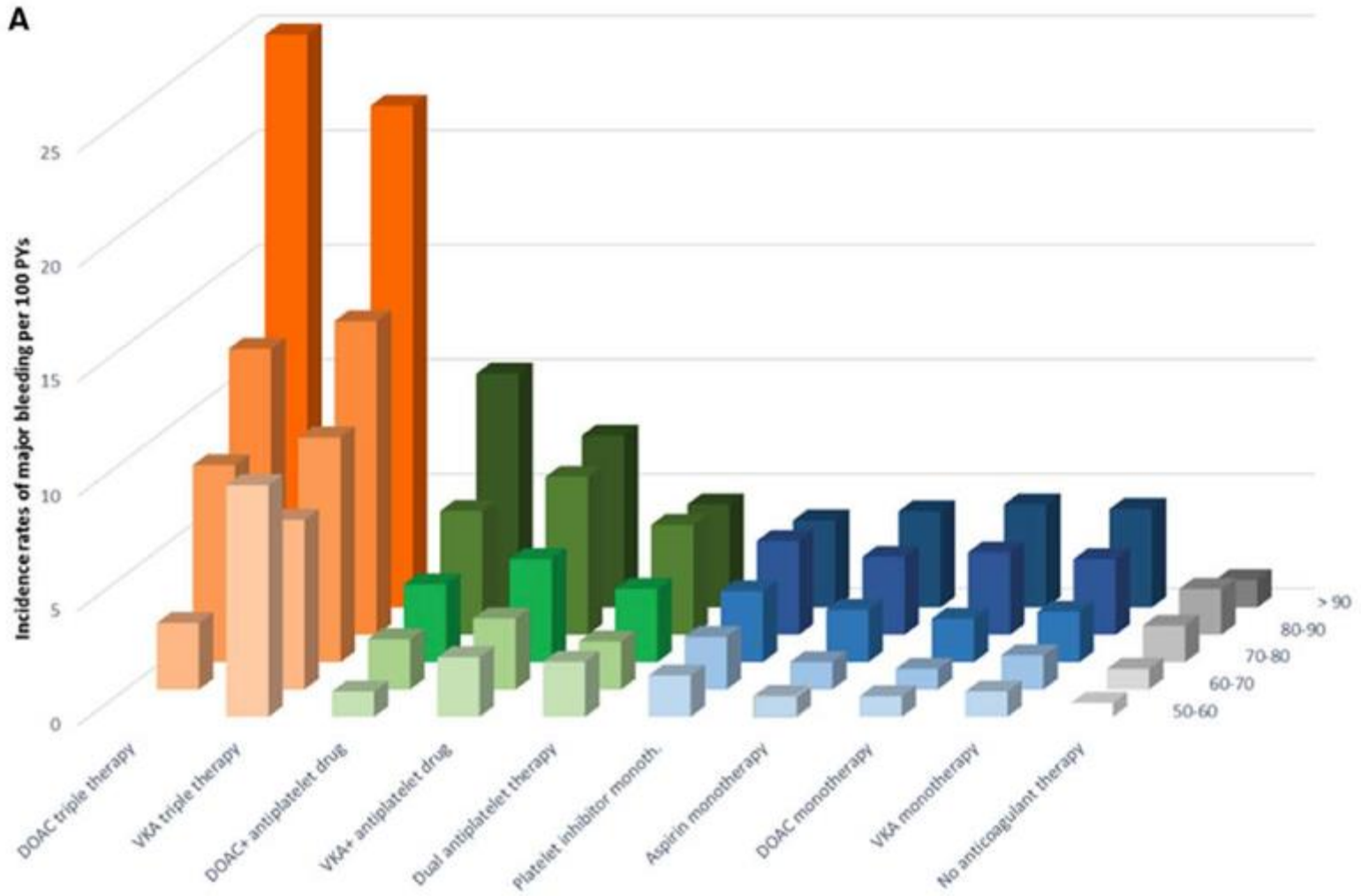
Terapia antitrombotica nei pazienti con fibrillazione atriale e coronaropatia cronica

