Journal of Arrhythmia

ORIGINAL ARTICLE OPEN ACCESS

Association Between History of Rhythm Control Therapy and Clinical Outcomes in Atrial Fibrillation Patients With Stable Coronary Artery Disease: A Sub-Analysis of the AFIRE Trial

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Received: 3 June 2025 | **Revised:** 21 September 2025 | **Accepted:** 26 September 2025

Funding: The authors received no specific funding for this work.

Keywords: anti-arrhythmia agents | atrial fibrillation | catheter ablation | coronary artery disease | treatment outcome

ABSTRACT

Background: Rhythm control therapy improves the quality of life and prognosis of patients with atrial fibrillation (AF). We assessed the characteristics and clinical outcomes of AF patients with stable coronary artery disease (CAD) undergoing rhythm control therapy.

Methods: We analyzed 2215 participants from the Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial, including 588 patients who received rhythm control therapy and 1627 who did not.

Results: At baseline, patients who received rhythm control therapy were generally younger, exhibited a higher prevalence of paroxysmal AF, experienced less heart failure, and had lower CHADS2 scores (CHF, hypertension, age ≥ 75 years, type 2 diabetes, and previous stroke or transient ischemic attack [doubled]) than those who did not. Among the rivaroxaban monotherapy and combination therapy groups, patients with a history of rhythm control therapy showed a lower incidence of the primary efficacy endpoint (a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death). However, following multivariate analysis and propensity score matching, no statistically significant difference in the primary efficacy endpoint was observed between patients with and without prior rhythm control therapy (adjusted HR 0.75, 95% CI 0.37–1.51, $p = 0.43$ in the rivaroxaban group; adjusted HR 0.75, 95% CI 0.43–1.30, $p = 0.30$ in the combination therapy group).

Conclusions: The initially observed benefit of rhythm control therapy was not significant after adjusting for baseline characteristics in patients with AF and stable CAD treated with rivaroxaban with or without additional antiplatelet therapy.

1 | Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of 0.6%–1.1% in Japan [1, 2]. AF is associated with stroke, heart failure, hospitalization, reduced quality of life, cognitive decline, and higher mortality [3]. The management of AF includes anticoagulation, rate control, rhythm control therapy, and lifestyle modifications based on each patient's characteristics and risk profiles.

AF and coronary artery disease (CAD) often coexist due to shared risk factors such as hypertension, diabetes, and obesity [4]. In patients with CAD, AF can increase the myocardial oxygen demand and may lead to worse clinical outcomes. Rhythm control therapies, including antiarrhythmic drugs (AADs) and catheter ablation (CA), are treatment options for improving symptoms and potentially preventing adverse events [5].

The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) showed that early rhythm control therapy reduced cardiovascular events in patients with newly diagnosed AF [6]. However, the benefits of rhythm control remain unclear in patients with stable CAD receiving current antithrombotic therapies. Observational data are important for evaluating real-world treatment practices and their impacts on outcomes.

Mid-regional pro-atrial natriuretic peptide has been reported as a predictor of new-onset AF after myocardial infarction [7]. Pulmonary vein isolation, a widely used form of catheter ablation, effectively suppresses ectopic triggers in patients [8]. However, the role of rhythm control therapy in patients with stable CAD, particularly in terms of long-term prognosis, is not fully understood.

This study used data from the Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial [9] to examine the association between the history of rhythm control therapy and clinical outcomes. We aimed to evaluate the characteristics and prognosis of patients with AF and stable CAD who received rhythm control therapy in actual clinical practice.

2 | Methods

2.1 | Trial Design and Oversight

The AFIRE trial is a randomized, multicenter, open-label, parallel-group trial conducted in Japan. The full methods of the AFIRE trial as well as the primary results have been reported [10]. A total of 2240 patients were enrolled at 294 centers from February 23, 2015, to September 30, 2017, in Japan, 2236 of whom were randomized, and 2215 were included in the modified intention-to-treat population. The median follow-up period was 24.1 months (interquartile range 17.3–31.5). Patients were randomly assigned in equal numbers to groups receiving either rivaroxaban monotherapy (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 and a single antiplatelet therapy with a P2Y12 inhibitor or aspirin, according to the discretion of the treating physician.

A history of rhythm control therapy was defined as patients who received CA and rhythm control drugs for AF before randomization. The patients were divided into those who received rhythm control drugs, CA, or both therapies. However, no data were available regarding the posttreatment rhythm status, such as sinus rhythm maintenance or AF recurrence. Continuous and intermittent electrocardiogram (ECG) monitoring results were excluded from the dataset. Therefore, the success or failure of rhythm control therapy in achieving sustained rhythm control could not be evaluated in this study. The decision to perform rhythm control therapy was made at the discretion of the treating physician. In the present prespecified sub-analysis, we analyzed all patients in the AFIRE study. All the participants provided written informed consent.

2.2 | Endpoints

The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, and death from any cause. The primary safety endpoint was major bleeding, defined according to the International Society on Thrombosis and Homeostasis criteria. Secondary endpoints were the individual components of the primary endpoint, death from any cause, revascularization (percutaneous coronary intervention and coronary artery bypass grafting not including those for stenosis observed prior to enrollment in the present study, acute myocardial infarctions, or unstable angina), thromboembolic events (ischemic strokes, myocardial infarctions, unstable angina requiring revascularization, and systemic embolisms), net adverse clinical events (death from any cause, myocardial infarctions, strokes, and major bleeding), nonmajor bleeding, and any bleeding event. Blinded adjudication of endpoints was conducted by an independent clinical event committee.

