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ORIGINAL RESEARCH

Medication Adherence and Antithrombotic Therapy Outcomes

Insights From a Post Hoc Analysis of the AFIRE Trial

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ABSTRACT

BACKGROUND The AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial demonstrated that rivaroxaban monotherapy has noninferior efficacy and superior safety compared with combination therapy (rivaroxaban plus a single antiplatelet) in patients with atrial fibrillation and stable coronary artery disease.

OBJECTIVES This post hoc analysis aimed to explore the impact of medication adherence on the AFIRE trial results.

METHODS A total of 2,120 patients were categorized into adherent and nonadherent groups based on self-reported assessments, which were further validated through on-site visits to the facilities. Adherence was defined as continuous medication use as prescribed. The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, revascularization requiring unstable angina, or all-cause death. The primary safety endpoint was major bleeding events.

RESULTS Among the 2,012 (94.9%) adherent patients, rivaroxaban monotherapy showed significantly better outcomes compared with combination therapy regarding both efficacy (HR: 0.72; 95% CI: 0.53-0.96; $P = 0.028$) and safety (HR: 0.63; 95% CI: 0.41-0.97; $P = 0.034$). However, no significant differences in outcomes were shown in nonadherent patients (n = 108). There was no interaction between medication adherence and the randomized treatment group. In clinically high-risk patients with a history of angina pectoris, compared with nonadherent patients (n = 68), those who demonstrated medication adherence (n = 1,281) exhibited significantly better efficacy outcomes (HR: 0.52; 95% CI: 0.30-0.97; $P = 0.041$).

CONCLUSIONS High adherence to rivaroxaban monotherapy was associated with improved outcomes, underscoring the importance of adherence in achieving optimal therapeutic effects (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease [AFIRE], NCT02642419; AFIRE Study: Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease Study, UMIN000016612). (JACC Asia. 2026;6:329-341) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CAD = coronary artery disease

DOAC = direct oral anticoagulant

PCI = percutaneous coronary intervention

The AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial demonstrated that rivaroxaban monotherapy was not inferior for cardiovascular events or death and more effective in reducing major bleeding events to rivaroxaban plus antiplatelet therapy (combination therapy) in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD).[1] These findings support the current guideline recommendation for direct oral anticoagulant (DOAC) monotherapy in AF with stable CAD.[2]

Adherence to medication in patients with cardiovascular disease is crucial because of the elevated risk of thrombotic and bleeding events associated with antithrombotic therapy.[3,4] Adherence ensures the prevention of thrombotic events such as myocardial infarction and stroke by maintaining effective antithrombosis.[5-7] It also manages bleeding risks by ensuring proper dosing, thus balancing antithrombotic effects and minimizing adverse outcomes.[8,9] Consistent medication use is essential for optimizing therapeutic efficacy, as demonstrated in previous studies on patients with either CAD or AF, in which better outcomes were observed in adherent patients.[7,10-12] However, it remains unclear whether the results of the AFIRE trial, which enrolled patients with both AF and CAD, were consistent across patients according to their medication adherence.

Therefore, we performed a subanalysis of the AFIRE trial to compare the effects of medication adherence assessed by self-reported questionnaires on clinical outcomes, such as thrombotic events, major bleeding, and all-cause mortality, between monotherapy and combination therapy groups.

METHODS

STUDY POPULATION AND TRIAL DESIGN. The AFIRE trial was a multicenter, randomized, open-label, parallel-group study.[13] Full details, including the study design and the results of the primary analysis, have been previously reported.[1] In summary, men and women aged 20 years or older with a diagnosis of AF and $CHADS_2$ scores of at least 1, as well as stable CAD were enrolled. Eligible patients met 1 of the following criteria: 1) angioplasty with or without stenting at least 1 year before enrollment; 2) exhbited ≥50% coronary stenosis as detected by coronary computed tomography or coronary angiography; or 3) a history of coronary artery bypass grafting performed at least 1 year before enrollment. The main exclusion criteria included a history of stent thrombosis, active malignancies, and uncontrolled hypertension. The trial was designed and conducted by the Executive Steering Committee.[1] The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Japan, as well as the institutional review boards of all participating institutions. An independent data and safety monitoring committee reviewed all data, and all participants provided written informed consent.

A total of 2,240 patients were enrolled, with 2,236 randomly assigned in a 1:1 ratio to receive rivaroxaban monotherapy (10 mg once daily for those with a creatinine clearance of 15-49 mL/min or 15 mg once daily for patients with a creatinine clearance of ≥50 mL/min) or combination therapy with rivaroxaban at previously stated doses plus an antiplatelet agent (aspirin or a P2Y12 inhibitor) according to the treating physician's discretion.

MEDICATION ADHERENCE. Adherence to rivaroxaban was assessed twice using self-reported questionnaires administered to patients at 6 months and at the end of the study. The consistency of patient responses between the 2 time points was examined to evaluate the stability of adherence classification. Patients were asked, "How often do you take your prescribed rivaroxaban?" with 5 response options: 1) "I take it as prescribed (daily/weekly as directed);" 2) "I occasionally miss doses (1-2 per week);" 3) "I frequently miss doses (≥3 per week);" 4) "I am not currently taking the medication;" and 5) "Unknown." Questionnaire completion was verified during on-site monitoring to ensure data accuracy. Patients selecting option 1 were categorized as adherent and those selecting options 2 to 4 were classified as nonadherent. Responses marked "Unknown" were excluded from the analysis. Therefore, adherence was defined as the consistent use as prescribed.[14,15] In addition, to ensure accuracy, a second self-reported questionnaire was administered at the end

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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of the study, and the same criteria were applied to define adherence and nonadherence based on these responses. A frequency table summarizing adherence responses at each time point has been added as Supplemental Table 1.

OUTCOMES. The primary efficacy endpoint was a composite of stroke, systemic embolism, myocardial infarction, revascularization requiring unstable angina, and all-cause death. The primary safety endpoint was major bleeding as defined according to the criteria of the International Society on Thrombosis and Hemostasis criteria. Individual components of efficacy and safety were analyzed as secondary endpoints. Additional analyses were conducted to evaluate the association between self-reported medication adherence and clinical outcomes, including thrombotic events, major bleeding, and all-cause death. These comparisons were performed both among all patients and specifically in those with a history of angina pectoris. To address potential bias from events occurring before adherence assessment, landmark analyses were conducted excluding patients who experienced clinical events before the 6-month adherence evaluation.

