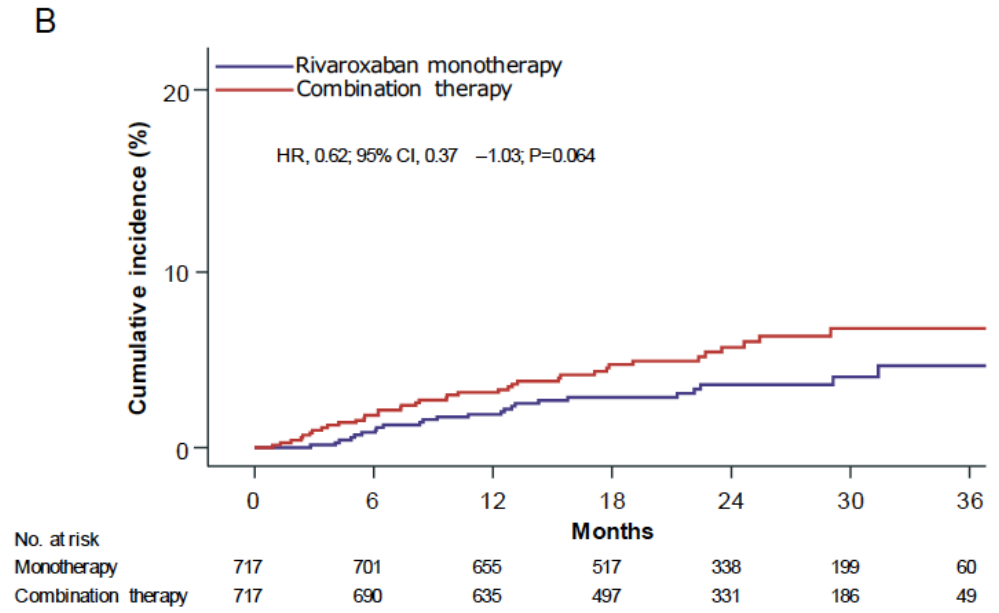
Kaplan-Meier curves for efficacy and safety endpoints among patients **with prior PCI** only (N=1,445)

A. **Efficacy endpoints:** patients receiving rivaroxaban monotherapy exhibited lower event rates

B. **Safety endpoints:** no significant intergroup variation





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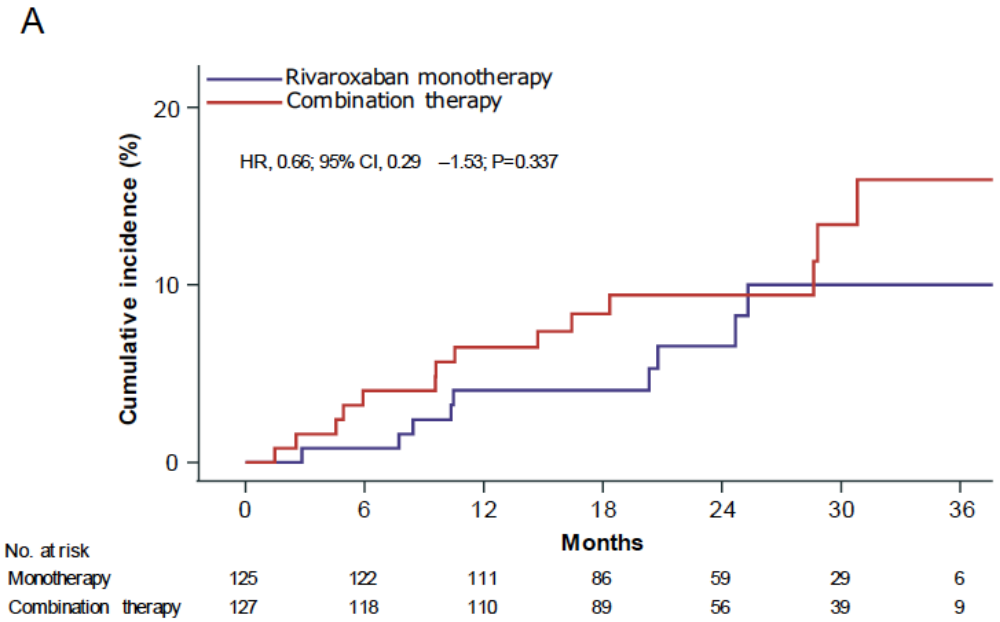
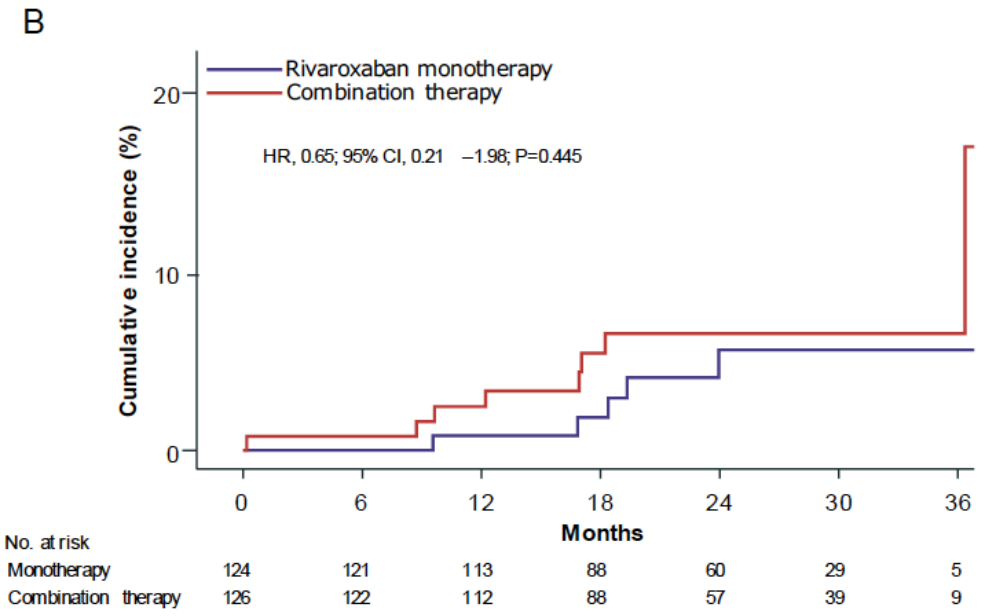
Kaplan-Meier curves for efficacy and safety endpoints among patients **with prior CABG** only (252)