2.3 | Statistical Analysis

This study assessed different backgrounds at enrollment and the outcomes of the primary efficacy endpoint between patients with and without a history of rhythm control therapy. Continuous variables, which are expressed as the mean ± standard deviation (SD), were compared using the Wilcoxon rank-sum test. Categorical variables, which are presented as counts and percentages, were compared using the χ^2 or Fisher's exact test. Multivariate Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of the effect of a history of rhythm control therapy on the primary efficacy outcome, thromboembolic events, and primary safety outcome. Age, history of chronic heart failure (CHF), AF type, and $CHADS_2$ scores (CHF, hypertension, age ≥ 75 years, type 2 diabetes, and previous stroke or transient ischemic attack [doubled]) were used as covariates in the models because they differed depending on the background between patients with and without rhythm control therapy in both the rivaroxaban monotherapy and combination therapy groups. The Kaplan–Meier method was used to estimate the

cumulative event rates, and differences in the incidence rates (shown as percentages per patient-year) were analyzed using the log-rank test. A Cox proportional hazards model was used to compare the outcomes between the groups, and the results were expressed as HR with 95% CI. To investigate the outcomes in patients with bleeding, we compared the incidence of outcomes in patients with and without bleeding during the follow-up period. Secondary endpoints were reported as HR and 95% CI. To account for any selection bias using rhythm control therapy, a propensity score was calculated for all patients, which assessed the HR with a 95% CI for a history of rhythm control therapy based on covariates such as age, history of CHF, type of AF, and $CHADS_2$ scores. All statistical analyses were conducted using the JMP 15 software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

3 | Results

3.1 | Patients

The baseline characteristics of the study population are summarized in Table 1. These include age, comorbidities, and prior revascularization procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). In the 2215 patients who were included in the intention-to-treat population, the mean age was 74 years, and 79% were men. Hypertension was seen in 1891 (85.4%) patients, CHF in 789 (35.6%), and a history of stroke in 323 patients (14.6%). The percentages of patients who underwent rhythm control therapy were 26.5% ($n = 588$) and 26.0% ($n = 288$) in the rivaroxaban monotherapy group and 27.1% ($n = 300$) in the combination therapy group. When the rhythm control therapy group was further divided, the percentage of patients receiving only antiarrhythmic drug therapy (AAD) was 67.7% ($n = 398$); only CA therapy, 18.9% ($n = 111$); and both AADs and CA therapy, 13.4% ($n = 79$). Patients with a history of rhythm control therapy were significantly younger, had a higher prevalence of paroxysmal AF (PAF), and were less likely to have CHF than those without such a history in both the rivaroxaban monotherapy and combination therapy groups. The values of creatinine clearance tended to be higher in patients receiving rhythm control therapy in the rivaroxaban monotherapy group and were significantly higher in the combination therapy group. Conventional risk factors for stroke, such as the $CHADS_2$ and CHA_2DS_2-VASc scores (CHF; hypertension; age ≥ 75 years [doubled]; type 2 diabetes; previous stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65–75 years; and sex category), were significantly lower in patients who received rhythm control therapy than in those who did not (Table 1; Table S1).

3.2 | Endpoints

The primary efficacy endpoint (composite of strokes, systemic embolisms, myocardial infarctions, unstable angina requiring revascularization, and death) incidences were lower with rhythm control therapy: 2.47% versus 4.75% ($p = 0.025$) in the rivaroxaban monotherapy group, 3.81% versus 6.50% ($p = 0.022$) in the combination therapy group, and 3.14% versus 5.60% ($p = 0.002$) in the overall patient cohort (Table 2; Figure 1A,B; Table S2). No interaction was observed between rivaroxaban monotherapy and combination therapy ($p = 0.77$). Thromboembolic events were lower in rhythm control therapy patients in the rivaroxaban monotherapy group (1.06% vs. 2.65%, $p = 0.035$), with no significant difference in the combination therapy group (1.91% vs. 2.82%, $p = 0.25$). Interaction analysis revealed no significant difference in thromboembolic events between the rivaroxaban and combination therapy groups ($p = 0.34$). The incidences of individual primary endpoint components are shown in Table 2. No significant differences were found in cardiovascular or non-cardiovascular deaths between the groups.

The primary safety endpoint (major bleeding) incidence with and without a history of rhythm control therapy was 1.23% and 1.75% ($p = 0.40$) in the rivaroxaban monotherapy group and 2.64% and 2.81% ($p = 0.83$) in the combination therapy group, respectively (Table 2). No interaction in the safety endpoint was observed between the rivaroxaban monotherapy and combination therapy groups ($p = 0.57$). Regarding the primary efficacy endpoint, favorable outcomes for patients with a history of rhythm control therapy were consistent across all prespecified subgroups, and there was no interaction in either the rivaroxaban monotherapy or combination therapy groups (Figure 2).

3.3 | Multivariate Analysis and Adjusted Incidence of Events

Table 3 summarizes the cumulative hazards of clinical outcomes in patients with and without a history of rhythm control therapy. In multivariate analysis, there were no significant differences in the primary efficacy outcome, thromboembolic events, or primary safety outcomes between patients with and without a history of rhythm control therapy (Table 3; Table S3).

In the Cox proportional hazards regression models using propensity score matching, there was no significant difference in the primary efficacy endpoint between patients with a history of rhythm control therapy and those without (adjusted HR 0.75, 95% CI 0.37–1.51, $p = 0.43$ and 0.75, 95% CI 0.43–1.30, $p = 0.30$ in the rivaroxaban monotherapy and combination therapy groups, respectively) (Figure 1C,D). Similarly, no significant difference in thromboembolic events was observed between the groups (adjusted HR 0.48, 95% CI 0.18–1.30, $p = 0.15$ and 0.77, 95% CI 0.35–1.70, $p = 0.52$ in the rivaroxaban monotherapy and combination therapy groups, respectively). Furthermore, there was no significant difference in the primary safety endpoint between the groups (adjusted HR 0.76, 95% CI 0.28–2.04, $p = 0.58$ and 1.34, 95% CI 0.62–2.92, $p = 0.46$ in the rivaroxaban monotherapy and combination therapy groups, respectively).

In response to the potential for residual confounding, we conducted additional stratified analyses by age category (< 75 vs. ≥ 75 years) and $CHADS_2$ score category (low [0–1] vs. high [≥ 2]) using Cox proportional hazards models within the propensity score-matched cohorts (Tables 4 and 5). Across all subgroups, there were no statistically significant differences in the clinical outcomes between patients with and without a history of rhythm control therapy. These findings further support the robustness

TABLE 1 | Characteristics of the patients at baseline (modified intention-to-treat population).[a]

