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Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

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ABSTRACT

BACKGROUND

There are limited data from randomized trials evaluating the use of antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease.

METHODS

In a multicenter, open-label trial conducted in Japan, we randomly assigned 2236 patients with atrial fibrillation who had undergone percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) more than 1 year earlier or who had angiographically confirmed coronary artery disease not requiring revascularization to receive monotherapy with rivaroxaban (a non–vitamin K antagonist oral anticoagulant) or combination therapy with rivaroxaban plus a single antiplatelet agent. The primary efficacy end point was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause; this end point was analyzed for noninferiority with a noninferiority margin of 1.46. The primary safety end point was major bleeding, according to the criteria of the International Society on Thrombosis and Hemostasis; this end point was analyzed for superiority.

RESULTS

The trial was stopped early because of increased mortality in the combination-therapy group. Rivaroxaban monotherapy was noninferior to combination therapy for the primary efficacy end point, with event rates of 4.14% and 5.75% per patient-year, respectively (hazard ratio, 0.72; 95% confidence interval [CI], 0.55 to 0.95; $P<0.001$ for noninferiority). Rivaroxaban monotherapy was superior to combination therapy for the primary safety end point, with event rates of 1.62% and 2.76% per patient-year, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; $P=0.01$ for superiority).

CONCLUSIONS

As antithrombotic therapy, rivaroxaban monotherapy was noninferior to combination therapy for efficacy and superior for safety in patients with atrial fibrillation and stable coronary artery disease. (Funded by the Japan Cardiovascular Research Foundation; AFIRE UMIN Clinical Trials Registry number, UMIN000016612; and ClinicalTrials.gov number, NCT02642419.)

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*A full list of the AFIRE investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

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THE USE OF DUAL ANTIPLATELET THERAPY (a P2Y₁₂ inhibitor plus aspirin) after percutaneous coronary intervention (PCI) reduces the risk of ischemic or atherothrombotic events, including stent thrombosis, recurrent myocardial infarction, and cardiovascular death.¹ Approximately 5 to 7% of patients with coronary artery disease who are undergoing PCI have an indication for long-term oral anticoagulant therapy.² The use of antiplatelet agents in combination with anticoagulation results in an increased risk of bleeding events, as shown recently in a nationwide Danish cohort study.³ As a consequence, the selection of the most effective anti-thrombotic treatment for patients with atrial fibrillation and stable coronary artery disease is a clinical challenge requiring careful assessment of the risks of ischemia and bleeding in each patient.²

During the past few years, research has focused on the treatment of patients with atrial fibrillation within the first 12 months after PCI.⁴⁻⁷ On the basis of these studies, current guidelines recommend triple therapy (an oral anticoagulant plus aspirin and a P2Y₁₂ inhibitor) for as short a duration as possible for the immediate anti-thrombotic treatment of patients with atrial fibrillation who have undergone PCI and for whom the ischemic risk outweighs the risk of bleeding.⁸⁻¹⁰ Such treatment is followed by combination therapy with an oral anticoagulant plus a P2Y₁₂ inhibitor for 4 to 6 weeks⁸ or up to 12 months in selected patients.^{9,10} After 12 months of combination therapy, or in patients with atrial fibrillation and stable coronary artery disease not requiring intervention, current guidelines recommend monotherapy with an oral anticoagulant.^{9,10} However, this approach has yet to be supported by evidence from randomized, controlled trials. Furthermore, substantial numbers of patients in this situation continue to be treated with combination therapy, which indicates a gap between guidelines and clinical practice.¹¹

One previous randomized, controlled trial has evaluated the efficacy and safety of monotherapy with an oral anticoagulant as compared with combination therapy with an oral anticoagulant plus a single antiplatelet agent in patients with atrial fibrillation and stable coronary artery disease more than 1 year after stenting, but this trial was underpowered and inconclusive be-

cause of the premature termination of enrollment.¹² In the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial, we aimed to investigate whether monotherapy with rivaroxaban (a non-vitamin K antagonist oral anticoagulant) is noninferior to combination therapy with rivaroxaban plus an antiplatelet agent in patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization.¹³

