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Atrial **F**ibrillation and **I**schemic events with **R**ivaroxaban in pati**E**nts with stable coronary artery disease

Rivaroxaban Monotherapy versus Combination Therapy in Patients with Atrial Fibrillation and Stable Coronary Artery Disease

Satoshi Yasuda, Koichi Kaikita, Masaharu Akao, Junya Ako, Tetsuya Matoba, Masato Nakamura, Katsumi Miyauchi, Nobuhisa Hagiwara, Kazuo Kimura, Atsushi Hirayama, Kunihiko Matsui, Hisao Ogawa,
on behalf of the **AFIRE** (**A**trial **F**ibrillation and **I**schemic events with **R**ivaroxaban in pati**E**nts with stable coronary artery disease) Investigators

Declaration of interest

- Research contracts (Takeda)
- Others (Daiichi-Sankyo, Bristol-Meyers, Abbott)

Conflict of Interest Statement

Dr. Yasuda	receiving grant support from Takeda and Abbott , and lecture fees from Daiichi Sankyo and Bristol-Myers Squibb
Dr. Kaikita	receiving grant support from Bayer Yakuhin, Daiichi Sankyo, Novartis Pharma, SBI Pharma, and the Ministry of Education, Culture, Sports, Science and Technology of Japan
Dr. Akao	receiving lecture fees from Bristol-Myers Squibb and Nippon Boehringer Ingelheim, grant support and lecture fees from Bayer Yakuhin and Daiichi Sankyo, and grants from Japan Agency for Medical Research and Development, AMED
Dr. Ako	receiving lecture fees from Bayer Yakuhin and Sanofi, and grant support and lecture fees from Daiichi Sankyo;
Dr. Matoba	receiving fees for serving on a speakers bureau from Nippon Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, and Bayer Yakuhin, and grant support from Japan Cardiovascular Research Foundation;
Dr. Nakamura	receiving grant support and honoraria from Bayer Yakuhin, Daiichi Sankyo, Sanofi, and Nippon Boehringer Ingelheim, and honoraria from Bristol-Myers Squibb;
Dr. Miyauchi	receiving lecture fees from Amgen Astellas BioPharma, Astellas Pharma, MSD, Bayer Yakuhin, Sanofi, Takeda, Daiichi Sankyo, Nippon Boehringer Ingelheim, and Bristol-Myers Squibb;
Dr. Hagiwara	receiving grant support and lecture fees from Bayer Yakuhin and Nippon Boehringer Ingelheim, lecture fees from Bristol-Myers Squibb, and grant support from Daiichi Sankyo and Pfizer Japan;
Dr. Kimura	receiving lecture fees from Bristol-Myers Squibb and Nippon Boehringer Ingelheim, grant support, lecture fees, and advisory fees from Bayer Yakuhin, and grant support and lecture fees from Daiichi Sankyo and Sanofi, and grant support from Japan Cardiovascular Research Foundation;
Dr. Hirayama	receiving fees for serving on a speakers bureau from Sanofi, Astellas Pharma, Sumitomo Dainippon Pharma, AstraZeneca, Nippon Boehringer Ingelheim and Amgen Astellas BioPharma, grant support and fees for serving on a speakers bureau from Bristol-Myers Squibb, Daiichi Sankyo, and Bayer Yakuhin, fees for serving on a speakers bureau and consulting fees from TOA EIYO, grant support from Pfizer Japan, serving as endowed chair for Boston Scientific Japan, Hokushin Medical, Abbott Japan, Active Medical, Fukuda Denshi, Medtronic Japan, Japan Lifeline, and Kurihaha Medical Instrument, and fees for serving on a speakers bureau and serving as endowed chair for Otsuka Pharma;
Dr. Ogawa	receiving fees for serving on a speakers bureau from TOWA Pharmaceutical and honoraria from Novartis Pharma.

No other potential conflict of interest relevant to this article was reported.