Characteristic	Rivaroxaban monotherapy, $n=1107$			Combination therapy, $n=1108$		
	Rhythm control (+) ($N=288$)	Rhythm control (−) ($N=819$)	p	Rhythm control (+) ($N=300$)	Rhythm control (−) ($N=808$)	p
Age, years	72.9 ± 8.9	74.7 ± 8.0	0.002	72.6 ± 8.4	75.0 ± 8.0	< 0.001
< 75 years—no. (%)	157 (54.5)	369 (45.1)	0.006	178 (59.3)	349 (43.2)	< 0.001
≥ 75 years—no. (%)	131 (45.5)	450 (55.0)		122 (40.7)	459 (56.8)	
Male sex—no. (%)	233 (80.9)	642 (78.4)	0.40	237 (79)	639 (79.1)	1
Type of rhythm control						
Antiarrhythmic drugs only	192 (66.7)			206 (68.7)		
Catheter ablation only	52 (18.1)			59 (19.7)		
Antiarrhythmic drugs and catheter ablation	44 (15.3)			35 (11.7)		
Body mass index, median[b]	24.7 ± 4.0	24.4 ± 3.5	0.28	24.4 ± 3.3	24.6 ± 3.9	0.96
Current smoker—no. (%)	37 (12.9)	109 (13.3)	0.92	37 (12.3)	109 (13.5)	0.69
Hypertension (%)	245 (85)	702 (86)	0.77	255 (85)	689 (85)	0.92
Diabetes (%)	110 (38.2)	351 (42.9)	0.19	112 (37.3)	354 (43.8)	0.056
Congestive heart failure (%)	69 (23)	322 (39)	< 0.001	73 (24)	325 (40)	< 0.001
Previous stroke—no. (%)	37 (12.9)	111 (13.6)	0.84	41 (13.7)	134 (16.6)	0.27
Previous myocardial infarction—no. (%)	94 (32.8)	292 (35.6)	0.39	96 (31.9)	295 (36.6)	0.16
Previous PCI—no. (%)	200 (69.4)	581 (70.9)	0.65	213 (71)	570 (70.5)	0.94
Type of stent—no./total no. (%)						
Drug-eluting	118 (41.0)	382 (46.6)	0.45	138 (46.0)	339 (42.0)	0.18
Bare-metal	50 (17.4)	120 (14.7)		45 (15.0)	127 (15.6)	
Both types	6 (2.1)	13 (1.6)		4 (1.3)	32 (4.0)	
Unknown	10 (3.5)	23 (2.8)		8 (2.7)	29 (4.0)	
Blank	104 (36.1)	281 (34.3)		105 (35.0)	282 (35.0)	
Previous CABG—no. (%)	35 (12.2)	91 (11.1)	0.59	22 (7.3)	104 (12.9)	0.01
Type of atrial fibrillation						
Paroxysmal	240 (83.3)	356 (43.5)	< 0.001	244 (81.3)	336 (41.6)	< 0.001
Persistent	31 (10.8)	133 (16.3)		32 (10.7)	143 (17.7)	
Permanent	17 (5.9)	330 (40.3)		24 (8.0)	329 (40.7)	
Creatinine clearance						
Mean—mL/min	59.6 ± 1.6	58.2 ± 0.9	0.054	62.3 ± 1.4	57.8 ± 1.4	0.003

(Continues)

TABLE 1 | (Continued)

Characteristic	Rivaroxaban monotherapy, $n=1107$			Combination therapy, $n=1108$		
	Rhythm control (+) ($N=288$)	Rhythm control (−) ($N=819$)	p	Rhythm control (+) ($N=300$)	Rhythm control (−) ($N=808$)	p
Distribution—no./total no. (%)						
< 30 mL/min	12/1053 (4.2)	42/1053 (5.1)	0.17	11/1039 (3.7)	49/1039 (6.1)	0.014
30 to < 50 mL/min	66/1053 (22.9)	233/1053 (28.4)		62/1039 (20.7)	231/1039 (28.6)	
≥ 50 mL/min	193/1053 (67.0)	507/1053 (61.9)		199/1039 (66.3)	487/1039 (60.3)	
$CHADS_2$ score, average	2.18	2.55	< 0.001	2.17	2.61	< 0.001
CHA_2DS_2-VASC score, average	3.64	4	< 0.001	3.62	4.19	< 0.001

Note: Rhythm control (+) refers to patients with a history of rhythm control therapy; rhythm control (−) refers to patients without a history of rhythm control therapy.
Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
[a]Plus-minus values are the means ± SD.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters. Data are missing for 56 patients with a history of rhythm control therapy and 105 patients without a history of rhythm control therapy.

of our main results and indicate that the lack of association between rhythm control therapy history and outcomes was consistent, irrespective of age or baseline stroke risk.

4 | Discussion

The major findings of the present post hoc study were as follows: (1) rhythm control therapy was used in 26% of AF patients with stable CAD; (2) those receiving rhythm control were younger, had fewer instances of CHF, more frequent PAF, and lower CHADS2 scores; and (3) a history of rhythm control therapy was linked to a lower incidence of the primary efficacy endpoint in both the rivaroxaban monotherapy and combination therapy groups; however, (4) multivariate analysis and propensity score-matched Cox proportional hazards modeling showed no significant differences in clinical outcomes between patients with and without a history of rhythm control therapy. Importantly, the confidence intervals were wide, and the study may have been underpowered to detect modest but clinically meaningful effects. Therefore, our findings should be interpreted as showing that no significant association was observed, rather than suggesting a definitive absence of effect.

AF and CAD often coexist because of shared risk factors such as aging, hypertension, and diabetes. Studies have shown that CAD is common in patients with AF and may contribute to AF progression. Conversely, AF may promote the development of atherosclerosis [11, 12]. Approximately 26% of the participants received rhythm control therapy, primarily in the form of AADs, although specific data on AAD types were unavailable. Patients selected for rhythm control tended to be younger, had a lower CHF prevalence, and exhibited higher rates of PAF. The decision to pursue rhythm control therapy likely reflects efforts to align with clinical guidelines that recommend individualized treatment approaches based on patient characteristics and AF burden. However, as this study did not include data on AF recurrence or long-term rhythm maintenance before or after enrollment, the influence of these factors on treatment selection and subsequent outcomes remains uncertain.

In the unadjusted analysis, patients who received rhythm control therapy had fewer primary efficacy events. However, this difference disappeared after multivariate adjustment. Previous studies, including the Fushimi AF Registry, have reported that patients with PAF have a lower risk of stroke and systemic embolism than those with sustained AF, regardless of the oral anticoagulant use [13]. Other studies have also shown that stroke and death rates are lower in patients with PAF than in those with sustained AF. Risk scores such as $CHADS_2$ and CHA_2DS_2-VASc, which include age and heart failure, have been widely used to estimate the risk of embolic events [14–16]. In addition, the $CHADS_2$ score predicted mortality in patients with CAD, even in those without AF [17].