METHODS

TRIAL DESIGN AND OVERSIGHT

AFIRE was a multicenter, randomized, open-label, parallel-group trial. Details regarding the trial design have been described previously.¹³ Funding was provided by the Japan Cardiovascular Research Foundation under a contract with Bayer Yakuhin. The company had no role in the design of the trial, in the collection or analysis of the data, in the interpretation of the trial results, or in the writing of the manuscript. Under the guidance of the authors, Mebix, a contract research organization, provided assistance in the selection of the participating centers, supervision or monitoring of the centers, collection and storage of trial data, data analysis, interpretation of the trial results, and preparation of the manuscript. The trial was designed and led by an executive steering committee.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of the National Cerebral and Cardiovascular Center, Japan, along with the institutional review boards of all participating institutions. Data were reviewed by an independent data and safety monitoring committee. The authors vouch for the completeness and accuracy of the data and all analyses, and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

TRIAL POPULATION AND ELIGIBILITY CRITERIA

Men and women who were 20 years of age or older and had received a diagnosis of atrial fibrillation and stable coronary artery disease were enrolled in Japan. During screening, we eval-

ated the patients on a CHADS₂ scale, which ranges from 0 to 6, with a higher score indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or transient ischemic attack is assigned 2 points. The patients were required to have a score of at least 1 on the scale. The patients were also required to meet at least one of the following criteria: a history of PCI, including angioplasty with or without stenting, at least 1 year before enrollment; a history of angiographically confirmed coronary artery disease (with stenosis of $\geq 50\%$) not requiring revascularization; or a history of coronary-artery bypass grafting (CABG) at least 1 year before enrollment. Key exclusion criteria were a history of stent thrombosis, coexisting active tumor, and poorly controlled hypertension. All the patients provided written informed consent.

OTHER RISK EVALUATIONS

To further evaluate the risk of stroke, we used the CHA₂DS₂-VASc scale, which has been associated with improved stratification among low-risk patients. Patients are evaluated on the basis of the five criteria of the CHADS₂ scale plus three additional criteria: the presence of vascular disease, an age of 64 to 74 years, and sex. This score ranges from 0 to 9, with 2 points for an age of 75 years or older; higher scores indicate a greater risk. We also evaluated the risk of major bleeding on the HAS-BLED scale, which ranges from 0 to 9, with higher scores indicating a greater risk of bleeding.

TREATMENT

We randomly assigned the patients in a 1:1 ratio to receive either monotherapy with rivaroxaban (10 mg once daily for patients with a creatinine clearance of 15 to 49 ml per minute or 15 mg once daily for patients with a creatinine clearance of ≥ 50 ml per minute) or combination therapy with rivaroxaban at the previously stated doses plus an antiplatelet agent (either aspirin or a P2Y₁₂ inhibitor, according to the discretion of the treating physician). Details regarding the randomization procedure and the administration of the trial drugs are provided in the Supplementary Appendix, available at NEJM.org. Trial follow-up assessments were planned at baseline, at 6 months, and at the end of the trial, with ad-

ditional assessments for routine clinical care as needed. The follow-up period was planned to be at least 24 months and up to 45 months.

END POINTS

The primary efficacy end point was the composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause. Originally, the end point included only death from cardiovascular causes, but this composite was changed to include death from any cause in August 2015. The primary safety end point was major bleeding, as defined according to the criteria of the International Society on Thrombosis and Hemostasis.

Secondary end points were the individual components of the primary end point; death from any cause; a composite of ischemic cardiovascular events or death (death from any cause, myocardial infarction, unstable angina requiring revascularization, stroke, transient ischemic attack, systemic arterial embolism, venous thromboembolism, revascularization, or stent thrombosis); net adverse clinical events (death from any cause, myocardial infarction, stroke, and major bleeding); and any bleeding events. The definitions of cardiovascular and bleeding events are provided in Table S1 in the Supplementary Appendix. Blinded adjudication of the end points was conducted by an independent clinical events committee.

STATISTICAL ANALYSIS

The trial was powered to assess the noninferiority of rivaroxaban monotherapy, as compared with combination therapy, for the primary efficacy end point. The calculation of the trial sample size is provided in the Supplementary Appendix. We estimated that the enrollment of 2200 patients and the occurrence of at least 219 primary efficacy end points were required.