A) **Efficacy endpoints**: no significant intergroup variation

B) **Safety endpoints:** no significant intergroup variation





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Type of revascularization

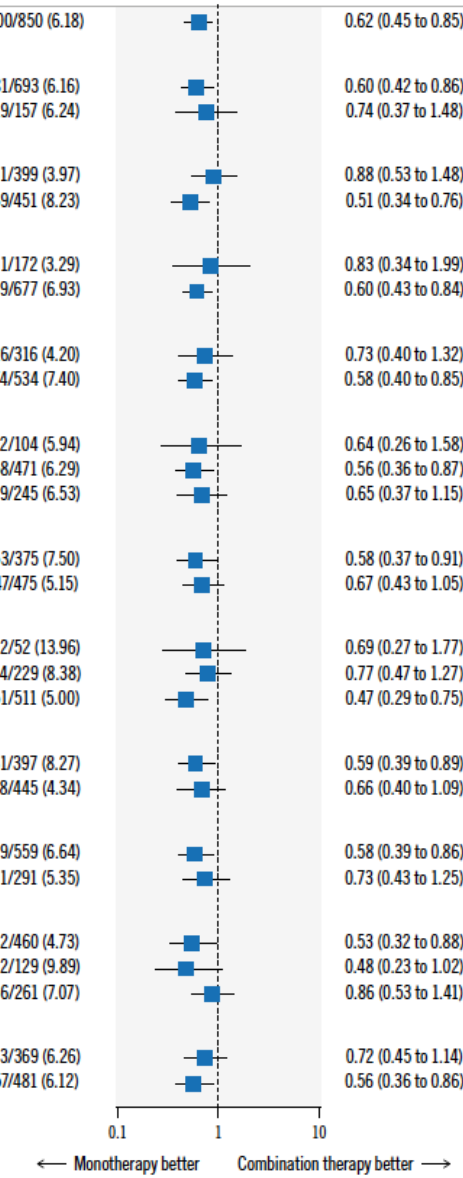
- There was no interaction in the primary efficacy endpoint between the type of revascularisation and the antithrombotic therapy (p=0.158).