After adjusting for baseline differences using propensity score matching, no significant difference was observed in the primary efficacy outcomes between patients with and without rhythm control therapy. Although matching helped in reducing bias, unmeasured factors, such as physician decision-making, patient comorbidities, and AF recurrence, may have affected the choice of rhythm control. These factors could also have influenced the clinical outcomes. As this study did not assess AF recurrence or rhythm status during follow-up, it remains unclear whether long-term rhythm control was achieved. This uncertainty may have weakened the link between rhythm control history and the clinical results.

Although the unadjusted analysis showed better outcomes for patients with a history of rhythm control therapy, these differences were no longer statistically significant after adjustment (Figure 1; Table 3; Table S3). This difference may be explained by the comparison of our study design with that of the EAST-AFNET 4 trial [6]. This trial had a larger sample size, initiated rhythm control earlier, and included a wider range of treatment

TABLE 2 | Primary and secondary efficacy and safety endpoints.[a]

Endpoint	Rivaroxaban monotherapy				Combination therapy			
	Rhythm control (+) (*N* = 288)	Rhythm control (−) (*N* = 819)	Hazard ratio (95% CI)	*p*	Rhythm control (+) (*N* = 300)	Rhythm control (−) (*N* = 808)	Hazard ratio (95% CI)	*p*
	No. of patients (% per patient-year)				No. of patients (% per patient-year)			
Primary efficacy endpoint								
Cardiovascular events or death from any cause	14 (2.47)	75 (4.75)	0.52 (0.29–0.92)	0.025	22 (3.81)	99 (6.50)	0.58 (0.37–0.92)	0.022
Secondary efficacy endpoints								
Ischemic stroke	1 (0.17)	20 (1.24)	0.14 (0.019–1.06)	0.057	7 (1.20)	21 (1.35)	0.89 (0.38–2.09)	0.79
Hemorrhagic stroke	2 (0.35)	2 (0.12)	2.88 (0.41–20.5)	0.29	3 (0.51)	10 (0.64)	0.79 (0.22–2.86)	0.72
Myocardial infarction	1 (0.17)	12 (0.74)	0.23 (0.030–1.80)	0.16	1 (0.17)	7 (0.45)	0.38 (0.047–3.09)	0.37
Unstable angina requiring revascularization	4 (0.70)	9 (0.55)	1.26 (0.39–4.10)	0.70	3 (0.52)	15 (0.96)	0.53 (0.15–1.84)	0.32
Systemic embolism	0	2 (0.12)			0	1 (0.06)		
Thromboembolic events[b]	6 (1.06)	42 (2.65)	0.40 (0.17–0.94)	0.035	11 (1.91)	43 (2.82)	0.68 (0.35–1.31)	0.25
Death	7 (1.22)	34 (2.08)	0.58 (0.26–1.31)	0.19	15 (2.56)	58 (3.68)	0.69 (0.39–1.22)	0.20
Cardiovascular	5 (0.87)	21 (1.28)	0.67 (0.25–1.78)	0.42	10 (1.70)	33 (2.10)	0.59 (0.41–1.67)	0.59
Noncardiovascular	2 (0.35)	13 (0.80)	0.44 (0.099–1.94)	0.28	5 (0.85)	25 (1.59)	0.52 (0.20–1.36)	0.18
Net clinical adverse events[c]	15 (2.63)	69 (4.36)	0.60 (0.34–1.05)	0.074	29 (5.12)	102 (6.73)	0.76 (0.50–1.14)	0.19
Primary safety endpoint								
Major bleeding[d]	7 (1.23)	28 (1.75)	0.70 (0.31–1.60)	0.40	15 (2.64)	43 (2.81)	0.94 (0.52–1.69)	0.83
Secondary safety endpoints								
Any bleeding	35 (6.63)	111 (7.40)	0.90 (0.61–1.31)	0.57	55 (10.64)	183 (13.48)	0.79 (0.58–1.07)	0.12
Nonmajor bleeding	30 (5.64)	91 (5.95)	0.95 (0.63–1.43)	0.80	46 (8.62)	152 (10.94)	0.79 (0.57–1.10)	0.16

[a]Primary and secondary efficacy analyses were performed in the modified intention-to-treat population, which included all patients who underwent randomization after excluding patients who had technical reasons for not participating in the trial. Primary and secondary safety analyses were performed in a population that included all 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 interval (CIs) have not been adjusted for multiple comparisons.
[b]The category of thrombotic events is a composite of ischemic strokes, myocardial infarctions, unstable angina requiring revascularization, and systemic embolisms.
[c]The category of net adverse clinical events was a composite of death from any cause, myocardial infarction, stroke, or major bleeding.
[d]Major and nonmajor bleeding events were classified according to the International Society on Thrombosis and Hemostasis criteria.