Background

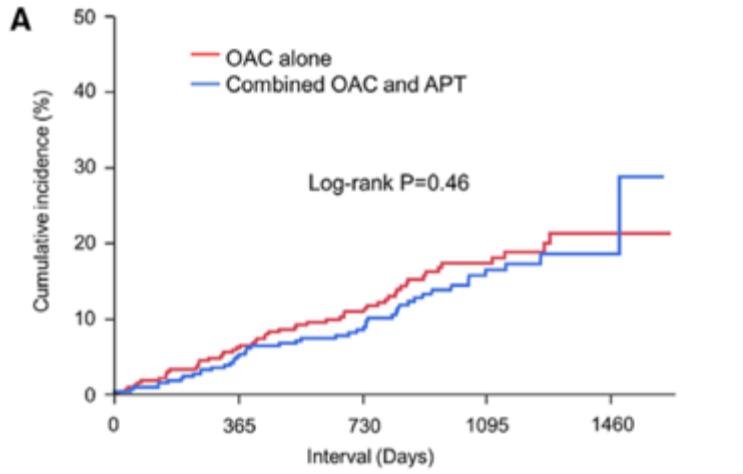
- 5 to 7% of patients with coronary artery disease who are undergoing PCI have an indication for long-term oral anticoagulant therapy.
- Research has focused on the treatment of patients with atrial fibrillation within the first 12 months after PCI
- After 12 months of combination therapy, or in patients with atrial fibrillation and stable coronary artery disease not requiring intervention, current guidelines recommend monotherapy with an oral anticoagulant.

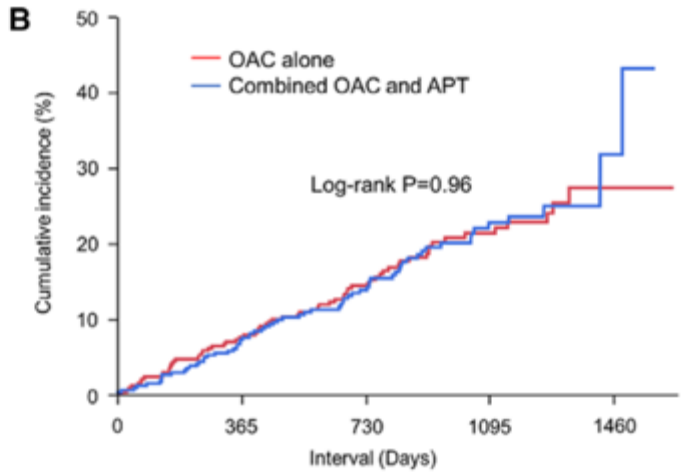


Danish registry

INCIDENCE RATES PER 100 PERSON-YEARS OF MAJOR BLEEDS BY AGE

van Rein N, et al., Circulation 2019;139:775-86.





Interval (Days)	0	365	730	1095	1460
OAC alone					
N of patients at risk	344	319	236	122	12
N of patients with event		21	36	50	54
Cumulative Incidence		6.1%	10.9%	17.3%	21.2%
Combined OAC and APT					
N of patients at risk	346	325	238	113	10
N of patients with event		17	28	44	46
Cumulative Incidence		4.9%	8.5%	16.4%	18.5%

Interval (Days)	0	365	730	1095	1460
OAC alone					
N of patients at risk	344	314	227	115	12
N of patients with event		26	47	62	67
Cumulative Incidence		7.6%	14.4%	21.4%	27.3%
Combined OAC and APT					
N of patients at risk	346	317	223	105	8
N of patients with event		25	45	63	66
Cumulative Incidence		7.3%	13.9%	22.7%	31.8%

CONCLUSIONS: This randomized trial did not establish noninferiority of OAC alone to combined OAC and APT in patients with atrial fibrillation and stable coronary artery disease beyond 1 year after stenting. Because patient enrollment was prematurely terminated, the study was underpowered and inconclusive. Future larger studies are required to establish the optimal antithrombotic regimen in this population.

OAC-alone trial

Matsumura-Nakano Y,et al,. Circulation 2019;139:604-16.