A Reduced Antithrombotic Regimen Recommended by Current Guidelines

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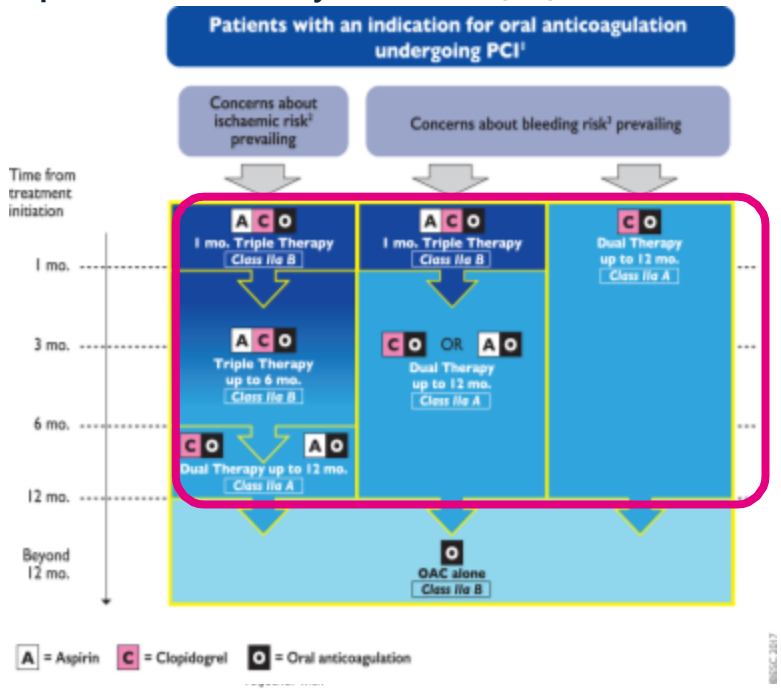
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). [1)]



The selection of the most effective antithrombotic treatment for patients with atrial fibrillation (AF) and coronary artery disease (CAD) is a clinical challenge.

A reduced antithrombotic regimen of patients with AF within the first 12 months after PCI was studied in PIONEER AF-PCI [2)], RE-DUAL PCI [3)], and AUGUSTUS [4)].

- **Triple therapy (an oral anticoagulant plus aspirin and a $P2Y_{12}$ inhibitor): for as short a duration as possible**
- **Combination therapy (an anticoagulant plus a $P2Y_{12}$ inhibitor.): up to 12 mo. in selected patients**

1) Valgimigli M, *et al.*, *Eur Heart J*, 2018
2) Gibson CM, et al. *N Engl J Med* 2016
3) Cannon CP, et al. *N Engl J Med* 2017
4) Lopes RD, et al. *N Engl J Med* 2019

After 1 year following PCI, Current Guidelines Recommend Oral Anticoagulant Monotherapy

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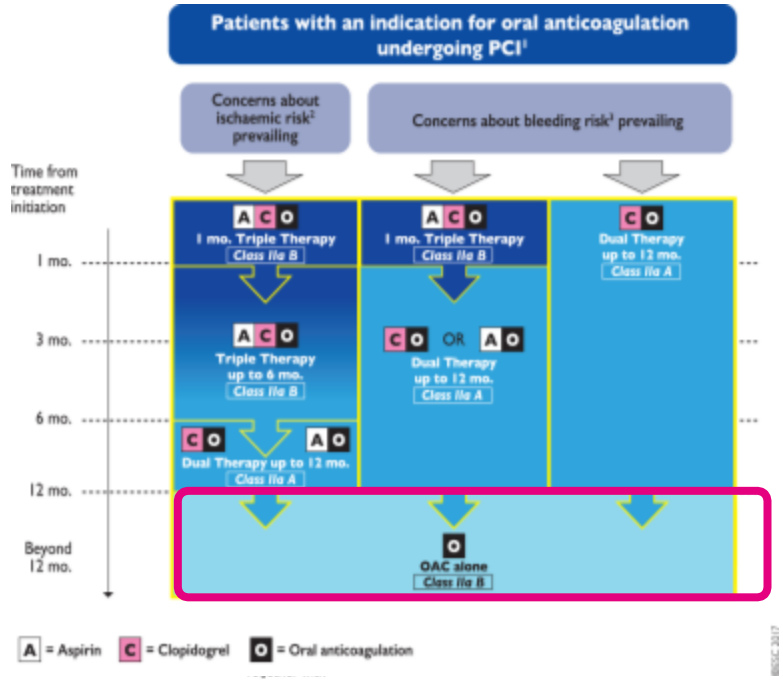
Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). [1)]



- After 12 months of combination therapy, or in patients with AF and stable CAD not requiring intervention, current guidelines recommend monotherapy with an oral anticoagulant.
- However, this approach has yet to be supported by evidence from randomized, controlled trials.
- Furthermore, substantial numbers of patients in this situation continue to be treated with combination therapy, which indicates a gap between guidelines and clinical practice.[2)]

1) Valgimigli M, *et al.*, *Eur Heart J*, 2018 2) Ancedy Y, *et al.*, *Int J Cardiol* 2016

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease: AFIRE Study

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In the AFIRE study, we **aimed** to investigate whether **rivaroxaban monotherapy** is **noninferior** to **combination therapy (rivaroxaban plus an antiplatelet agent)** in patients with AF and stable CAD more than 1 year after revascularization or in those with angiographically confirmed CAD not requiring revascularization.