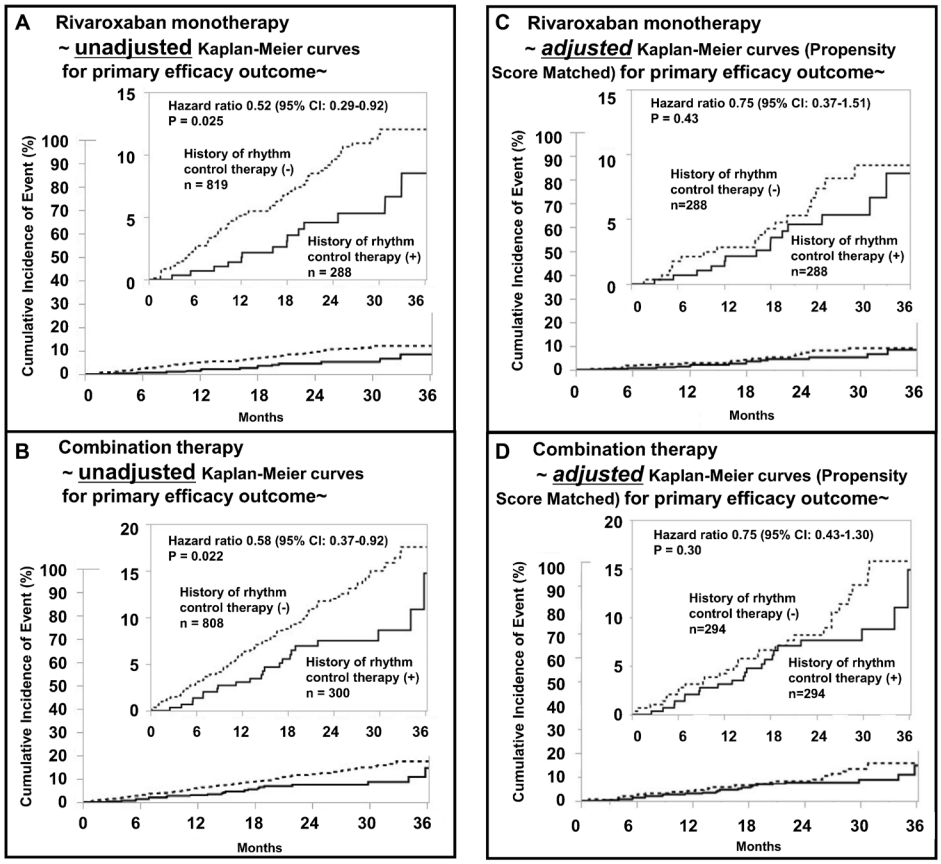

FIGURE 1 | Comparison of unadjusted and adjusted Kaplan–Meier curves for clinical outcomes between patients with a history of rhythm control therapy (solid line) and those without (dotted line). (A, B) Unadjusted Kaplan–Meier curves. (A) Primary efficacy endpoint in the rivaroxaban monotherapy group, defined as a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, and all-cause mortality, compared with patients with and without a history of rhythm control therapy. (B) Primary efficacy endpoints in the combination therapy group. For clarity, the insets display the same data as an expanded *y*-axis. (C, D) Adjusted Kaplan–Meier curves. (C) Adjusted outcomes for the primary efficacy endpoint in the rivaroxaban monotherapy group compared with those with and without rhythm control therapy. (D) Adjusted outcomes for the combination therapy group. The inset graphs show the same data with an expanded *y*-axis.

approaches, such as antiarrhythmic drugs and catheter ablation. It also monitored AF recurrence using regular ECG and counted heart failure events as part of the main outcomes. In contrast, our study did not include heart failure as the primary efficacy endpoint and focused only on thromboembolic events and all-cause mortality. Moreover, we did not have data on the timing of rhythm control therapy in relation to AF diagnosis or study enrollment, making it difficult to distinguish between early and late interventions. The clinical reasons for choosing rhythm control, such as symptom severity, previous failure of rate control, and patient preference, were also not available. In addition, our study did not assess whether the sinus rhythm was maintained during follow-up; therefore, the actual therapeutic effect of rhythm control could not be evaluated. These differences in the study design, patient selection, monitoring methods, and outcome definitions may have influenced the results. This limitation should be considered when interpreting and comparing our findings to those of other studies.

In the AFIRE trial, rivaroxaban monotherapy was demonstrated to be noninferior to combination therapy for efficacy and superior for safety in patients with AF and stable CAD. Within this framework, clinical management often requires choosing between these two antithrombotic strategies. Our sub-analysis was not specifically designed or adequately powered to determine whether a history of rhythm control therapy modifies the comparative effects of rivaroxaban monotherapy versus combination therapy, which resulted in wide confidence intervals that make it difficult to exclude modest differences. Because of these limitations, our findings should be interpreted as applying only to patients in the AFIRE population who remained on anticoagulation, and they should not be regarded as contradicting the overall AFIRE trial results regarding antithrombotic strategy. Furthermore, stratified analyses by age and $CHADS_2$ score categories revealed no significant differences in outcomes between patients with and without a history of rhythm control therapy. These findings suggest that the lack of a prognostic benefit was consistent across important clinical subgroups, including older patients and those at a higher risk of stroke. This consistent trend supports the idea that a history of rhythm control therapy without evidence of maintained sinus rhythm may not independently affect major clinical outcomes in patients with AF and stable CAD.

A critical limitation is that the AFIRE dataset did not include information on whether patients who had undergone rhythm control therapy were able to discontinue anticoagulation, for example, after ablation. As a result, individuals who stopped

A

Subgroup	History of rhythm control (+) (n=288) no. of events/total no. (%,per patient-yr)	History of rhythm control (-) (n=819)	Hazard Ratio (95% CI)	P value	P value for interaction
Overall	14/288 (2.5)	75/819 (4.7)	0.52 (0.29-0.92)	0.025	
Age					0.71
≧75 years	7/128 (2.7)	49/454 (5.7)	0.49 (0.22-1.08)	0.076	
<75 years	7/160 (2.3)	26/365 (3.6)	0.61 (0.27-1.41)	0.25	
Sex					0.76
Male	11/233 (2.4)	55/642 (4.5)	0.55 (0.29-1.05)	0.069	
Female	3/55 (2.7)	20/177 (5.8)	0.44 (0.13-1.49)	0.19	
Type of atrial fibrillation					0.76
Paroxysmal	12/240 (2.5)	25/356 (3.7)	0.70 (0.35-1.38)	0.3	
Persistent	1/31 (1.6)	12/133 (4.9)	0.34 (0.045-2.65)	0.31	
Permanent	1/17 (2.8)	38/330 (5.9)	0.48 (0.065-3.47)	0.46	
Diabetes					0.34
Yes	5/110 (2.3)	40/351 (6.0)	0.38 (0.15-0.96)	0.042	
No	9/178 (2.6)	35/468 (3.8)	0.68 (0.33-1.41)	0.3	
Congestive heart failure					0.50
Yes	4/69 (3.1)	42/322 (6.9)	0.44 (0.16-1.21)	0.11	
No	10/219 (2.3)	33/497 (3.4)	0.68 (0.33-1.37)	0.28	
Previous stroke					0.74
Yes	3/37 (3.8)	12/111 (6.0)	0.63 (0.18-2.23)	0.47	
No	11/251 (2.6)	63/708 (4.6)	0.49 (0.26-0.94)	0.031	
Creatinine clearance					0.3
<30 ml/min	3/12 (15.5)	8/42 (10.9)	1.45 (0.38-5.50)	0.59	
30 to <50 ml/min	5/66 (3.9)	34/234 (7.9)	0.49 (0.19-1.26)	0.14	
≧50 ml/min	5/193 (1.3)	31/506 (3.1)	0.42 (0.16-1.08)	0.072	
Rivaroxaban dose					0.75
10 mg once daily	8/120 (3.4)	44/377 (6.2)	0.54 (0.25-1.15)	0.11	
15 mg once daily	5/163 (1.5)	30/436 (3.5)	0.44 (0.17-1.14)	0.092	
Use of PPI					0.14
Yes	6/174 (1.8)	48/489 (5.1)	0.35 (0.15-0.81)	0.014	
No	8/114 (3.5)	27/330 (4.2)	0.83 (0.38-1.82)	0.64	
Previous PCI or CABG					0.49
Yes	9/221 (2.0)	54/626 (4.5)	0.46 (0.23-0.93)	0.030	
No	5/67 (3.9)	21/193 (5.6)	0.69 (0.26-1.84)	0.46	
$CHADS_2$ score					0.56
1	3/75 (2.1)	6/155 (1.9)	1.13 (0.28-4.51)	0.87	
2-6	11/212 (2.6)	69/662 (5.5)	0.47 (0.25-0.90)	0.022	
CH_2DS_2-VASc score					0.79
0-3	4/137 (1.5)	18/292 (3.1)	0.50 (0.17-1.46)	0.49	
≧4	10/151 (3.3)	57/527 (5.7)	0.58 (0.30-1.14)	0.11	
HAS-BLED score					0.95
0 or 1	3/68 (2.3)	13/156 (4.2)	0.55 (0.16-1.92)	0.35	
2	6/148 (2.0)	36/414 (4.5)	0.45 (0.19-1.08)	0.074	
3-5	4/62 (3.2)	24/221 (5.8)	0.55 (0.19-1.59)	0.27	