STATISTICAL ANALYSES. Continuous variables are presented as median (IQR) and categorical variables are reported as count (percentage). For the analysis of baseline characteristics, continuous variables were compared using the Wilcoxon rank-sum test, whereas categorical variables were assessed via Fisher's exact tests. Cumulative event rates were estimated using the Kaplan-Meier method and compared using the log-rank test, with incidence rates in each treatment arm shown as percentages per patient-year. A Cox proportional hazards model was employed to evaluate clinical outcomes between treatment strategies (rivaroxaban monotherapy vs combination therapy) stratified by adherence status, as well as between adherent and nonadherent groups within each treatment arm. This analysis aimed to explore whether the effects of treatment differed according to adherence, and results were expressed as HRs and 95% CIs. Analyses were adjusted for age and sex. Notably, in the original AFIRE trial, randomization was performed using a minimization method for age, sex, history of percutaneous coronary intervention (PCI), cardiac insufficiency, heart failure, hypertension, diabetes mellitus, and stroke. All statistical analyses were conducted using R Foundation for Statistical Computing software, version 4.2.3 (R Core Team). All reported P values were 2-tailed, with those <0.05 considered statistically significant.

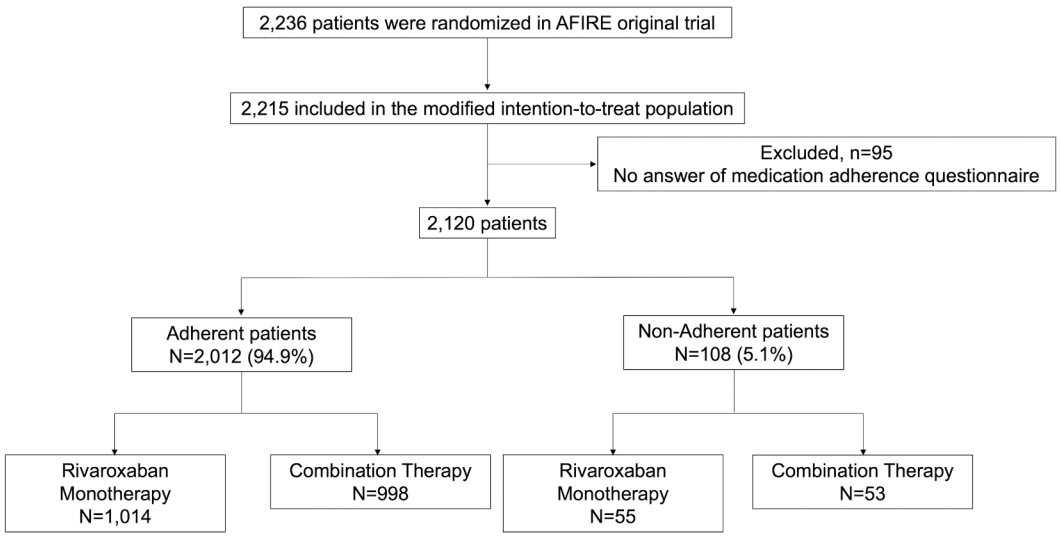
RESULTS

MEDICATION ADHERENCE. In this post hoc subanalysis of the modified intention-to-treat population from the AFIRE trial, we evaluated 2,215 patients. We excluded 95 patients because of a lack of response or an "unknown" indication on the self-reported questionnaires at 6 months, resulting in a final analysis of 2,120 patients. Among these, 2,012 (94.9%) were classified as adherent and 108 (5.1%) as nonadherent based on their responses (**Figure 1**). To further validate the adherence patterns observed at 6 months, we used a similar approach using the second questionnaire, which showed 1,901 (95.0%) adherent and 100 (5.0%) nonadherent patients. The distribution of responses to the adherence questionnaire is shown in Supplemental Table 1. To assess the stability of adherence classification over time, responses at 6 months and at the end of the study were compared. Overall, 93.1% of patients remained in the same adherence category across both time points, indicating high temporal consistency.

BASELINE CHARACTERISTICS. **Table 1** presents the baseline characteristics of the patients by treatment group (rivaroxaban monotherapy and combination therapy), stratified by adherence status, with separate analyses for the adherent and nonadherent groups. No significant differences were observed between the treatment groups when the subgroups were compared. Supplemental Table 2 shows the baseline characteristics of the adherent and nonadherent groups among all participants and those with a prior history of angina pectoris. Among all patients, multivessel PCI was more frequently observed in the adherent group than in the nonadherent group. In addition, the nonadherent group was prescribed a 10-mg dose of rivaroxaban more frequently than the adherent group. No other significant differences were found between the medication adherence groups.

PRIMARY EFFICACY AND SAFETY ENDPOINTS. **Figure 2A** shows the primary efficacy endpoints in the monotherapy and combination therapy groups. Among the 2,012 adherent patients, rivaroxaban monotherapy was superior to combination therapy. Primary efficacy endpoint events were observed in 76 of the 1,014 patients receiving rivaroxaban monotherapy and 101 of the 998 patients receiving combination therapy, with incidence rates of 3.80% and 5.19% per patient-year, respectively (adjusted HR: 0.72; 95% CI: 0.53-0.96; $P = 0.028$). No significant difference was noted in the primary efficacy endpoints between the monotherapy and combination

FIGURE 1 Patient Flow of the Subanalysis Population



This figure illustrates the patient selection process for the adherence subanalysis within the AFIRE study. Of the total AFIRE population, 2,120 patients answered the self-reported adherence questionnaire and were included in this subanalysis. Patients were subsequently categorized based on adherence to rivaroxaban (adherent vs nonadherent) and treatment strategy (rivaroxaban monotherapy vs combination therapy). This classification formed the basis for evaluating efficacy and safety outcomes. AFIRE = Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease.

therapy groups among the 108 nonadherent patients. Primary efficacy endpoint events occurred in 6 of the 55 patients receiving rivaroxaban monotherapy and 9 of the 53 patients receiving combination therapy, with incidence rates of 5.85% and 9.19% per patient-year, respectively (adjusted HR: 0.63; 95% CI: 0.22-1.82; $P = 0.396$). There was no interaction in the primary efficacy outcomes between medication adherence and antithrombotic therapy ($P = 0.814$).

Regarding the primary safety endpoint (**Figure 2B**), rivaroxaban monotherapy was superior to combination therapy in the 2,012 adherent patients. Primary safety endpoint events were observed in 35 of the 1,014 patients receiving rivaroxaban monotherapy and 53 of the 998 patients receiving combination therapy, corresponding to incidence rates of 1.73% and 2.73% per patient-year, respectively (adjusted HR: 0.63; 95% CI: 0.41-0.97; $P = 0.034$). Among the 108 nonadherent patients, primary safety endpoint events were observed in 4 of the 53 patients receiving combination therapy, corresponding to an incidence rate of 4.05% per patient-year. There were no significant differences between the monotherapy and combination therapy groups. In addition, there was no interaction between medication adherence and antithrombotic therapy in terms of the primary safety outcomes ($P = 0.990$).