ORIGINAL ARTICLE

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

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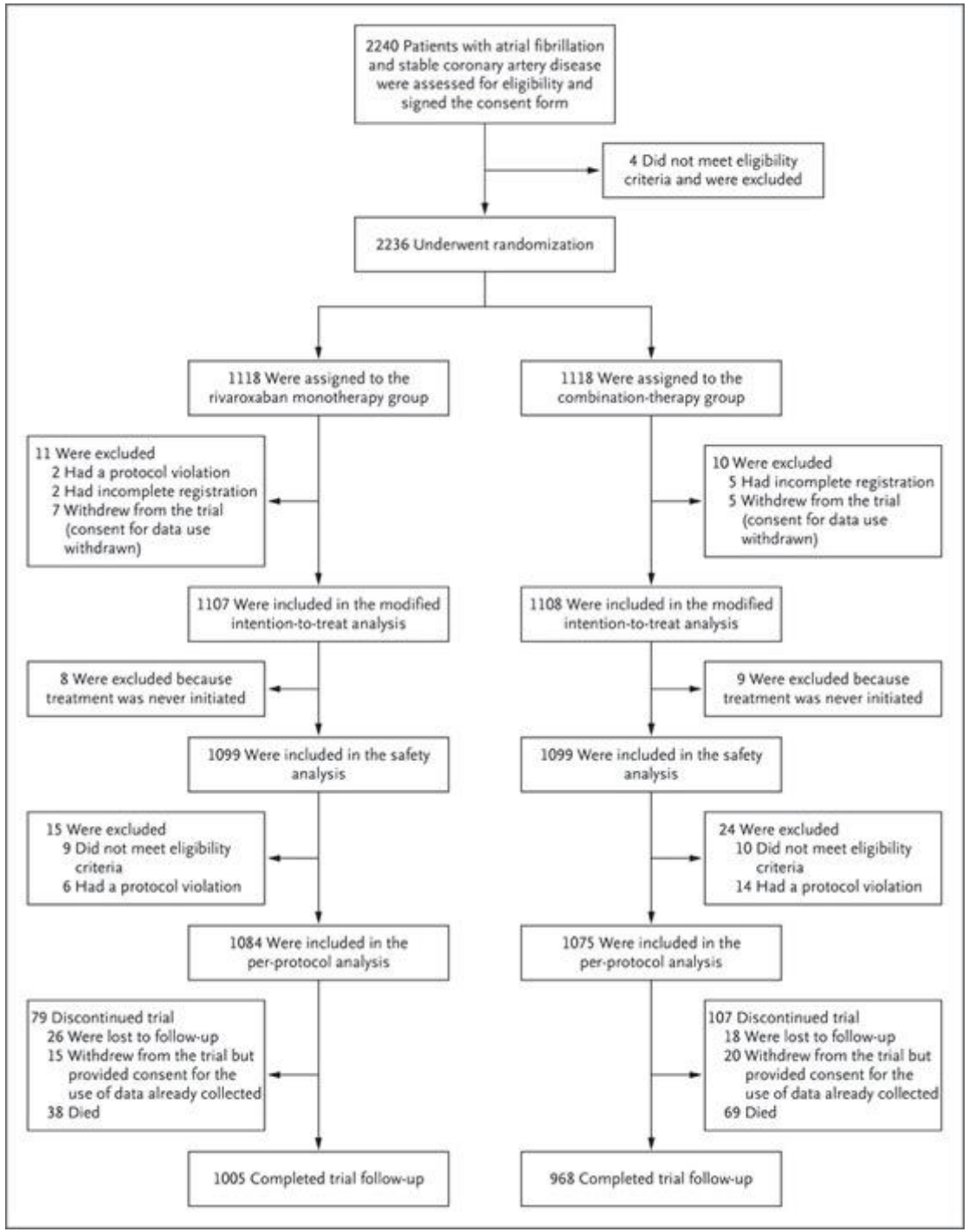