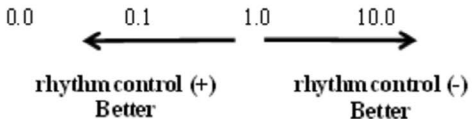

FIGURE 2 | Primary efficacy endpoint according to the subgroups. (A) Subgroup analysis for the rivaroxaban monotherapy group, and (B) for the combination therapy group. The hazard ratio for the primary efficacy endpoint—a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, and all-cause mortality—is shown for each subgroup in both groups. The 95% confidence intervals (CIs) are not adjusted for multiple comparisons. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor. Scales: CHADS2: ranges from 0 to 6, with higher scores indicating increased stroke risk. CHA2DS2-VASc: extends CHADS2 with factors for vascular disease, age 65–74 years, and sex; scores range from 0 to 9, with higher scores indicating a greater stroke risk. HAS-BLED ranges from 0 to 9, with higher scores indicating an increased bleeding risk. The maximum HAS-BLED score in this study was 5 points.

anticoagulation were not represented in the trial population. Our findings should be interpreted within the limited clinical context of the AFIRE trial, which included patients with a history of rhythm control therapy who required continued anticoagulation. In this setting, both rivaroxaban monotherapy and rivaroxaban plus single antiplatelet therapy were evaluated, and the lack of interaction between rhythm control history and treatment assignment suggests that rhythm control status did not substantially influence the comparative outcomes of these antithrombotic strategies.

This study used standard statistical methods, including Cox proportional hazards models, Kaplan–Meier curves, and propensity score matching, to adjust for baseline differences and reduce

B

Subgroup	History of rhythm control (+) (n=300) no. of events/total no. (%per patient-yr)	History of rhythm control (-) (n=808)	Hazard Ratio (95% CI)	P value	P value for interaction
Overall	22/300 (3.8)	99/808 (6.5)	0.58 (0.37-0.92)	0.022	
Age					0.66
≧75 years	14/124 (6.0)	70/457 (8.3)	0.69 (0.39-1.23)	0.21	
<75 years	8/176 (2.3)	29/351 (4.3)	0.55 (0.25-1.21)	0.14	
Sex					0.80
Male	17/237 (3.7)	78/639 (6.5)	0.58 (0.34-0.98)	0.04	
Female	5/63 (4.3)	21/169 (6.6)	0.67 (0.25-1.77)	0.42	
Type of atrial fibrillation					0.19
Paroxysmal	17/244 (3.6)	31/336 (5.0)	0.71 (0.39-1.28)	0.26	
Persistent	1/32 (1.9)	25/143 (9.7)	0.19 (0.026-1.41)	0.10	
Permanent	4/24 (9.4)	43/329 (6.73)	1.44 (0.52-4.02)	0.49	
Diabetes					0.83
Yes	11/112 (5.3)	54/354 (8.2)	0.63 (0.33-1.21)	0.16	
No	11/188 (3.0)	45/454 (5.2)	0.57 (0.29-1.10)	0.095	
Congestive heart failure					0.50
Yes	4/69 (2.9)	42/322 (7.0)	0.44 (0.16-1.21)	0.11	
No	10/219 (2.3)	33/497 (3.6)	0.68 (0.33-1.37)	0.28	
Previous stroke					0.74
Yes	3/41 (3.9)	19/134 (8.1)	0.48 (0.14-1.63)	0.24	
No	19/259 (3.8)	80/674 (6.2)	0.61 (0.37-1.00)	0.05	
Creatinine clearance					0.40
<30 ml/min	3/11 (17.2)	11/49 (13.3)	1.33 (0.37-4.84)	0.66	
30 to <50 ml/min	6/62 (5.3)	37/231 (9.1)	0.58 (0.25-1.39)	0.22	
≧50 ml/min	11/199 (2.8)	50/487 (5.2)	0.54 (0.28-1.04)	0.54	
Rivaroxaban dose					0.50
10 mg once daily	13/119 (5.9)	59/394 (8.1)	0.71 (0.39-1.30)	0.26	
15 mg once daily	9/179 (2.5)	39/406 (5.0)	0.51 (0.25-1.06)	0.070	
Use of PPI					0.42
Yes	13/184 (3.7)	69/510 (7.3)	0.51 (0.28-0.92)	0.027	
No	9/116 (4.0)	30/298 (5.2)	0.78 (0.37-1.64)	0.51	
Previous PCI or CABG					0.21
Yes	20/224 (4.6)	80/626 (6.8)	0.67 (0.41-1.10)	0.11	
No	2/76 (1.4)	19/182 (5.6)	0.25 (0.059-1.09)	0.066	
$CHADS_2$ score					0.96
1	4/93 (2.2)	9/148 (3.1)	0.75 (0.23-2.46)	0.64	
2-6	18/206 (4.5)	90/659 (7.3)	0.61 (0.37-1.01)	0.056	
CH_2DS_2-VASc score					0.39
0-3	6/152 (2.0)	25/284 (4.5)	0.50 (0.19-1.12)	0.087	
≧4	16/148 (5.6)	74/524 (7.7)	0.72 (0.42-1.24)	0.24	
HAS-BLED score					0.40
0 or 1	6/62 (4.9)	11/131 (4.4)	1.13 (0.42-3.05)	0.81	
2	11/150 (3.7)	60/433 (7.1)	0.51 (0.27-0.97)	0.041	
3-5	5/76 (3.6)	27/214 (7.0)	0.50 (0.19-1.31)	0.16	