We also examined the differences between adherent and nonadherent patients. Adherent patients exhibited improved primary efficacy outcomes relative to nonadherent patients, although this difference was not statistically significant (Supplemental Figure 1A) (adjusted HR: 0.62; 95% CI: 0.36-1.04; $P = 0.072$). Regarding the primary safety outcomes, no difference or trend was observed between the medication adherence groups (Supplemental Figure 1B) (adjusted HR: 1.19, 95% CI: 0.44-3.25; $P = 0.732$). In clinically high-risk patients with a history of angina pectoris, those who demonstrated adherence to medication (n = 1,281) exhibited significantly better efficacy outcomes compared with nonadherent patients (n = 68) (**Figure 3A**) (adjusted HR: 0.52; 95% CI: 0.30-0.97; $P = 0.041$). In contrast, no significant difference was observed in the safety outcomes among patients with angina pectoris history (**Figure 3B**) (adjusted HR: 3.13; 95% CI: 0.41-21.19; $P = 0.258$).

INDIVIDUAL COMPONENTS OF EFFICACY AND SAFETY ENDPOINTS. Supplemental Table 3 shows the incidence rates of the individual components comprising the efficacy and safety endpoints, comparing medication therapy as part of the secondary endpoints. In the adherent group, all-cause mortality was significantly lower in patients

TABLE 1 Patients' Clinical Characteristics by Study and Medication Adherence Groups

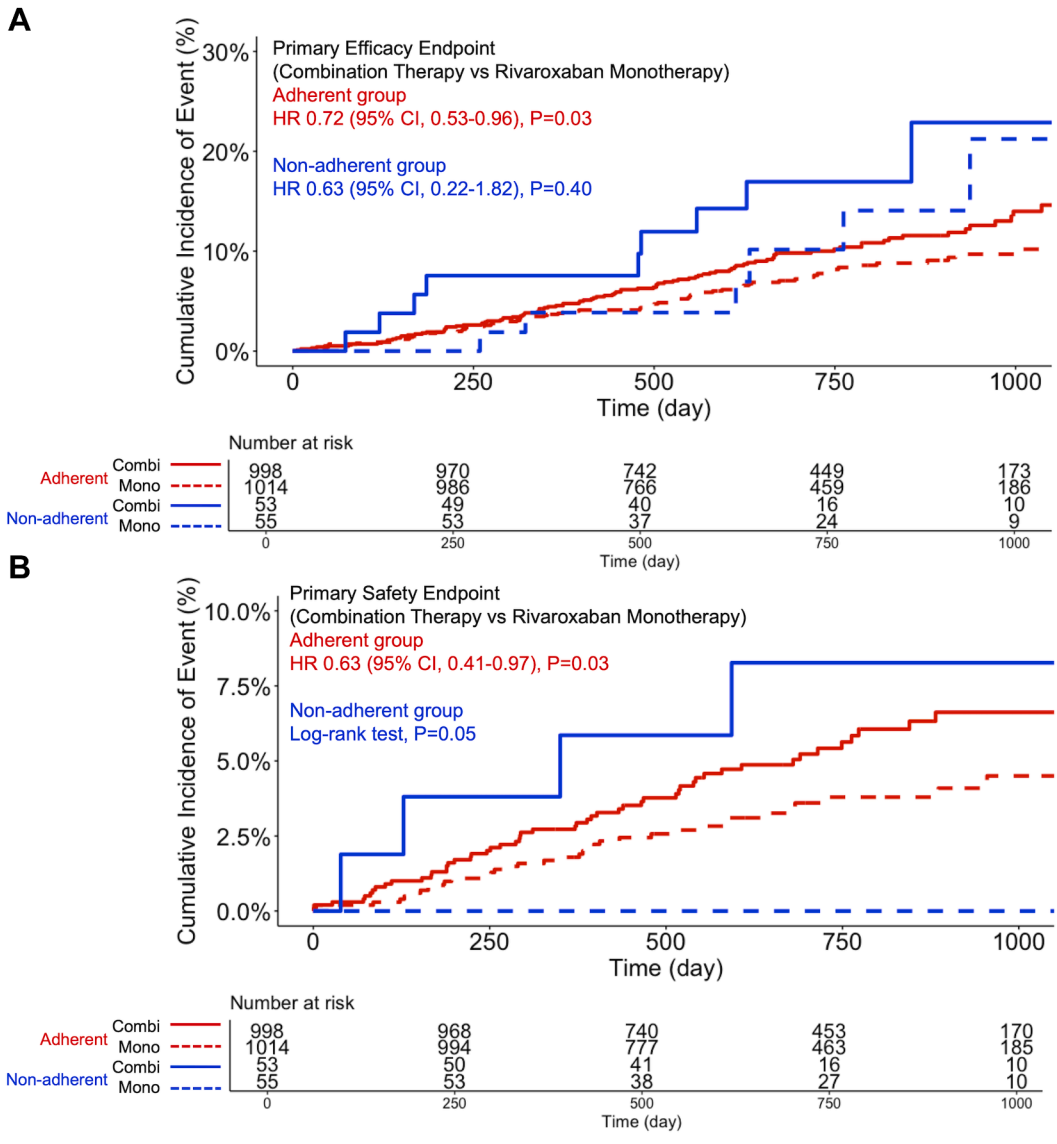
	Adherent Group			Nonadherent Group		
	Rivaroxaban Monotherapy (n = 1,014)	Combination Therapy (n = 998)	*P* Value	Rivaroxaban Monotherapy (n = 55)	Combination Therapy (n = 53)	*P* Value
Combination therapy	0 (0.0)	998 (100.0)		0 (0.0)	53 (100.0)	
Age, y	75.0 (69.0-80.0)	75.0 (69.0-80.0)	0.538	74.0 (67.0-80.5)	78.0 (70.0-84.0)	0.103
Age ≧75 y	539 (53.2)	518 (51.9)	0.592	26 (47.3)	32 (60.4)	0.183
Female	215 (21.2)	206 (20.6)	0.784	9 (16.4)	13 (24.5)	0.344
BMI, kg/m^2	24.1 (22.0-26.7)	24.2 (22.1-26.6)	0.796	23.2 (21.2-25.7)	23.7 (22.0-26.1)	0.336
Current smoker	130 (12.8)	125 (12.5)	0.893	7 (12.7)	7 (13.2)	1.000
Previous HT	869 (85.7)	856 (85.8)	1.000	46 (83.6)	43 (81.1)	0.804
Previous DM	423 (41.7)	419 (42.0)	0.928	25 (45.5)	24 (45.3)	1.000
Previous DLp	723 (71.3)	687 (68.8)	0.243	32 (58.2)	36 (67.9)	0.324
Previous AP	634 (62.5)	647 (64.8)	0.287	34 (61.8)	34 (64.2)	0.844
Previous HF	355 (35.0)	359 (36.0)	0.675	22 (40.0)	19 (35.8)	0.695
Previous stroke	136 (13.4)	156 (15.6)	0.164	6 (10.9)	11 (20.8)	0.192
Previous MI	339 (33.4)	357 (35.8)	0.281	22 (40.0)	19 (35.8)	0.695
Previous PCI	718 (70.8)	711 (71.2)	0.844	36 (65.5)	34 (64.2)	1.000
PCI lesion						
RCA	270 (26.6)	269 (27.0)	0.880	15 (27.3)	13 (24.5)	0.828
LMT	24 (2.4)	20 (2.0)	0.648	0 (0.0)	1 (1.9)	0.491
LAD	432 (42.6)	406 (40.7)	0.390	20 (36.4)	20 (37.7)	1.000
LCX	189 (18.6)	215 (21.5)	0.107	6 (10.9)	8 (15.1)	0.576
Other	1 (0.1)	4 (0.4)	0.215	0 (0.0)	0 (0.0)	NA
Unknown	26 (2.6)	16 (1.6)	0.160	2 (3.6)	0 (0.0)	0.496
MV	178 (17.6)	182 (18.2)	0.727	5 (9.1)	6 (11.3)	0.759
MV/LMT	184 (18.1)	184 (18.4)	0.908	5 (9.1)	6 (11.3)	0.759
Previous PCI or CABG	779 (76.8)	770 (77.2)	0.874	39 (70.9)	38 (71.7)	1.000
Type of stent			0.813			0.794
1st Gen DES	98 (14.8)	105 (16.0)		4 (11.4)	6 (18.8)	
2nd Gen DES	370 (55.7)	349 (53.3)		16 (45.7)	15 (46.9)	
BMS	168 (25.3)	170 (26.0)		12 (34.3)	8 (25.0)	
Unknown	28 (4.2)	31 (4.7)		3 (8.6)	3 (9.4)	
Type of AF			0.755			0.357
Paroxysmal	545 (53.7)	522 (52.3)		29 (52.7)	26 (49.1)	
Persistent	152 (15.0)	160 (16.0)		8 (14.5)	4 (7.5)	
Permanent	317 (31.3)	316 (31.7)		18 (32.7)	23 (43.4)	
Ccr	58.6 (46.0-75.0)	59.7 (45.2-74.1)	0.977	60.5 (40.7-77.3)	59.7 (40.4-70.2)	0.732
Distribution			0.859			0.899
<30 mL/min	49 (5.0)	49 (5.2)		4 (8.3)	4 (8.7)	
30-<50 mL/min	282 (28.9)	262 (27.8)		13 (27.1)	15 (32.6)	
≧50 mL/min	645 (66.1)	633 (67.1)		31 (64.6)	27 (58.7)	
PPI	608 (60.0)	623 (62.4)	0.272	33 (60.0)	35 (66.0)	0.555
CHA_2DS_2VASc score ≧4	619 (61.0)	607 (60.8)	0.927	36 (65.5)	34 (64.2)	1.000
Rivaroxaban dose			0.805			0.765
10 mg	459 (45.4)	460 (46.1)		27 (51.9)	27 (54.0)	
15 mg	552 (54.5)	538 (53.9)		25 (48.1)	22 (44.0)	
Other dose	1 (0.1)	0 (0.0)		0 (0.0)	1 (2.0)	
Inappropriate dose	205 (21.1)	214 (22.7)	0.407	12 (26.7)	11 (25.6)	1.000