The primary efficacy analysis was based on the modified intention-to-treat approach. This population included all the patients who had undergone randomization after the exclusion of patients who had a technical reason for not participating in the trial. We used the Kaplan-Meier method to estimate cumulative event rates, with incidence rates in each treatment group shown as percentages per patient-year. A Cox proportional-hazards model was used to compare outcomes between the two groups, with the results ex-

pressed as a hazard ratio with a 95% confidence interval. We used a one-sided alpha level of 0.025 to analyze the noninferiority of rivaroxaban monotherapy, as compared with combination therapy, with a noninferiority margin of 1.46.

If noninferiority was shown for the primary efficacy end point, a closed testing procedure was to be conducted to determine superiority for the primary safety end point. The primary analysis of the safety end points was performed in the safety population, which included the patients who had undergone randomization and received at least one dose of a trial drug during the follow-up period.

An assessment of superiority for the primary efficacy end point, which was not prespecified before the database lock, was performed after the demonstration of noninferiority for efficacy and superiority for the primary safety end point. Secondary end points are reported with hazard ratios and 95% confidence intervals. The confidence intervals have not been adjusted for multiple comparisons, so inferences drawn from these intervals may not be reproducible. All the statistical analyses were performed with the use of SAS software, version 9.4 for Windows (SAS Institute).

RESULTS

PATIENTS

From February 23, 2015, to September 30, 2017, a total of 2240 patients were enrolled at 294 centers; of these patients, 2236 underwent randomization, and 2215 patients (1107 in the monotherapy group and 1108 in the combination-therapy group) were included in the modified intention-to-treat population (Fig. 1). At baseline, the characteristics of the patients were similar in the two treatment groups (Table 1, and Table S2 in the Supplementary Appendix). The mean age was 74 years, and 79% of the patients were men. A total of 1564 patients (70.6%) had undergone previous PCI, and 252 (11.4%) had undergone previous CABG. The median CHADS₂ score was 2, the median CHA₂DS₂-VASc score was 4, and the median HAS-BLED score was 2. Among the patients in the combination-therapy group, 778 (70.2%) received aspirin, and 297 (26.8%) received a P2Y₁₂ inhibitor (Table S3 in the Supplementary Appendix).

EARLY TERMINATION OF THE TRIAL

The evaluation of the patients was planned to continue until September 2018. However, because of a higher risk of death from any cause in the combination-therapy group, the independent data and safety monitoring committee recommended early termination of the trial in July 2018. All the patients were contacted and a final follow-up assessment was scheduled. The trial database was locked in January 2019. The median treatment duration was 23.0 months (interquartile range, 15.8 to 31.0), and the median follow-up period was 24.1 months (interquartile range, 17.3 to 31.5).

PRIMARY EFFICACY AND SAFETY END POINTS

In the modified intention-to-treat population, the primary efficacy end-point event occurred in 89 patients receiving monotherapy and in 121 patients receiving combination therapy, corresponding to incidence rates of 4.14% and 5.75% per patient-year, respectively (hazard ratio, 0.72; 95% confidence interval [CI], 0.55 to 0.95; $P<0.001$ for noninferiority) (Table 2 and Fig. 2A). The incidence of the primary safety end point was lower in the monotherapy group than in the combination-therapy group (1.62% vs. 2.76% per patient-year; hazard ratio, 0.59; 95% CI, 0.39 to 0.89; $P=0.01$) (Table 2 and Fig. 2B).

In the assessment of superiority for the primary efficacy end point (which was not a pre-specified analysis), the P value was 0.02. The results of the analyses in the safety population and the per-protocol population were consistent with the findings in the modified intention-to-treat analysis (Tables S4 and S5 in the Supplementary Appendix). A sensitivity analysis using the original efficacy end point also showed consistent results (Table S6 in the Supplementary Appendix).