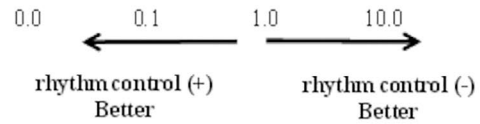

FIGURE 2 | (Continued)

confounding factors. These approaches helped improve the reliability of the outcome comparisons. However, the study may not have had sufficient power to detect smaller but clinically meaningful differences, especially after dividing patients into subgroups. Future research with larger sample sizes is needed to confirm our results and explore the subtle outcome differences between patients with and without rhythm control therapy.

This sub-analysis, based on observational data from the AFIRE trial, focused on the presence or absence of a history of rhythm control therapy rather than on the efficacy of the therapy itself. This approach offers several advantages for understanding real-world clinical practice. Specifically, it reflects the actual characteristics of patients selected for rhythm control strategies, including age, comorbidities, and AF type, which are often underrepresented in randomized controlled trials (RCTs) due to strict inclusion criteria.

By analyzing the outcomes based on treatment history, this study provides insights into the practical implications and limitations of rhythm control therapy beyond its direct effect on sinus rhythm maintenance. Importantly, the present analysis focused on hard clinical endpoints such as death and thromboembolic events rather than on surrogate outcomes such as AF burden or recurrence, which are commonly assessed in interventional trials.

TABLE 3 | Clinical outcomes associated with rhythm control therapy: multivariate and propensity score-matched Cox regression analyses.

	Rivaroxaban monotherapy				Combination therapy			
	Multivariate[a] ($n=1107$)		Adjusted[b] ($n=576$)		Multivariate ($n=1108$)		Adjusted ($n=588$)	
Endpoint	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Primary efficacy endpoint								
Cardiovascular events or death from any cause	0.70 (0.76–2.68)	0.27	0.75 (0.37–1.51)	0.43	0.57 (0.51–1.46)	0.86	0.75 (0.43–1.30)	0.30
Thromboembolic events	0.49 (0.20–1.22)	0.13	0.48 (0.18–1.30)	0.15	0.95 (0.46–1.99)	0.90	0.72 (0.33–1.56)	0.40
Primary safety endpoint								
Major bleeding	0.69 (0.28–1.71)	0.43	0.76 (0.28–2.04)	0.58	1.32 (0.67–2.57)	0.42	1.34 (0.62–2.92)	0.46

Note: Hazard ratios (HRs) were calculated for patients who received rhythm control therapy compared to those who did not using both multivariate Cox regression and propensity score-matched models.
[a]Multivariate Cox regression models adjusted for covariates that differed between the groups, including age, history of congestive heart failure, type of atrial fibrillation, and $CHADS_2$ score.
[b]Propensity score-matched analysis used the same covariates for matching and applied Cox proportional hazards modeling to the matched cohorts.

TABLE 4 | Propensity score-matched, age-stratified cox models for the primary efficacy, thromboembolic, and safety endpoints (<75 vs. ≥75 years).

	Rivaroxaban monotherapy adjusted ($n=576$)				Combination therapy adjusted ($n=588$)			
	<75 years		≥75 years		<75 years		≥75 years	
Endpoint	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Primary efficacy endpoint								
Cardiovascular events or death from any cause	0.83 (0.28–2.47)	0.74	0.70 (0.28–1.74)	0.44	0.78 (0.31–1.83)	0.54	0.75 (0.37–1.53)	0.43
Thromboembolic events	0.49 (0.09–2.67)	0.41	0.49 (0.15–1.62)	0.24	0.92 (0.30–2.86)	0.89	0.58 (0.20–1.74)	0.33
Primary safety endpoint								
Major bleeding	4.90 (0.57–42.0)	0.15	0.25 (0.05–1.19)	0.08	1.37 (0.39–4.86)	1.37	1.43 (0.53–3.83)	0.48

Note: Hazard ratios (HRs) were calculated for patients with a history of rhythm control therapy compared to those without, stratified by age group (<75 and ≥75 years). Cox proportional hazards models were applied separately for each age group using matched cohorts from the propensity score analysis. No significant association was observed between rhythm control therapy history and clinical outcomes in either age group.

Nonetheless, the absence of systematic rhythm monitoring was a key limitation. No information was available regarding whether sinus rhythm was successfully maintained following rhythm control therapy, nor were there any data on the AF burden during follow-up. As the therapeutic benefits of rhythm control are likely dependent on sustained rhythm control rather than the mere initiation of therapy, this limitation restricts our ability to assess the true clinical efficacy of rhythm control strategies. Without clear checks on how well rhythm control worked, such as maintaining sinus rhythm or reducing AF episodes through regular or occasional ECG monitoring, it is difficult to determine whether the results were due to the rhythm control treatment itself or the types of patients who received it. Accordingly, the findings should be interpreted as associations based on treatment history rather than as evidence of therapeutic efficacy or causality. Observational studies such as this can add value to RCTs by including a wider range of patients and showing how treatments work in real-world practice. These results suggest that the apparent benefit of rhythm control therapy in unadjusted analyses likely reflected baseline patient characteristics, such as younger age, lower $CHADS_2$ score, and fewer comorbidities, rather than necessarily the therapy itself. Future prospective studies that incorporate longitudinal rhythm data and stratify patients according to rhythm control success may help clarify the true impact of these therapies on clinical outcomes in patients with both AF and stable CAD.

4.1 | Study Limitations

This study was a prespecified sub-analysis of the AFIRE trial and was conducted exclusively in Japan, where the approved dose of rivaroxaban differs from international standards [18].

TABLE 5 | Propensity score-matched, $CHADS_2$-stratified Cox models for the primary efficacy, thromboembolic, and safety endpoints (0–1 vs. ≥2).