Values are n (%) or median (IQR).

1st GEN DES = first-generation drug eluting stent; 2nd GEN DES = second-generation drug eluting stent; AF = atrial fibrillation; AP = angina pectoris; BMI = body mass index; BMS = bare metal stent; CABG = coronary artery bypass grafting; Ccr = creatinine clearance; DLp = dyslipidemia; DM = diabetes mellitus; HF = heart failure; HT = hypertension; LAD = left anterior descending artery; LCX = left circumflex artery; LMT = left main trunk; MI = myocardial infarction; MV = multi vessels; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; RCA = right coronary artery.

receiving rivaroxaban monotherapy compared with those receiving combination therapy (event rates of 1.60% and 2.90%, respectively; unadjusted HR: 0.55; 95% CI: 0.36-0.85; $P = 0.006$). Cardiovascular death occurred in 0.97% of patients receiving rivaroxaban monotherapy and in 1.80% of those receiving combination therapy per patient-year (unadjusted HR: 0.54; 95% CI: 0.31-0.93; $P = 0.027$). The event rate of

FIGURE 2 Outcomes by Medication Adherence and Treatment Strategy

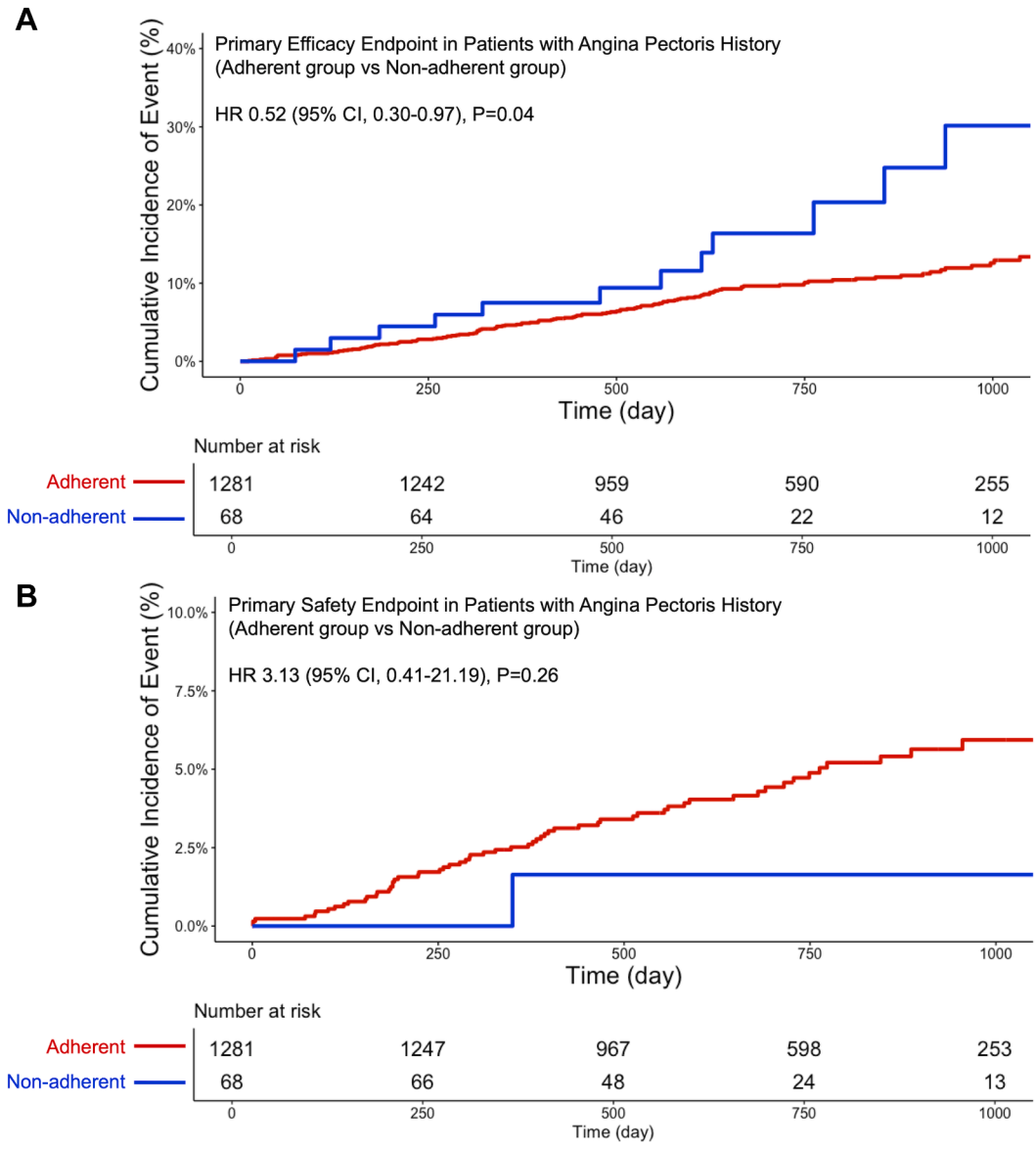


Kaplan-Meier curves show the primary efficacy (A) and safety (B) endpoints in the combination therapy group vs rivaroxaban monotherapy among adherent (red) and nonadherent patients (blue). Medication adherence was evaluated using a self-reported questionnaire. Cox regression models adjusted for age and sex were used to estimate HRs. Rivaroxaban monotherapy was associated with improved efficacy and safety in adherent patients, whereas such advantages were not apparent in nonadherent patients. Combi = combination therapy; Mono = rivaroxaban monotherapy.