Enrollment, Randomization and Follow-up

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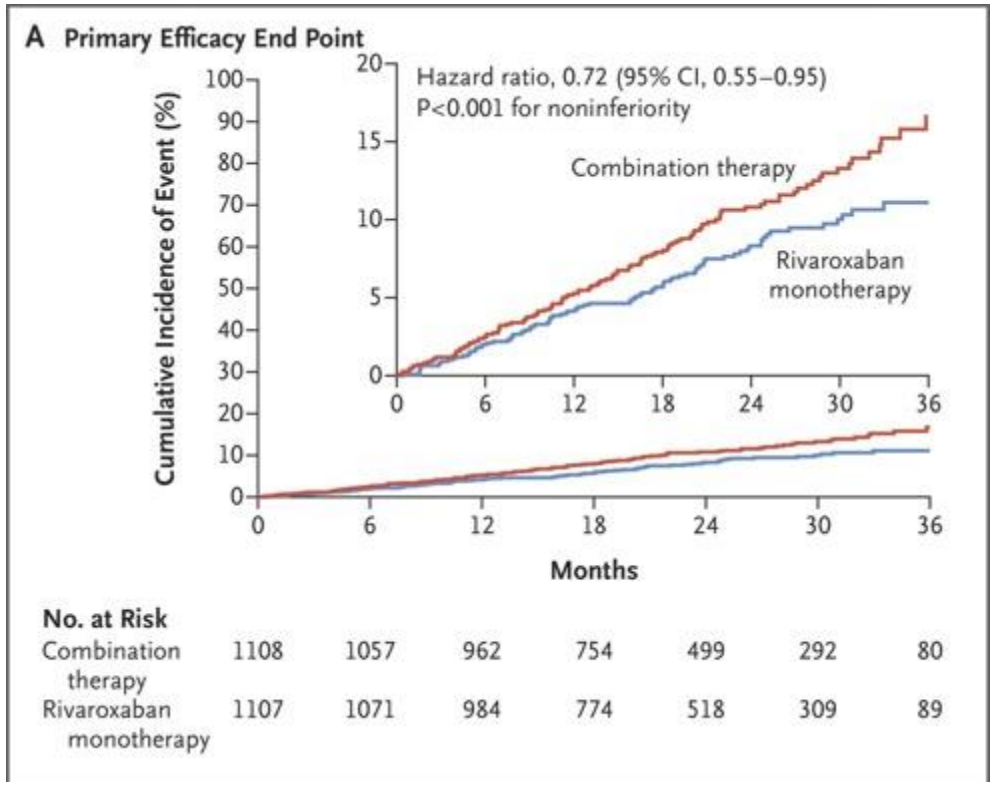
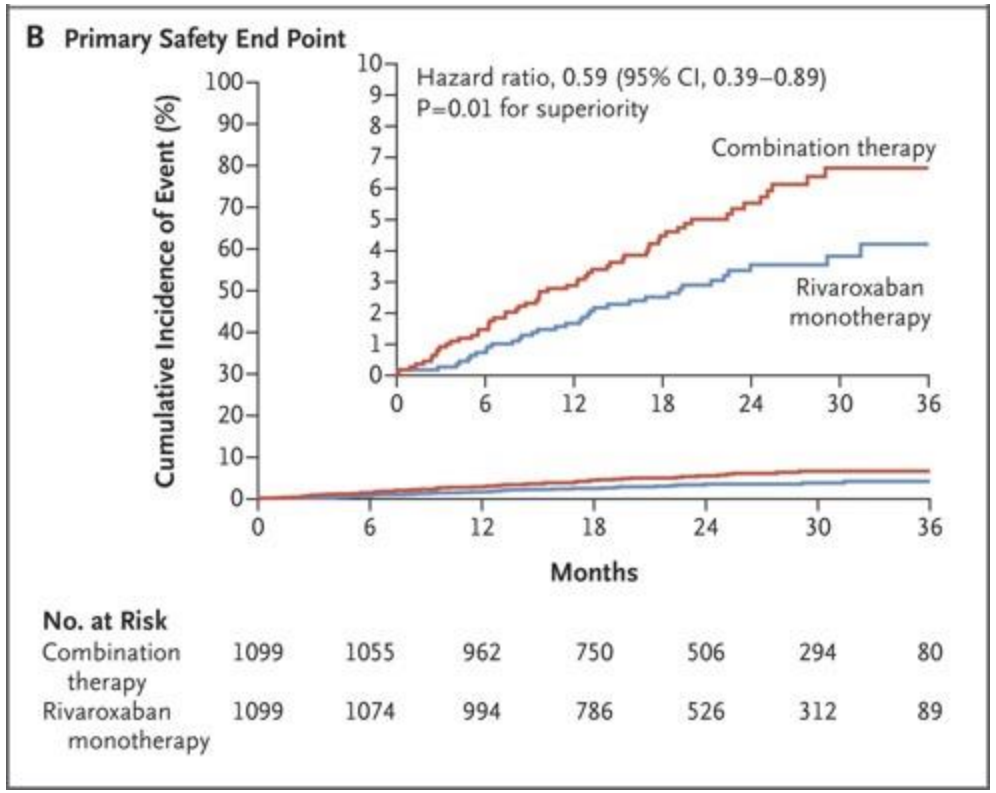
Primary Efficacy and Safety End Points