Trial Organization

Principal Investigator	Satoshi Yasuda
Steering Committee	Hisao Ogawa (Deputy Principal Investigator), Kazuo Kimura, Nobuhisa Hagiwara, Atsushi Hirayama, Masato Nakamura, Katsumi Miyauchi
Protocol Committee	Junya Ako (Chair), Masaharu Akao, Koichi Kaikita, Tetsuya Matoba
Clinical Events Committee	
Cardiac Region:	Tetsuya Sumiyoshi, Yukihiro Koretsune, Takafumi Hiro
Brain Region:	Yoichiro Hashimoto, Kazumi Kimura, Teruyuki Hirano
Data Safety and Monitoring Committee	Hiroyuki Daida (Chair), Yasushi Okada, Tsutomu Yamazaki
Principal Statistician	Kunihiko Matsui
Funding	Japan Cardiovascular Research Foundation

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease: AFIRE Study

A multicenter, prospective, randomized, open-label, parallel-group trial [1)]

2200 patients with AF ($CHADS_2 \geq 1$) and stable CAD

Key inclusion criteria

- Underwent PCI or CABG more than 1 year earlier
- Angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization

Key exclusion criteria

- A history of stent thrombosis
- Coexisting active tumor
- Poorly controlled hypertension

RANDOMIZE

Rivaroxaban Monotherapy

- **Rivaroxaban** 10 or 15 mg/day [2)*]

*The level of rivaroxaban in blood samples obtained from Japanese patients who were taking rivaroxaban at the 15-mg dose was similar to the level in white patients who were taking the 20-mg dose.

Combination Therapy

- **Rivaroxaban** 10 or 15 mg/day
- **Single antiplatelet**
  Aspirin 81 or 100 mg/day,
  Clopidogrel 50 or 75 mg/day, Prasugrel 2.5 or 3.75 mg/day

UMIN Clinical Trials Registry number, UMIN000016612.
ClinicalTrials.gov number, NCT02642419.

1) Yasuda S, et al. *Int J Cardiol.* 2018. *2*) Tanigawa T, et al. *Drug Metab Pharmacokinet.* 2013.

Primary End Points

Primary efficacy end point [1] ;

- **The composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause**
- Assessed **noninferiority** of **rivaroxaban monotherapy**, as compared with **combination therapy** (**noninferiority margin: 1.46** for the 95% CI, with **a power of 80%)**
- Performed in the modified ITT population

Primary safety end point [1] ;