any bleeding was significantly lower in the rivaroxaban monotherapy group vs the combination therapy group (7.44% vs 12.65% per patient-year, respectively; unadjusted HR: 0.59; 95% CI: 0.48-0.74; $P < 0.001$). Among the nonadherent group, no significant differences were observed in any parameter of the efficacy and safety endpoints.

Supplemental Table 4 compares the incidence rates of the individual components that comprised the efficacy and safety endpoints between the adherent and nonadherent groups. In both the overall patient cohort and those with a history of angina pectoris, the incidence of unstable angina was significantly higher among nonadherent patients (all

FIGURE 3 **Outcomes in the Angina Subgroup by Medication Adherence**

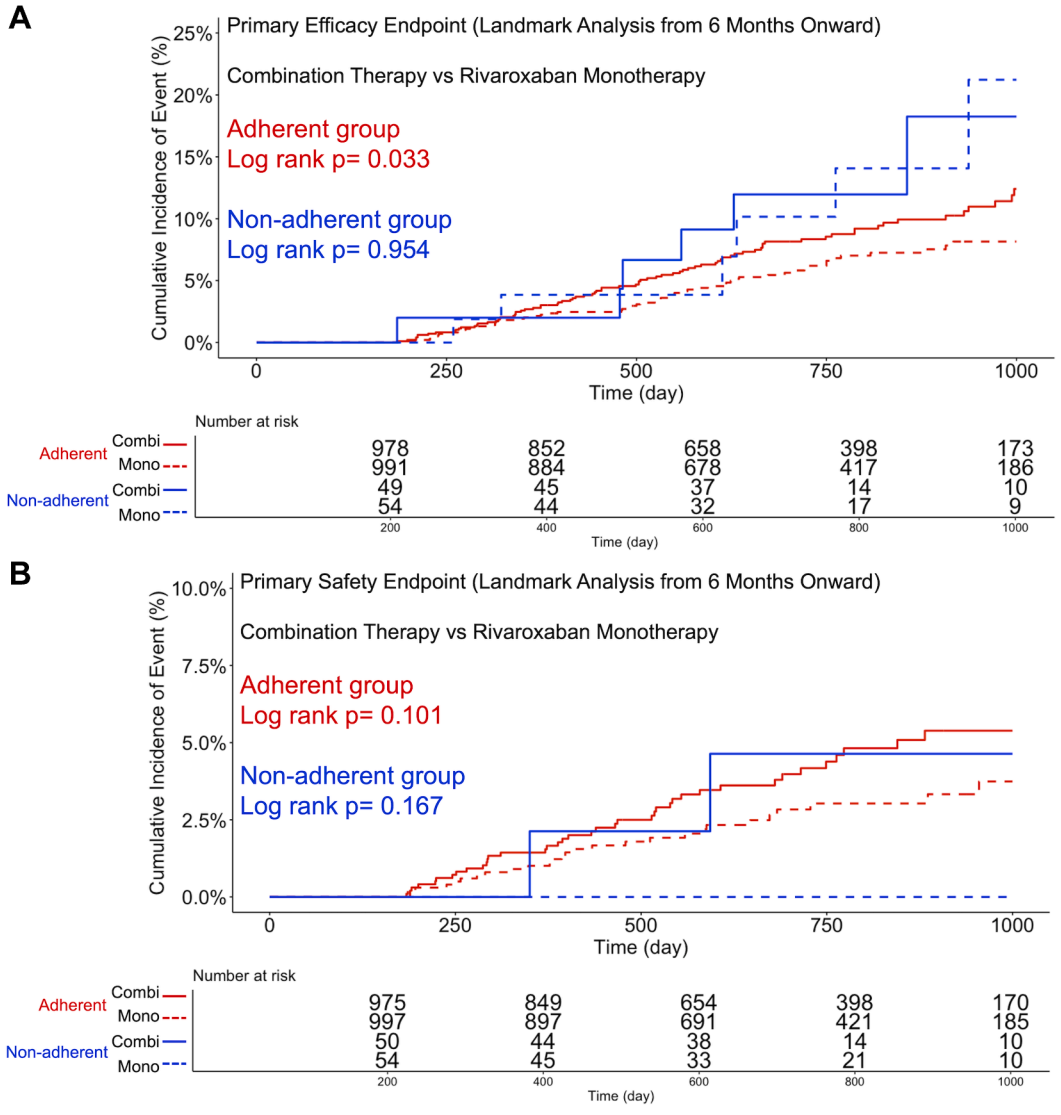


Kaplan-Meier curves show the primary efficacy (A) and safety (B) endpoints among adherent (red) and nonadherent (blue) groups with a history of angina pectoris. Medication adherence was assessed using self-reported questionnaires. In the primary efficacy endpoint, adherent patients showed better outcomes than nonadherent patients ($P = 0.04$), whereas no significant difference was observed in the primary safety endpoint. Cox regression models adjusted for age and sex were used to estimate HRs.

patients: unadjusted HR: 0.26; 95% CI: 0.10-0.68; $P = 0.006$; patients with a history of angina pectoris: unadjusted HR: 0.20; 95% CI: 0.08-0.54; $P = 0.001$). No differences were observed in the other components examined.