- There was no interaction in the primary safety endpoint between the type of revascularisation and the antithrombotic therapy (p=0.891)

Primary efficacy endpoint according to subgroup based on revascularisation history

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

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_2DS_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	



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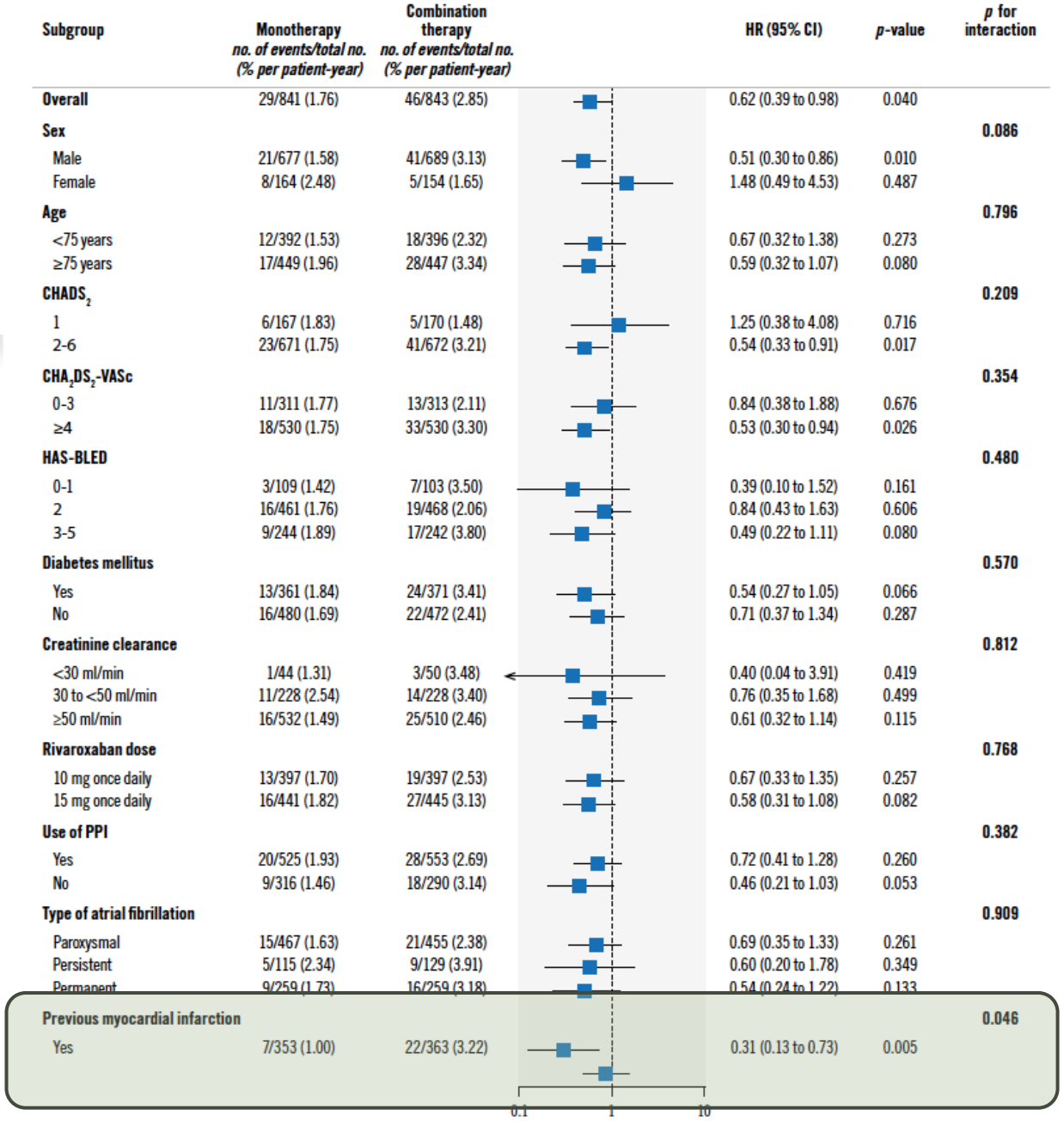
Primary safety endpoint among patients with prior revascularisation history

- With respect to the primary safety endpoint, there was similar consistency in the effect of rivaroxaban monotherapy in patients with a history of prior revascularization
- There was a statistically significant interaction for the primary safety endpoint between patients with versus without previous myocardial infarction.