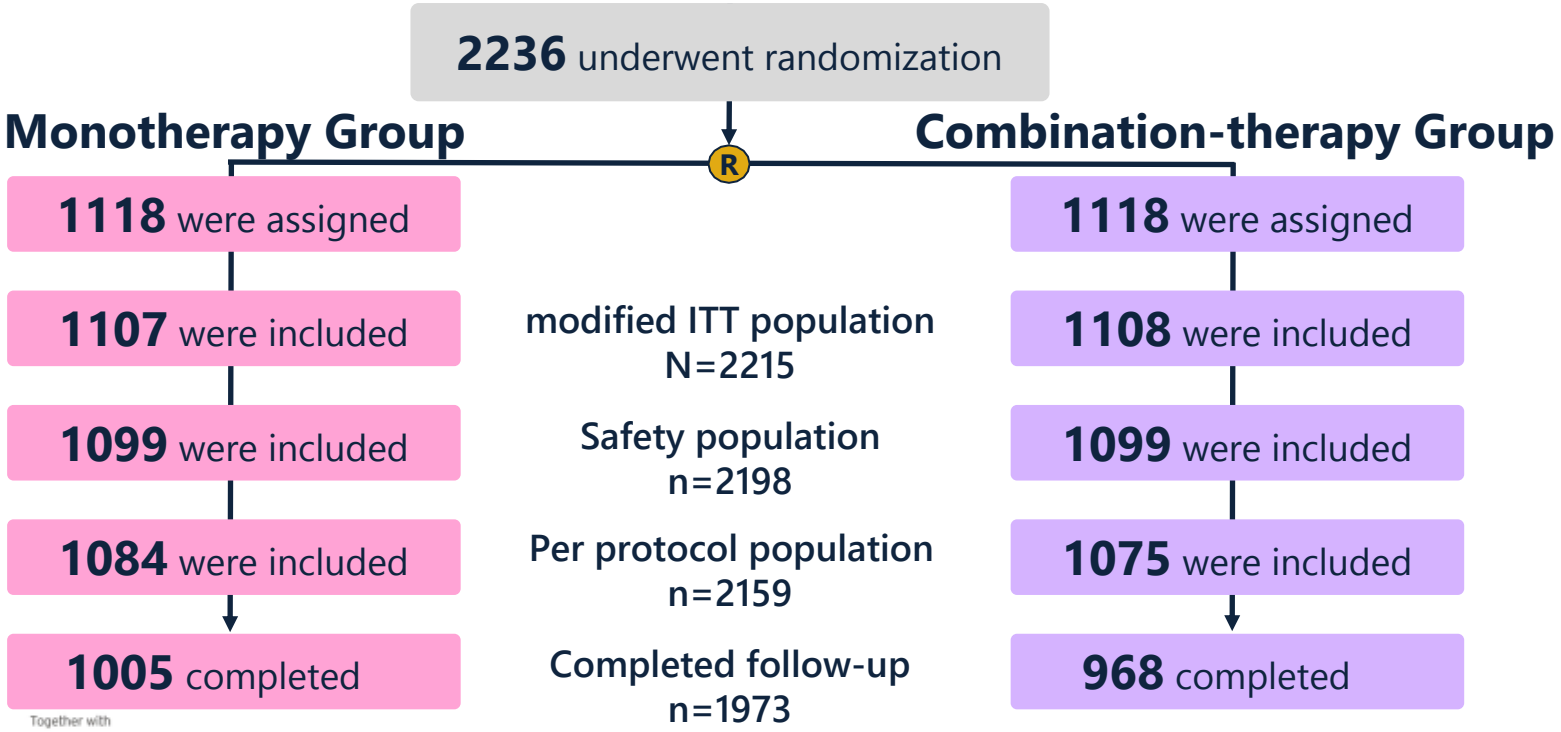
- **A closed testing procedure** was conducted after assessment of primary efficacy endpoint
- To determine superiority of **rivaroxaban monotherapy**, as compared with **combination therapy**
- **Major bleeding, as defined according to the criteria of the ISTH***
- Performed in the safety population

Sample size; Estimated that the enrollment of 2200 patients and the occurrence of at least 219 primary efficacy end points were required. [1]

1) Yasuda S, et al. *Int J Cardiol.* 2018. *ISTH: *the International Society on Thrombosis and Hemostasis*

Study Flow: Randomization and Follow-up

Enrollment Period: From February 23, 2015 to September 30, 2017



Characteristics of Patients at Baseline

modified ITT population

	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Age – (yr) mean ± SD	74.3±8.3	74.4±8.2
Male sex – no. (%)	875 (79.0)	876 (79.1)
BMI – (kg/m^2) mean ± SD	24.5±3.7	24.5±3.7
CrCl – (ml/min) mean ± SD	62.8±25.7	61.7±24.0
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 MI – no. (%)	384 (34.7)	393 (35.5)
Previous PCI – no. (%)	781 (70.6)	783 (70.7)
Previous CABG – no. (%)	125 (11.3)	127 (11.5)

	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Type of stent – no. /total no. (%)		
DES	500/723 (69.2)	477/721 (66.2)
BMS	171/723 (23.7)	171/721 (23.7)
DES and BMS	19/723 (2.6)	36/721 (5.0)
Unknown	33/723 (4.6)	37/721 (5.1)
Type of AF – no. (%)		
Paroxysmal	596 (53.8)	580 (52.3)
Persistent	164 (14.8)	175 (15.8)
Permanent	347 (31.3)	353 (31.9)
$CHADS_2$ score - median	2	2
CHA_2DS_2 -VASc score - median	4	4
HAS-BLED score - median	2	2
Received Aspirin - no. (%)	8 (0.7)	778 (70.2)
Received $P2Y_{12}$ inhibitor- no. (%)	4 (0.4)	297 (26.8)

Early Termination of the Trial

- The evaluation of the patients was planned to continue until September 2018.
- Because of a higher risk of death from any cause in the combination-therapy group, the independent data and safety monitoring committee recommended early termination of the trial in July 2018.
- The median treatment duration was 23.0 months (interquartile range, 15.8 to 31.0)
- The median follow-up period was 24.1 months (interquartile range, 17.3 to 31.5).