To further explore the association between adherence and clinical outcomes within each treatment arm, we conducted within-group comparisons of adherent vs nonadherent patients in both the monotherapy and combination therapy groups. Kaplan-Meier curves are presented in Supplemental Figure 2, and event rates with corresponding HRs are summarized in Supplemental Table 5. No significant differences in the primary efficacy endpoint were

FIGURE 4 Landmark Analysis From 6 Months by Adherence Status



Kaplan-Meier curves from 6 months onward for primary efficacy (A) and safety (B) endpoints comparing combination therapy with rivaroxaban monotherapy among adherent (red) and nonadherent (blue) patients. Only patients who were event-free at 6 months were included in this analysis. Medication adherence was assessed using self-reported questionnaires. Among adherent patients, trends consistent with the full cohort was observed for both efficacy and safety, although the difference in safety was not statistically significant ($P = 0.101$). This difference was not apparent among nonadherent patients. *P* values were calculated using the log-rank test. Abbreviations as in Figure 2.

observed between adherent and nonadherent patients in either group.

LANDMARK ANALYSIS FROM 6 MONTHS ONWARD. Patients who experienced the primary outcome before 6 months were excluded from this analysis. The baseline characteristics for the landmark analysis are provided in Supplemental Tables 6 and 7. In the adherent group, rivaroxaban monotherapy was associated with a significantly lower incidence of primary efficacy events compared with combination therapy ($P = 0.033$) (Figure 4A). In the nonadherent group, however, the incidence of primary efficacy events appeared similar between the 2 treatment strategies ($P = 0.954$). No significant difference in primary safety outcomes was observed in either adherence group (Figure 4B).

When comparing adherence status, adherent patients tended to have better efficacy outcomes than nonadherent patients, although this was not statistically significant ($P = 0.059$) (Supplemental Figure 3A). No difference was observed in primary safety outcomes (Supplemental Figure 3B, $P = 0.465$). Among patients with a history of angina pectoris, adherence was significantly associated with better efficacy outcomes ($P = 0.014$) (Supplemental Figure 4A); however, no significant difference was observed in safety outcomes in this subgroup ($P = 0.423$) (Supplemental Figure 4B). These landmark analyses support the overall trends observed in the main analysis.

OUTCOMES EVALUATED BY MEDICATION ADHERENCE USING THE SECOND QUESTIONNAIRES. Baseline characteristics based on medication adherence through the second questionnaire are presented in Supplemental Table 8, showing no significant differences between adherence groups. In the analysis of primary efficacy outcomes, no significant differences were detected; however, the adherent group, as assessed by the second questionnaire, exhibited a trend toward favorable HRs (adjusted HR: 0.52; 95% CI: 0.25-1.07; $P = 0.073$). These trends were consistent with the patterns observed in the results derived from the 6 months questionnaire (Supplemental Figure 5A).

Regarding the primary safety outcomes, no difference or trend was observed between the medication adherence groups (Supplemental Figure 5B) (adjusted HR: 0.68; 95% CI: 0.27-1.69; $P = 0.409$). The details of each primary and secondary endpoint are presented in Supplemental Table 9. It is important to note that all fatal cases were excluded because of nonresponse at the end of the study questionnaire, resulting in zero-reported events.

DISCUSSION

In this post hoc analysis of the AFIRE trial, the main findings—as summarized in the **Central Illustration**—included the following: 1) the analysis demonstrated high adherence to rivaroxaban according to the self-reported questionnaire; 2) rivaroxaban monotherapy had a greater clinical impact on efficacy and safety endpoints among adherent patients, but not apparent in nonadherent patients; and 3) among clinically high-risk patients with a history of angina pectoris, the efficacy endpoints were notably lower in adherent patients than in nonadherent patients, whereas no significant difference was observed between the medication adherence groups in terms of safety outcomes.

The proportion of the adherent group was approximately 95%, which is higher than that reported in previous studies.[7,15-18] The AFIRE study is a prospective randomized controlled trial that included many patients who underwent PCI. Previous research has suggested that prospective studies tend to report higher rates of medication adherence than observational studies, particularly retrospective studies.[19] In addition, a history of cardiovascular risk factors, such as prior PCI and the once-daily dosing frequency of rivaroxaban, has been associated with improved adherence.[15,20] These factors likely contributed to the increased medication adherence rates observed in this study. In a Japanese prospective cohort study using proportion of days covered and defining rivaroxaban adherence as ≥80% coverage, 96% of patients were classified as adherent.[21] Despite differences in the definition of adherence, the comparably high rate observed supports the notion that high adherence to rivaroxaban is prevalent in Japanese clinical settings.

Among adherent patients, rivaroxaban monotherapy demonstrated more favorable safety and efficacy outcomes than combination therapy. This study focused on rivaroxaban administered once daily. The effects of rivaroxaban were maintained and decreased to minimal levels within 24 h of administration.[22] This consistency may improve medication adherence, leading to better efficacy outcomes. There were no significant differences in safety outcomes between the adherent and nonadherent groups. Although bleeding complications are generally associated with lower medication adherence, some studies suggest that nonadherence to DOACs can paradoxically reduce the incidence of bleeding events because patients are exposed to anticoagulants for shorter periods.[23,24] However, this potential reduction in the bleeding risk does not outweigh the risks associated with poor adherence, such as increased thromboembolic events.

Medication adherence is particularly important in patients with cardiovascular risk factors.[4] This study observed a significant increase in efficacy endpoints among nonadherent patients with a history of angina pectoris, highlighting the critical need for strategies to improve medication adherence in this high-risk, symptomatic population. Treatment-related factors significantly influence medication adherence.[25,26] Studies indicate that adherence improves with a single-pill, once-daily dosing regimen.[4,27-29] Specifically, adherence to DOACs may be improved with once-daily regimens.[15,30] Furthermore, treatment strategies that minimize side effects such as bleeding complications are crucial for improving