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_2DS_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	

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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

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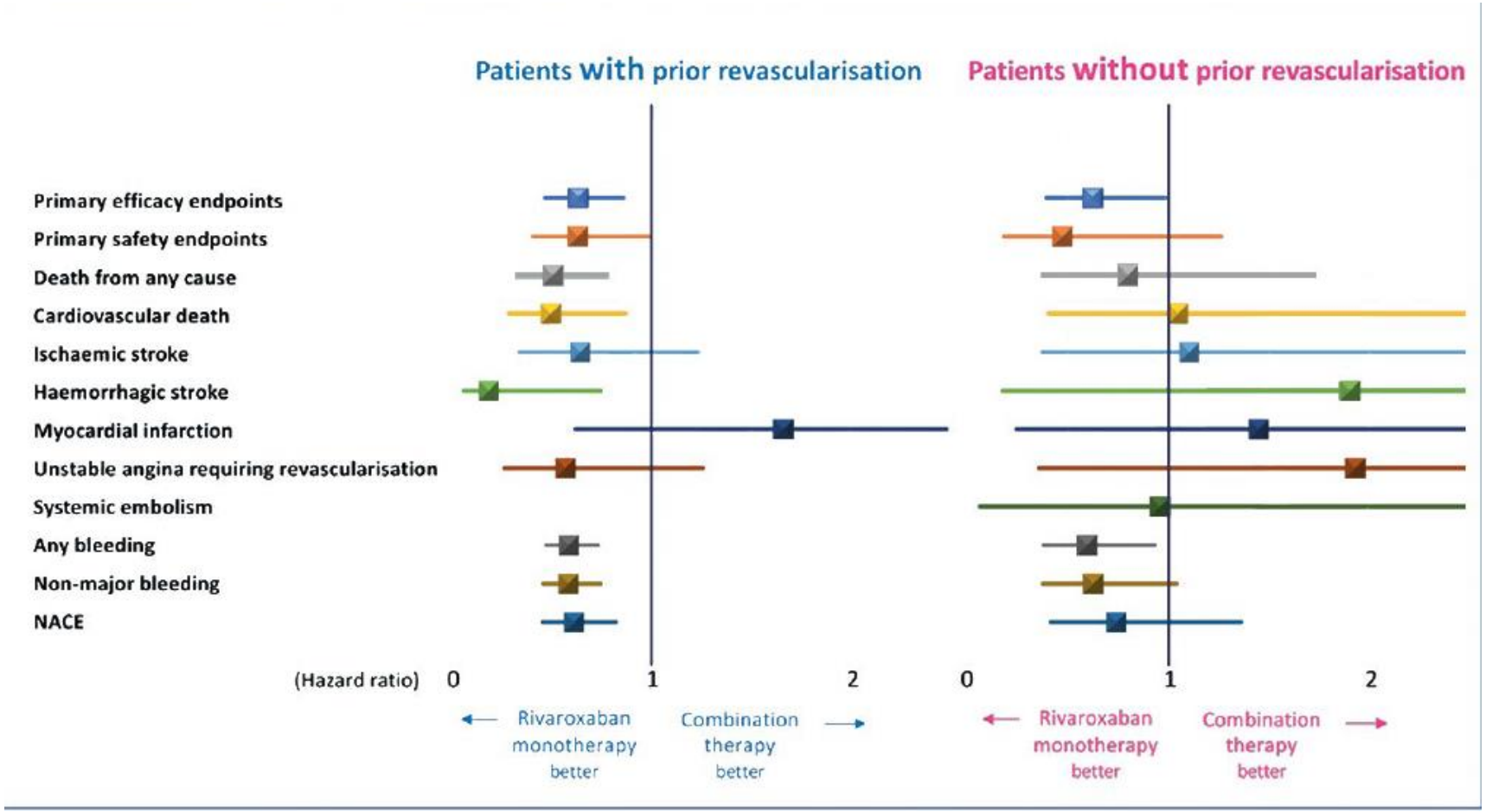
Primary and secondary endpoints among patients with versus without prior revascularisation



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Limitations

- The post hoc design was a limitation of the study. The entire cohort was divided into several groups; therefore, the number of patients in these analyses was relatively small, which may have influenced the results.
- 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).
- The selection of an antiplatelet agent was made at the discretion of the treating physicians. However, no significant differences were found in efficacy and safety outcomes between the P2Y12 inhibitor and aspirin groups in a post hoc analysis.
- 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 patients at high risk of thrombosis 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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Impact on daily practice

This post hoc subgroup analysis of patients at high risk of thrombosis with a history of prior revascularisation with PCI or CABG 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 CAD, or extensive complex coronary stenting.

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