Primary Efficacy End Point

The composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause

Kaplan-Meier Estimates of First Occurrence of Primary Efficacy Events

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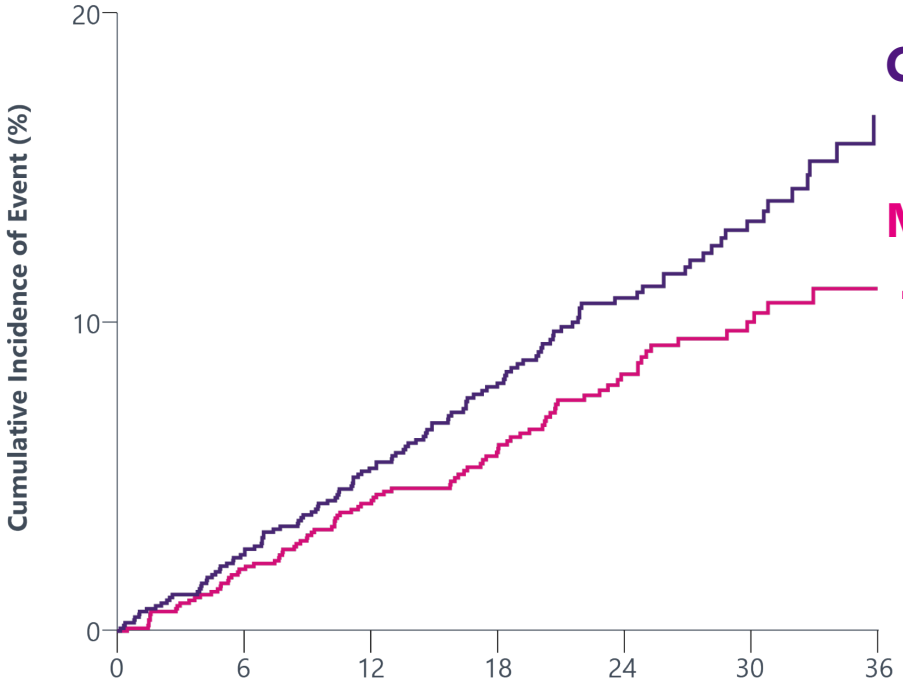

No. at Risk							
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89
Combination therapy	1108	1057	962	754	499	292	80

Combination therapy
5.75% per patient-year

Monotherapy
4.14% per patient-year

HR, **0.72** (**0.55** to **0.95**)
P<0.001 (noninf.)

*In the assessment for **superiority for the primary efficacy end point** (that was not prespecified), the **P value was 0.02.**

Primary Safety End Point

Major bleeding, as defined according to the criteria of the ISTH

Kaplan-Meier Estimates of First Occurrence of Primary Safety Events

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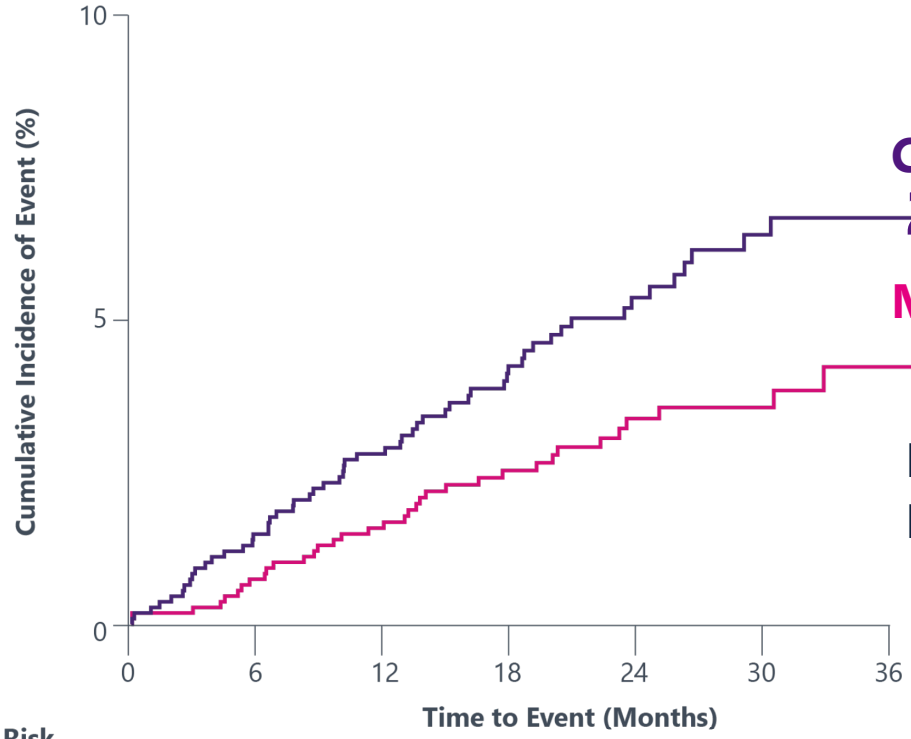