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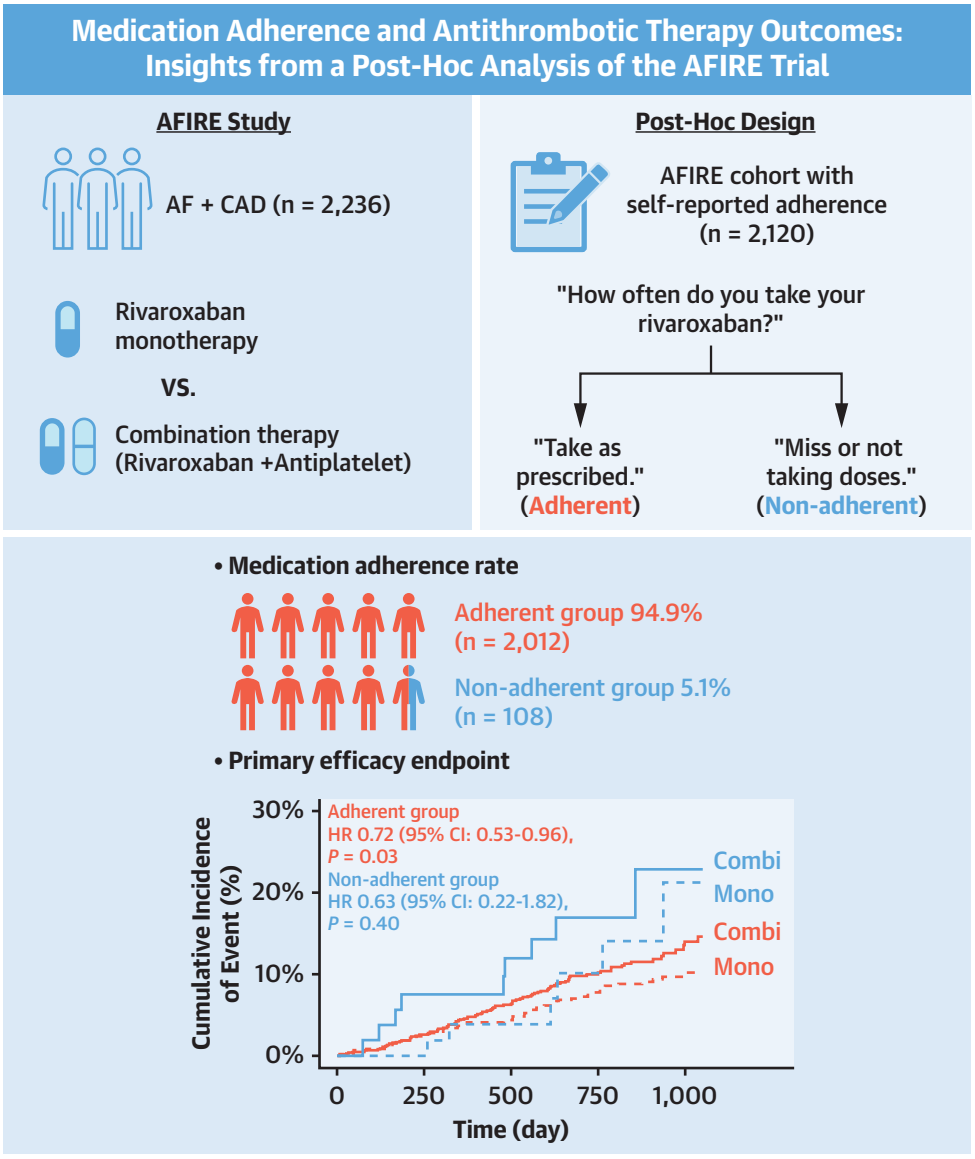
CENTRAL ILLUSTRATION **Clinical Outcomes Based on Medication Adherence in the Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study**



Chiba N, et al. JACC Asia. 2026;6(3):329–341.

In this post hoc analysis of the AFIRE (Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease) trial comparing rivaroxaban monotherapy with combination therapy in patients with atrial fibrillation (AF) and coronary artery disease (CAD), medication adherence was assessed using a self-reported questionnaire (n = 2,120). Patients who answered "I take it as prescribed" were defined as adherent, accounting for 94.9% of the population. Among adherent patients (red), rivaroxaban monotherapy showed greater benefit in the primary efficacy endpoint, whereas these advantages were not apparent in nonadherent patients (blue). HRs were adjusted for age and sex. This post hoc analysis highlights the importance of adherence in optimizing clinical outcomes for patients with AF and CAD. Combi = combination therapy; Mono = rivaroxaban monotherapy.

adherence.[4,23] Therefore, rivaroxaban monotherapy, which is associated with fewer bleeding complications than the combination therapy, may play a key role in enhancing medication adherence.

STUDY LIMITATIONS. First, as a post hoc analysis, the study may be subject to inherent biases and limited statistical power, especially given the relatively small size of the nonadherent group (approximately 5%). This may have reduced the ability to detect significant differences in clinical outcomes. Because of the limited number of patients in each nonadherent response category, subgroup analyses within this group could not be performed, necessitating a combined analysis. Second, the approved rivaroxaban dose in Japan is 15 mg once daily, which is lower than the 20-mg dose commonly used in other countries. The pharmacokinetic equivalence observed in the AFIRE trial (in which 15 mg rivaroxaban in Japanese patients is comparable to 20 mg globally) suggests that the findings may be relevant to other populations.[31] However, further research in more diverse populations remains essential to ensure appropriate application across varying clinical settings. In addition, the trial setting may not fully capture patients with more complex clinical profiles, such as those with multimorbidity[32] or recent DOAC initiation,[33] in whom adherence behavior may differ.Third, adherence was evaluated using simple, single-item, self-reported questionnaires that lack formal validation and are subject to recall and social desirability bias.[3,25] Objective measures, such as pill counts or electronic monitoring, were not employed. Although this may limit precision, prior studies have shown acceptable consistency between self-report and refill-based measures,[25,34] and the simplicity of this method allowed for broad implementation in a large-scale, multicenter trial with strict site monitoring. Furthermore, no financial incentives were provided, and data collection occurred in a neutral research environment, reducing the likelihood of response bias. Importantly, this approach may offer practical clinical utility for identifying patients at risk of nonadherence in routine care settings. Previous cardiovascular studies have also demonstrated the feasibility and clinical relevance of similarly simple adherence assessments.[35,36] Fourth, although the questionnaire used predefined frequency-based categories, interindividual variability in interpreting these categories may have affected adherence classification. Although the instrument was not formally validated, assessment at 2 time points allowed for evaluation of internal consistency, lending some support to classification stability. Fifth, the high adherence rates observed may partly reflect the controlled nature of the clinical trial and the influence of Japan's universal health insurance system, which facilitates continuous access to medications.[21] Finally, the low number of clinical events in the nonadherent group (15 for primary efficacy and 4 for primary safety) limited the ability to perform multivariable analyses that adjust for a broader range of confounders, although age and sex were included in the models. Despite these limitations, the findings underscore the relevance of adherence behavior in determining clinical outcomes in patients receiving antithrombotic therapy.

CONCLUSIONS

Rivaroxaban monotherapy demonstrated favorable efficacy and safety outcomes compared with combination therapy in patients with high medication adherence, consistent with the overall AFIRE trial. However, these benefits were not clearly observed in patients with low adherence. Therefore, adherence to rivaroxaban may be crucial for achieving the maximum therapeutic effect as a monotherapy.

DATA AVAILABILITY Data are available from the corresponding author upon reasonable request.