	Rivaroxaban monotherapy adjusted ($n = 576$)				Combination therapy adjusted ($n = 588$)			
	$CHADS_2$ 0–1		$CHADS_2 \geq 2$		$CHADS_2$ 0–1		$CHADS_2 \geq 2$	
Endpoint	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Primary efficacy endpoint								
Cardiovascular events or death from any cause	1.72 (0.29–10.3)	0.55	0.63 (0.29–1.35)	0.24	0.71 (0.20–2.55)	0.60	0.76 (0.41–1.40)	0.38
Thromboembolic events	1.11 (0.16–7.92)	0.91	0.37 (0.12–1.19)	0.10	0.94 (0.19–4.67)	0.94	0.65 (0.27–1.59)	0.34
Primary safety endpoint								
Major bleeding	0.53 (0.05–5.85)	0.60	0.81 (0.27–2.42)	0.71	1.51 (0.25–9.02)	0.65	1.29 (0.54–3.06)	0.57

Note: Hazard ratios (HRs) were calculated using stratified Cox proportional hazards models by CHADS2 score category (low: 0–1, high: ≥2) among patients treated with rivaroxaban monotherapy or combination therapy. The models were adjusted for propensity score-matched cohorts. No significant association was observed between a history of rhythm control therapy and clinical outcomes in the CHADS2 risk category.

Therefore, these findings may not be directly generalizable to populations with different dosing regimens.

Second, as noted in Section 4, this study did not assess whether sinus rhythm was successfully maintained after rhythm control therapy. Without systematic rhythm monitoring, we could not determine the actual efficacy of the therapy in reducing the AF burden or maintaining rhythm stability. This limitation makes it difficult to assess the long-term effects of rhythm control interventions on clinical outcomes.

Third, our analysis lacked detailed information on the timing of the initiation of rhythm control therapy. This prevents the differentiation between early and late intervention strategies, which have been shown to affect outcomes in trials such as the EAST-AFNET 4 [6]. In addition, we could not evaluate the clinical reasons that led to the use of rhythm control, such as symptom burden, failure of rate control, or physician and patient preferences, limiting our ability to explore differences in treatment effects or perform subgroup analyses based on clinical motivation.

Furthermore, owing to the inclusion criteria of the AFIRE trial requiring continued oral anticoagulation, patients who had undergone successful catheter ablation and were considered to have a low risk for thromboembolic events, and thus were possibly eligible to stop OAC, were likely not included. This creates a selection bias, in which patients with the most favorable outcomes after rhythm control therapy may have been systematically excluded. As a result, the rhythm control group in this analysis mainly consisted of patients with either persistent or recurrent AF or those needing ongoing anticoagulation owing to a high thromboembolic risk. Therefore, the possible benefits of effective rhythm control, especially in well-selected low-risk patients, may have been underestimated.

Finally, as a post hoc analysis, this study has methodological limitations. Post hoc studies are exploratory in nature, with a higher chance of type I error due to multiple comparisons and possible bias, because there is no predefined hypothesis [19]. In addition, as the data came from a previous trial, we could not adjust for unmeasured factors such as rhythm durability, AF recurrence, or how long rhythm control therapy was continued. These limitations indicate that our findings should be interpreted with caution and support the need for future prospective studies that include rhythm monitoring, the timing of therapy, and complete baseline evaluations to better understand the role of rhythm control therapy in patients with AF and stable CAD.

5 | Conclusions

In patients with AF and stable CAD treated with rivaroxaban with or without antiplatelet therapy, unadjusted analyses suggested lower rates of thromboembolic events and mortality among those with a history of rhythm control therapy. However, after adjustment for baseline characteristics, no significant associations were observed. These findings should be interpreted cautiously, as the study may have been underpowered to detect clinically meaningful effects. Importantly, the results should be understood within the limited clinical context of the AFIRE trial, which included patients with a history of rhythm control therapy who required continued anticoagulation. Therefore, our conclusions do not extend to patients who may have been able to discontinue anticoagulation after rhythm control interventions. Further studies with larger sample sizes, systematic rhythm monitoring, and inclusion of patients across a broader spectrum of rhythm control outcomes are needed to clarify the prognostic role of rhythm control in AF with stable CAD.

Acknowledgments

We thank the AFIRE investigators for their support in patient registration and data collection.

Ethics Statement

The trial was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Japan, along with the institutional review boards of all participating institutions.

Conflicts of Interest

D.W., K. Kimura, and K. Matsui declare no conflicts of interest. H.S. reports receiving research funding support from Abbott, Amgen, CV Quest, CMIC, Bayer Yakuhin, JIMRO, SRD, Nippon Boehringer Ingelheim, and Medtronic Japan, lecture fees from Medtronic, and scholarship funds from Abbott, JCT, Pfizer, and Ono pharmaceutical; K. Kaikita reports receiving lecture fees from Bayer Yakuhin, Daiichi Sankyo, Novartis Pharma, and Otsuka Pharma and grant support from Bayer Yakuhin and Daiichi Sankyo; M.A. reports receiving lecture fees from Pfizer, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim and grant support and lecture fees from Bayer Yakuhin and Daiichi Sankyo; J.A. reports receiving lecture fees from Bayer Yakuhin, Sanofi, Daiichi Sankyo, and Sanofi; T.M. reports receiving lecture fees from Abbott and Bayer Yakuhin; M.N. reports receiving grant support and honoraria from Bayer Yakuhin and Daiichi Sankyo and has received donations to the endowed department from Boston Scientific Japan, Kaneka, Terumo, Nipro, Otsuka Medical, Japan Lifeline, Asahi Intec, and Biotronik Japan; K. Miyauchi reports receiving lecture fees from Amgen Astellas BioPharma, Astellas Pharma, Merck Sharp & Dohme, Bayer Yakuhin, Sanofi, Takeda, Daiichi Sankyo, Nippon Boehringer Ingelheim, and Bristol-Myers Squibb; N.H. reports receiving grant support and lecture fees from Bayer Yakuhin and Nippon Boehringer Ingelheim and lecture fees from Bristol-Myers Squibb; A.H. reports receiving grant support and lecture fees from Daiichi Sankyo and Bayer Yakuhin and lecture fees from Novartis Pharma; H.O. reports receiving lecture fees from Bayer Yakuhin; and S.Y. reports receiving grant support from Takeda and Abbott and lecture fees from Daiichi Sankyo and Bristol-Myers Squibb. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Data are available on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Tables S1–S3:** joa370210-sup-0001-TablesS1-S3.docx.