Combination therapy
2.76% per patient-year

Monotherapy
1.62% per patient-year

HR, **0.59** (**0.39** to **0.89**)
P=0.01 (sup.)

No. at Risk							
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89
Combination therapy	1099	1055	962	750	506	294	80

Secondary End Points

- The individual components of the primary efficacy end point
- All-cause mortality
- Net adverse clinical events
  (death from any cause, myocardial infarction, stroke, and major bleeding)
- Any bleeding events
- Selected subgroup analysis for efficacy and safety

The Respective Incidence Rates of Secondary End Points

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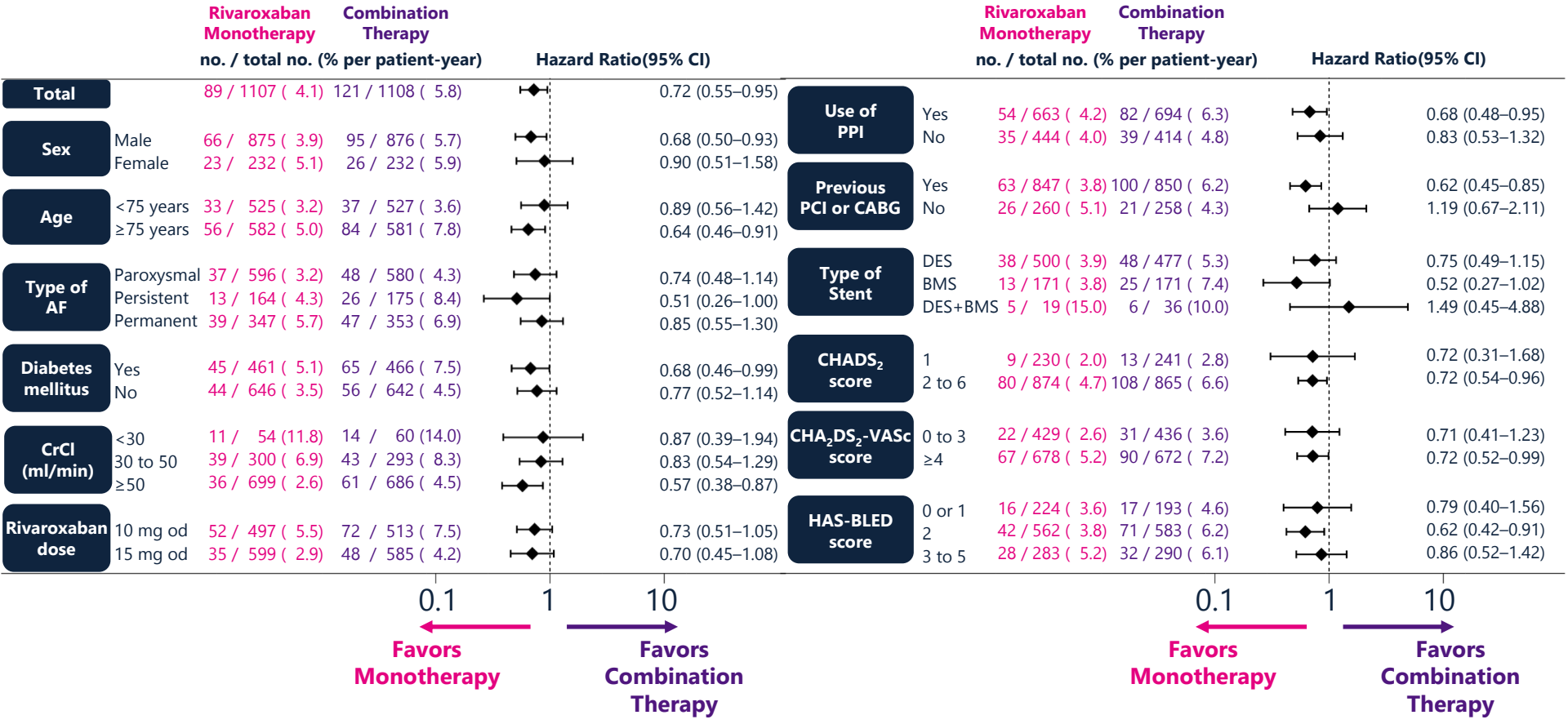
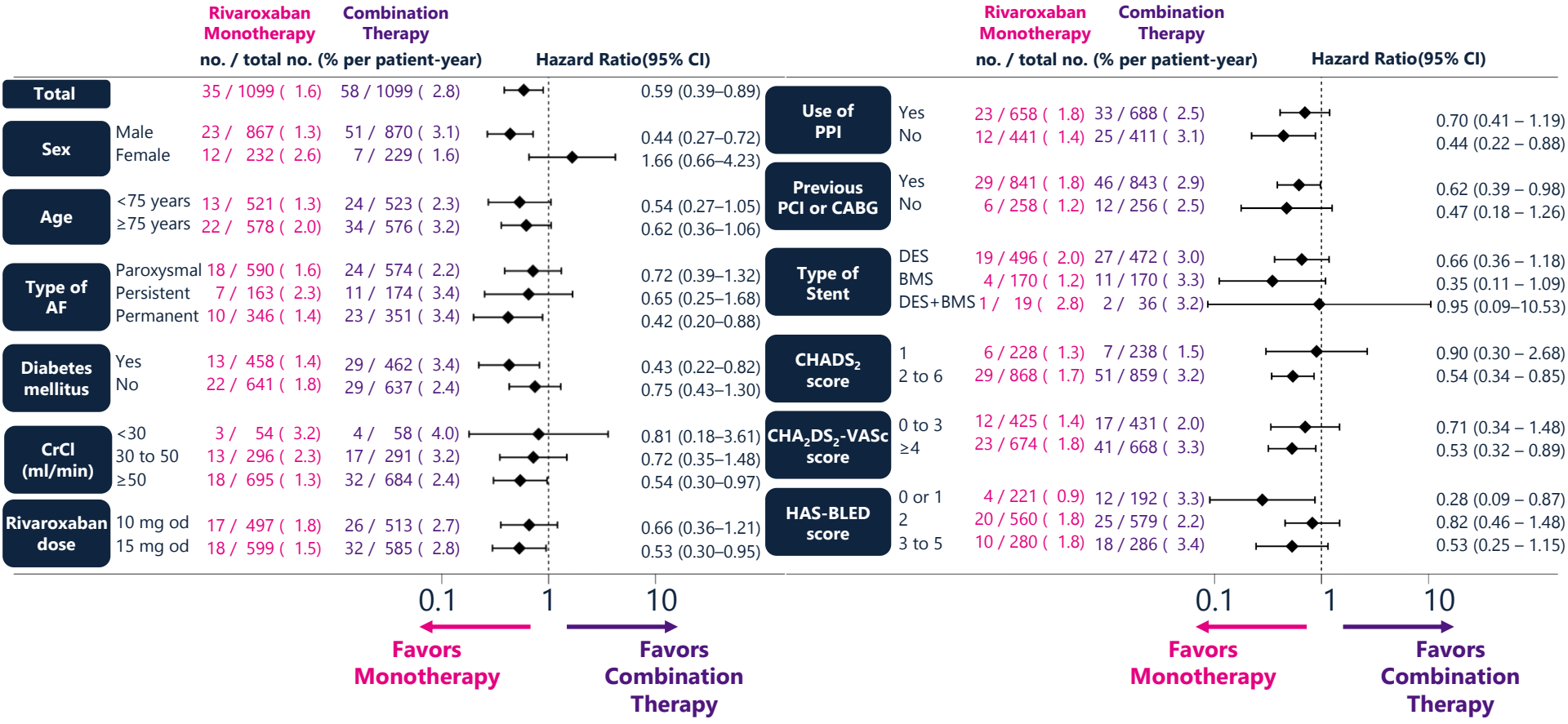
End Point – no. (% per patient-year)	**Rivaroxaban Monotherapy**	**Combination Therapy**	**HR (95% CI)***
All-cause death #	41 (1.85)	73 (3.37)	0.55 (0.38 to 0.81)
Cardiovascular	26 (1.17)	43 (1.99)	0.59 (0.36 to 0.96)
Noncardiovascular	15 (0.68)	30 (1.39)	0.49 (0.27 to 0.92)
CV events			
Ischemic stroke #	21 (0.96)	28 (1.31)	0.73 (0.42 to 1.29)
Hemorrhagic stroke #	4 (0.18)	13 (0.60)	0.30 (0.10 to 0.92)
Myocardial infarction #	13 (0.59)	8 (0.37)	1.60 (0.67 to 3.87)
Unstable angina requiring revascularization	13 (0.59)	18 (0.84)	0.71 (0.35 to 1.44)
Systemic embolism	2 (0.09)	1 (0.05)	1.97 (0.18 to 21.73)
Bleeding events			
Major bleeding #	35 (1.62)	58 (2.76)	0.59 (0.39 to 0.89)
Nonmajor bleeding	121 (5.89)	198 (10.31)	0.58 (0.46 to 0.72)
All bleeding	146 (7.22)	238 (12.72)	0.58 (0.47 to 0.71)
Net adverse clinical events	84 (3.90)	131 (6.28)	0.62 (0.47 to 0.82)