SECONDARY END POINTS

The incidence of individual components of the primary end point in the two groups are provided in Table 2. All-cause mortality was lower among patients receiving monotherapy than among those receiving combination therapy, with rates of 1.85% and 3.37% per patient-year, respectively (hazard ratio, 0.55; 95% CI, 0.38 to 0.81). This was due to lower incidences of both cardio-

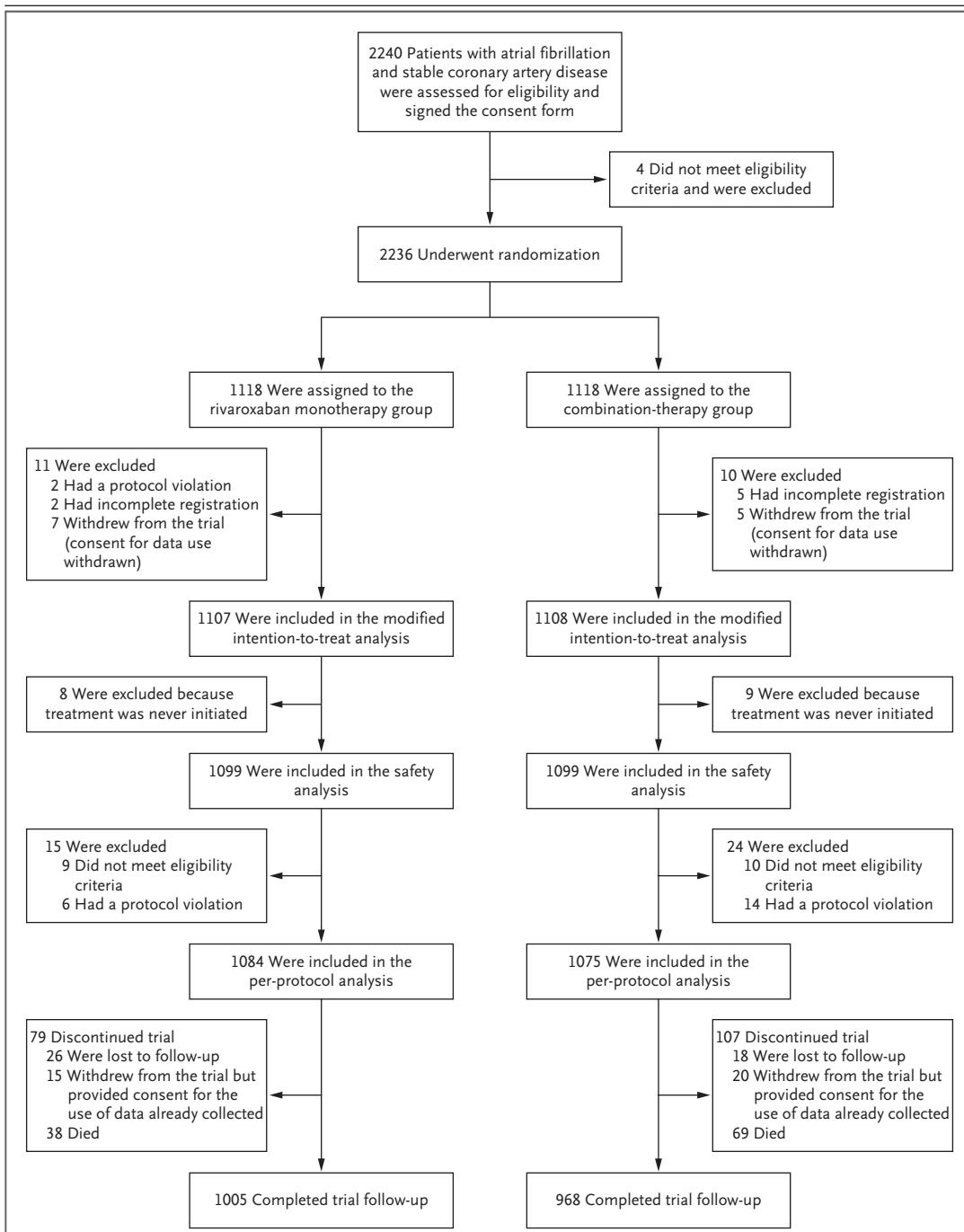


Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).^a

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

* Plus-minus values are means ±SD. There were no significant differences between the two groups in the characteristics listed. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data are missing for 75 patients in the monotherapy group and 86 patients in the combination-therapy group.

vascular death, which occurred in 1.17% of the patients in the monotherapy group and in 1.99% of those in the combination-therapy group per patient-year (hazard ratio, 0.59; 95% CI, 0.36 to 0.96), and noncardiovascular death, which occurred in 0.68% and 1.39% per patient-year, respectively (hazard ratio, 0.49; 95% CI, 0.27 to 0.92). The most frequent causes of death were heart failure (6 patients in the monotherapy group and 10 in the combination-therapy group), stroke (2 vs. 10 patients), and cancer (6 vs.