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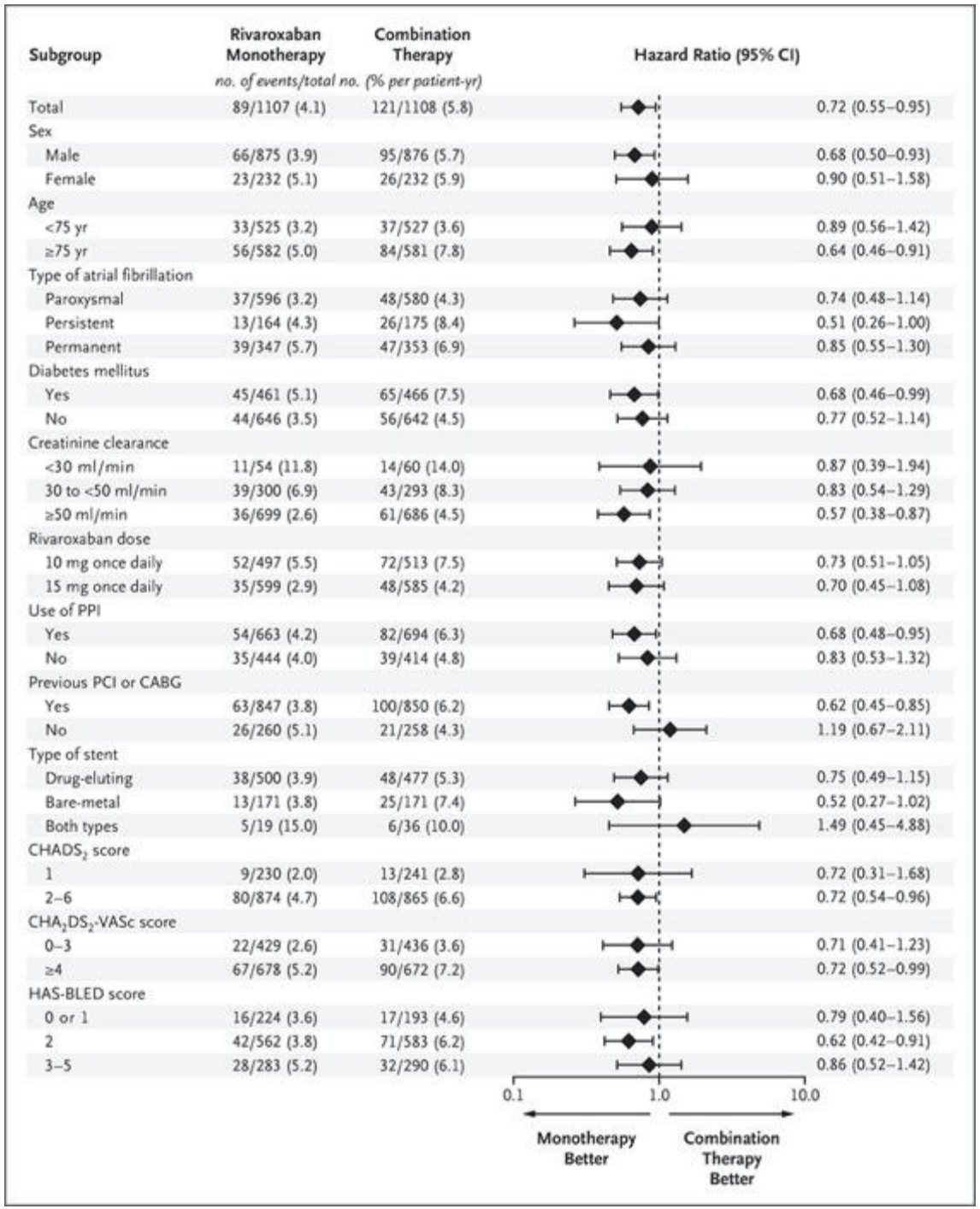

Primary Efficacy End Point, According to Subgroup

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Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Age — yr	74.3±8.3	74.4±8.2
<75 yr — no. (%)	525 (47.4)	527 (47.6)
≥75 yr — no. (%)	582 (52.6)	581 (52.4)
Male sex — no. (%)	875 (79.0)	876 (79.1)
Body-mass index†	24.5±3.7	24.5±3.7
Current smoker — no. (%)	146 (13.2)	146 (13.2)
Diabetes — no. (%)	461 (41.6)	466 (42.1)
Previous stroke — no. (%)	148 (13.4)	175 (15.8)
Previous myocardial infarction — no. (%)	384 (34.7)	393 (35.5)
Previous PCI — no. (%)	781 (70.6)	783 (70.7)
Type of stent — no./total no. (%)		
Drug-eluting	500/723 (69.2)	477/721 (66.2)
Bare-metal	171/723 (23.7)	171/721 (23.7)
Both types	19/723 (2.6)	36/721 (5.0)
Unknown	33/723 (4.6)	37/721 (5.1)
Previous CABG — no. (%)	125 (11.3)	127 (11.5)
Type of atrial fibrillation — no. (%)		
Paroxysmal	596 (53.8)	580 (52.3)
Persistent	164 (14.8)	175 (15.8)
Permanent	347 (31.3)	353 (31.9)
Creatinine clearance		
Mean — ml/min	62.8±25.7	61.7±24.0
Distribution — no./total no. (%)		
<30 ml/min	54/1053 (5.1)	60/1039 (5.8)
30 to <50 ml/min	300/1053 (28.5)	293/1039 (28.2)
≥50 ml/min	699/1053 (66.4)	686/1039 (66.0)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in the characteristics listed. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data are missing for 75 patients in the monotherapy group and 86 patients in the combination-therapy group.