* The 95% CIs presented in this table have not been adjusted for multiplicity; therefore, # Components of net adverse clinical events.

Primary Efficacy End Point, According to Subgroup



Primary Safety End Point, According to Subgroup



Limitations

- The open-label trial design had the potential to introduce bias.
- There were relatively high rates of withdrawal of consent and loss of patients to follow-up.
- The trial population received the rivaroxaban dose approved in Japan (10 mg or 15 mg once daily, according to the patient's creatinine clearance) rather than the globally approved once-daily dose of 20 mg.
- The choice of antiplatelet regimen, either aspirin or a $P2Y_{12}$ inhibitor, is a factor that makes it uncertain whether the benefit of rivaroxaban monotherapy applies equally to the two combination regimens
- The early termination of the trial may overestimate the efficacy data.
- The reductions in rate of ischemic events and death from any cause with rivaroxaban monotherapy were unanticipated and are difficult to explain.

Conclusion

The AFIRE study demonstrated that **rivaroxaban monotherapy** was **noninferior** to **combination therapy** with rivaroxaban plus an antiplatelet agent with respect to **CV events and death from any cause** and **superior** with respect to **major bleeding** in patients with AF and stable CAD.

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Murozono (Oita Red Cross Hospital), T. Owada (Fukushima Red Cross Hospital), T. Doke (Kohka Public Hospital), T. Matsumura (Kumamoto Rosai Hospital), M. Horiuchi (Medical Association Sugimura Hospital), A. Takaishi (Mitoyo General Hospital), M. Yamamoto (National Center for Global Health and Medicine), H. Nakashima (National Hospital Organization Kagoshima Medical Center), M. Munemasa (National Hospital Organization Okayama Medical Center), Y. Sakata (Osaka University Hospital), N. Inoue (Sendai Kousei Hospital), T. Ota (Takanohara Central Hospital), Y. Hamano (Tawaramachi Hamano Hospital), N. Abe (Tokyo Medical University Ibaraki Medical Center), T. Tsubokura (Tsubokura Cardiovascular Clinic), M. Goto (Watanabe Hospital), I. Kubota (Yamagata University Hospital), M. Yano (Yamaguchi University Hospital), K. Umetani (Yamanashi Prefectural Central Hospital), A. Matsumura (Awa Regional Medical Center), T. Date (Date Naika Clinic), H. Morimoto (Fukagawa Municipal Hospital), T. 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Satoshi Yasuda, M.D., Ph.D., Koichi Kaikita, M.D., Ph.D.,
Masaharu Akao, M.D., Ph.D., Junya Ako, M.D., Ph.D., Tetsuya Matoba, M.D., Ph.D.,
Masato Nakamura, M.D., Ph.D., Katsumi Miyauchi, M.D., Ph.D.,
Nobuhisa Hagiwara, M.D., Ph.D., Kazuo Kimura, M.D., Ph.D.,
Atsushi Hirayama, M.D., Ph.D., Kunihiko Matsui, M.D., M.P.H.,
and Hisao Ogawa, M.D., Ph.D., for the AFIRE Investigators*