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REFERENCES

1. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med*. 2019;381(12):1103–1113. https://doi.org/10.1056/NEJMoa1904143

2. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498. https://doi.org/10.1093/eurheartj/ehaa612

3. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence. *Circulation*. 2009;119(23):3028–3035. https://doi.org/10.1161/CIRCULATIONAHA.108.768986

4. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2021;42(34):3227–3337. https://doi.org/10.1093/eurheartj/ehab484

5. Valgimigli M, Frigoli E, Vranckx P, et al. Impact of medication nonadherence in a clinical trial of dual antiplatelet therapy. *J Am Coll Cardiol*. 2022;80(8):766–778. https://doi.org/10.1016/j.jacc.2022.04.065

6. Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol*. 2016;68(8):789–801. https://doi.org/10.1016/j.jacc.2016.06.005

7. Ozaki AF, Choi AS, Le QT, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2020;13(3):e005969. https://doi.org/10.1161/CIRCOUTCOMES.119.005969

8. Rymer JA, Chiswell K, Young L, et al. Analysis of oral anticoagulant dosing and adherence to therapy among patients with nonvalvular atrial fibrillation. *JAMA Netw Open*. 2023;6(6):e2317156. https://doi.org/10.1001/jamanetworkopen.2023.17156

9. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation. *Stroke*. 2018;49(1):98–106. https://doi.org/10.1161/STROKEAHA.117.018395

10. Du L, Cheng Z, Zhang Y, Li Y, Mei D. The impact of medication adherence on clinical outcomes of coronary artery disease: a meta-analysis. *Eur J Prev Cardiol*. 2017;24(9):962–970. https://doi.org/10.1177/2047487317695628

11. Kim D, Yang PS, Jang E, et al. The optimal drug adherence to maximize the efficacy and safety of non-vitamin K antagonist oral anticoagulant in real-world atrial fibrillation patients. *EP Europace*. 2020;22(4):547–557. https://doi.org/10.1093/europace/euz273

12. Yang SY, Kang DW, Nam JH, et al. Adherence is an optimal factor for maximizing the effective and safe use of oral anticoagulants in patients with atrial fibrillation. *Sci Rep*. 2022;12(1):3413. https://doi.org/10.1038/s41598-022-07316-y

13. Yasuda S, Kaikita K, Ogawa H, et al. Atrial fibrillation and ischemic events with rivaroxaban in patients with stable coronary artery disease (AFIRE): protocol for a multicenter, prospective, randomized, open-label, parallel group study. *Int J Cardiol*. 2018;265:108–112. https://doi.org/10.1016/j.ijcard.2018.04.131

14. Khatib R, Marshall K, Silcock J, Forrest C, Hall AS. Adherence to coronary artery disease secondary prevention medicines: exploring modifiable barriers. *Open Heart*. 2019;6(2):e000997. https://doi.org/10.1136/openhrt-2018-000997

15. Suzuki T, Shiga T, Omori H, Tatsumi F, Nishimura K, Hagiwara N. Adherence to medication and characteristics of Japanese patients with nonvalvular atrial fibrillation. *J Cardiol*. 2017;70(3):238–243. https://doi.org/10.1016/j.jjcc.2016.11.009

16. Garcia RA, Spertus JA, Benton MC, et al. Association of medication adherence with health outcomes in the ISCHEMIA trial. *J Am Coll Cardiol*. 2022;80(8):755–765. https://doi.org/10.1016/j.jacc.2022.05.045

17. An J, Bider Z, Luong TQ, et al. Long-term medication adherence trajectories to direct oral anticoagulants and clinical outcomes in patients with atrial fibrillation. *J Am Heart Assoc*. 2021;10(21):e021601. https://doi.org/10.1161/JAHA.121.021601

18. Chen N, Brooks MM, Hernandez I. Latent classes of adherence to oral anticoagulation therapy among patients with a new diagnosis of atrial fibrillation. *JAMA Netw Open*. 2020;3(2):e1921357. https://doi.org/10.1001/jamanetworkopen.2019.21357

19. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J*. 2014;35(46):3267–3276. https://doi.org/10.1093/eurheartj/ehu364

20. Di Martino M, Alagna M, Lallo A, et al. Chronic polytherapy after myocardial infarction: the trade-off between hospital and community-based providers in determining adherence to medication. *BMC Cardiovasc Disord*. 2021;21(1):180. https://doi.org/10.1186/s12872-021-01969-9

21. Akao M, Tsuji H, Kusano K, et al. Clinical characteristics and outcomes of Japanese atrial fibrillation patients with poor medication adherence: a sub-analysis of the GENERAL study. *J Cardiol*. 2023;81(2):209–214. https://doi.org/10.1016/j.jjcc.2022.07.022

22. Samama MM, Contant G, Spiro TE, et al. Laboratory assessment of rivaroxaban: a review. *Thromb J*. 2013;11(1):11. https://doi.org/10.1186/1477-9560-11-11

23. Millenaar D, Schumacher H, Brueckmann M, et al. Cardiovascular outcomes according to polypharmacy and drug adherence in patients with atrial fibrillation on long-term anticoagulation (from the RE-LY trial). *Am J Cardiol*. 2021;149:27–35. https://doi.org/10.1016/j.amjcard.2021.03.024

24. Valgimigli M, Garcia-Garcia HM, Vrijens B, et al. Standardized classification and framework for reporting, interpreting, and analysing medication non-adherence in cardiovascular clinical trials: a consensus report from the Non-adherence Academic Research Consortium (NARC). *Eur Heart J*. 2019;40(25):2070–2085. https://doi.org/10.1093/eurheartj/ehy377

25. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–497. https://doi.org/10.1056/NEJMra050100

26. Ferdinand KC, Senatore FF, Clayton-Jeter H, et al. Improving medication adherence in cardiometabolic disease: practical and regulatory implications. *J Am Coll Cardiol*. 2017;69(4):437–451. https://doi.org/10.1016/j.jacc.2016.11.034

27. Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: a population-based retrospective cohort study. *PLoS Med*. 2018;15(6):e1002584. https://doi.org/10.1371/journal.pmed.1002584

28. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Therapeut*. 2001;23(8):1296–1310. https://doi.org/10.1016/S0149-2918(01)80109-0

29. Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence. *J Am Coll Cardiol*. 2014;64(20):2071–2082. https://doi.org/10.1016/j.jacc.2014.08.021

30. Beyer-Westendorf J, Ehlken B, Evers T. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *EP Europace*. 2016;18(8):1150–1157. https://doi.org/10.1093/europace/euv421

31. Tanigawa T, Kaneko M, Hashizume K, et al. Model-based dose selection for phase III rivaroxaban study in Japanese patients with non-valvular atrial fibrillation. *Drug Metab Pharmacokinet*. 2013;28(1):59–70.

32. Walsh CA, Bennett KE, Wallace E, Cahir C. Identifying adherence patterns across multiple medications and their association with health outcomes in older community-dwelling adults with multimorbidity. *Value Health*. 2020;23(8):1063–1071. https://doi.org/10.1016/j.jval.2020.03.016

33. Bartoli-Abdou JK, Patel JP, Vadher B, et al. Long-term adherence to direct acting oral anticoagulants and the influence of health beliefs after switching from vitamin-K antagonists: findings from the Switching Study. *Thrombos Res*. 2021;208:162–169. https://doi.org/10.1016/j.thromres.2021.11.003

34. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34(38):2940–2948. https://doi.org/10.1093/eurheartj/eht295

35. Nguyen TMU, Caze AL, Cottrell N. What are validated self-report adherence scales really measuring? A systematic review. *Br J Clin Pharmacol*. 2014;77(3):427–445. https://doi.org/10.1111/bcp.12194

36. Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease. *Arch Intern Med*. 2007;167(16):1798–1803. https://doi.org/10.1001/archinte.167.16.1798

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APPENDIX For supplemental tables and figures, please see the online version of this paper.

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