Characteristics of the Patients at Baseline

(Modified Intention-to-Treat Population)

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Primary and Secondary Efficacy and Safety End Points

Table 2. Primary and Secondary Efficacy and Safety End Points.*

End Point	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)	Hazard Ratio (95% CI)	P Value†
	no. of patients (% per patient-yr)			
Primary efficacy end point				
Cardiovascular events or death from any cause	89 (4.14)	121 (5.75)	0.72 (0.55–0.95)	<0.001
Secondary efficacy end points				
Cardiovascular events				
Ischemic stroke	21 (0.96)	28 (1.31)	0.73 (0.42–1.29)	
Hemorrhagic stroke	4 (0.18)	13 (0.60)	0.30 (0.10–0.92)	
Myocardial infarction	13 (0.59)	8 (0.37)	1.60 (0.67–3.87)	
Unstable angina requiring revascularization	13 (0.59)	18 (0.84)	0.71 (0.35–1.44)	
Systemic embolism	2 (0.09)	1 (0.05)	1.97 (0.18–21.73)	
Death	41 (1.85)	73 (3.37)	0.55 (0.38–0.81)	
Cardiovascular	26 (1.17)	43 (1.99)	0.59 (0.36–0.96)	
Noncardiovascular	15 (0.68)	30 (1.39)	0.49 (0.27–0.92)	
Ischemic cardiovascular events or death‡	114 (5.37)	141 (6.77)	0.80 (0.62–1.02)	
Net adverse clinical events§	84 (3.90)	131 (6.28)	0.62 (0.47–0.82)	
Primary safety end point				
Major bleeding¶	35 (1.62)	58 (2.76)	0.59 (0.39–0.89)	0.01
Secondary safety end points				
Any bleeding	146 (7.22)	238 (12.72)	0.58 (0.47–0.71)	
Nonmajor bleeding	121 (5.89)	198 (10.31)	0.58 (0.46–0.72)	

* The primary and secondary efficacy analyses were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization after the exclusion of patients who had technical reasons for not participating in the trial. The primary and secondary safety analyses were performed in the population that included all the patients who had undergone randomization and received at least one dose of a trial drug during the follow-up period (1099 patients in the monotherapy group and 1099 in the combination-therapy group). The 95% confidence intervals have not been adjusted for multiple comparisons.

† In the primary efficacy analysis, the P value for noninferiority was calculated at a one-sided alpha level of 0.025 with a noninferiority margin of 1.46. Since noninferiority was shown for the primary efficacy end point, a closed testing procedure was conducted to determine superiority for the primary safety end point.

‡ The category of ischemic cardiovascular events or death is a composite of death from any cause, myocardial infarction, unstable angina requiring revascularization, stroke, transient ischemic attack, systemic arterial embolism, venous thromboembolism, revascularization, or stent thrombosis.

§ The category of net adverse clinical events is a composite of death from any cause, myocardial infarction, stroke, or major bleeding.

¶ Major and nonmajor bleeding events were classified according to the criteria of the International Society on Thrombosis and Hemostasis.

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Study limitations

- Open-label design had the potential to introduce bias (all the events were adjudicated by an independent committee).
- Relatively high rates of withdrawal of consent and loss of patients to follow-up (values were within the anticipated 5% rate of discontinuation)
- Rivaroxaban dose approved in Japan (10 mg or 15 mg once daily, according to eGFR)
- The choice of antiplatelet regimen was at the discretion of the treating physicians
- The early termination of the trial because of an increased risk of death from any cause in the combination-therapy group may overestimate the efficacy data.
- The reductions in the rate of ischemic events and death from any cause with rivaroxaban monotherapy were unanticipated and may be due to the play of chance.

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Conclusions

- 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.

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