13 patients) (Table S7 in the Supplementary Appendix).

The incidence of the composite end point of ischemic cardiovascular events or death was lower in the monotherapy group than in the combination-therapy group, with rates of 5.37% and 6.77% per patient-year, respectively (hazard ratio, 0.80; 95% CI, 0.62 to 1.02). The occurrence of net adverse clinical events, which was the composite of all-cause death, myocardial infarction, stroke, or major bleeding, was lower in the mono-

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

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

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

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

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

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

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

therapy group than in the combination-therapy group, with rates of 3.90% and 6.28% per patient-year, respectively (hazard ratio, 0.62; 95% CI, 0.47 to 0.82). There was a lower incidence of nonmajor bleeding events in patients receiving monotherapy than in those receiving combination therapy, with rates of 5.89% and 10.31% per patient-year, respectively (hazard ratio, 0.58; 95% CI, 0.46 to 0.72). Detailed information regarding bleeding sites is provided in Table S8 in the Sup-

plementary Appendix. There were two fatal bleeding events in each group (Table S9 in the Supplementary Appendix). Investigator-reported data regarding adverse events are provided in Tables S10 and S11 in the Supplementary Appendix.

SELECTED SUBGROUP ANALYSES

With respect to the primary efficacy end point, the effect of monotherapy, as compared with combination therapy, was generally consistent

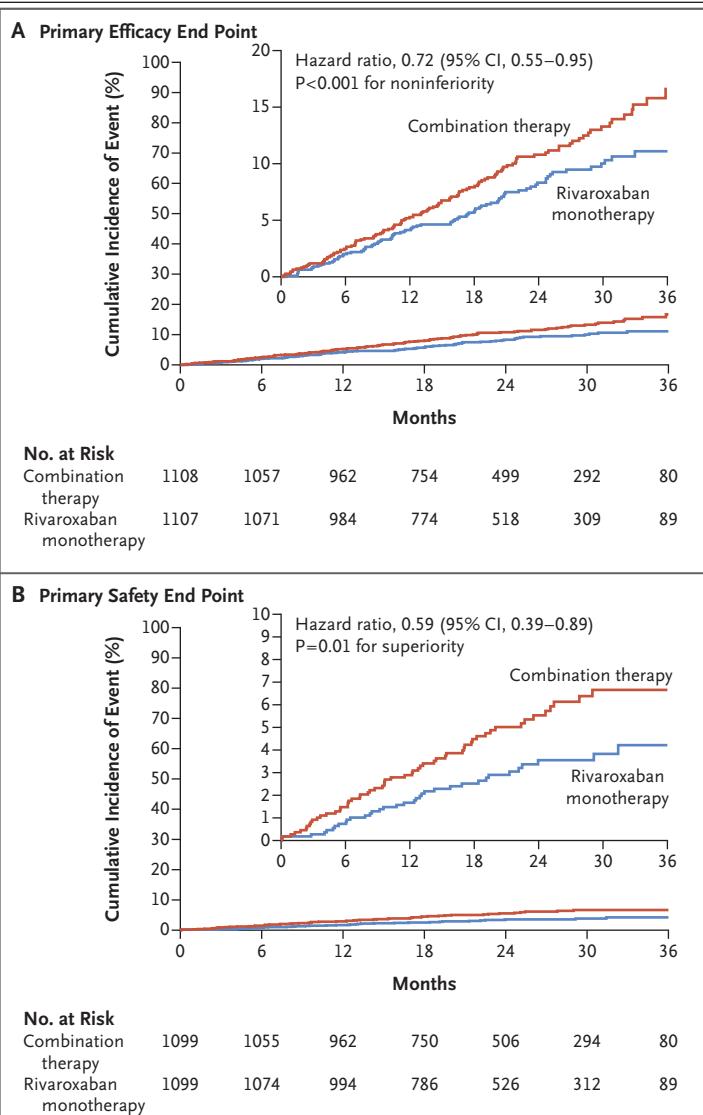


Figure 2. Primary Efficacy and Safety End Points.

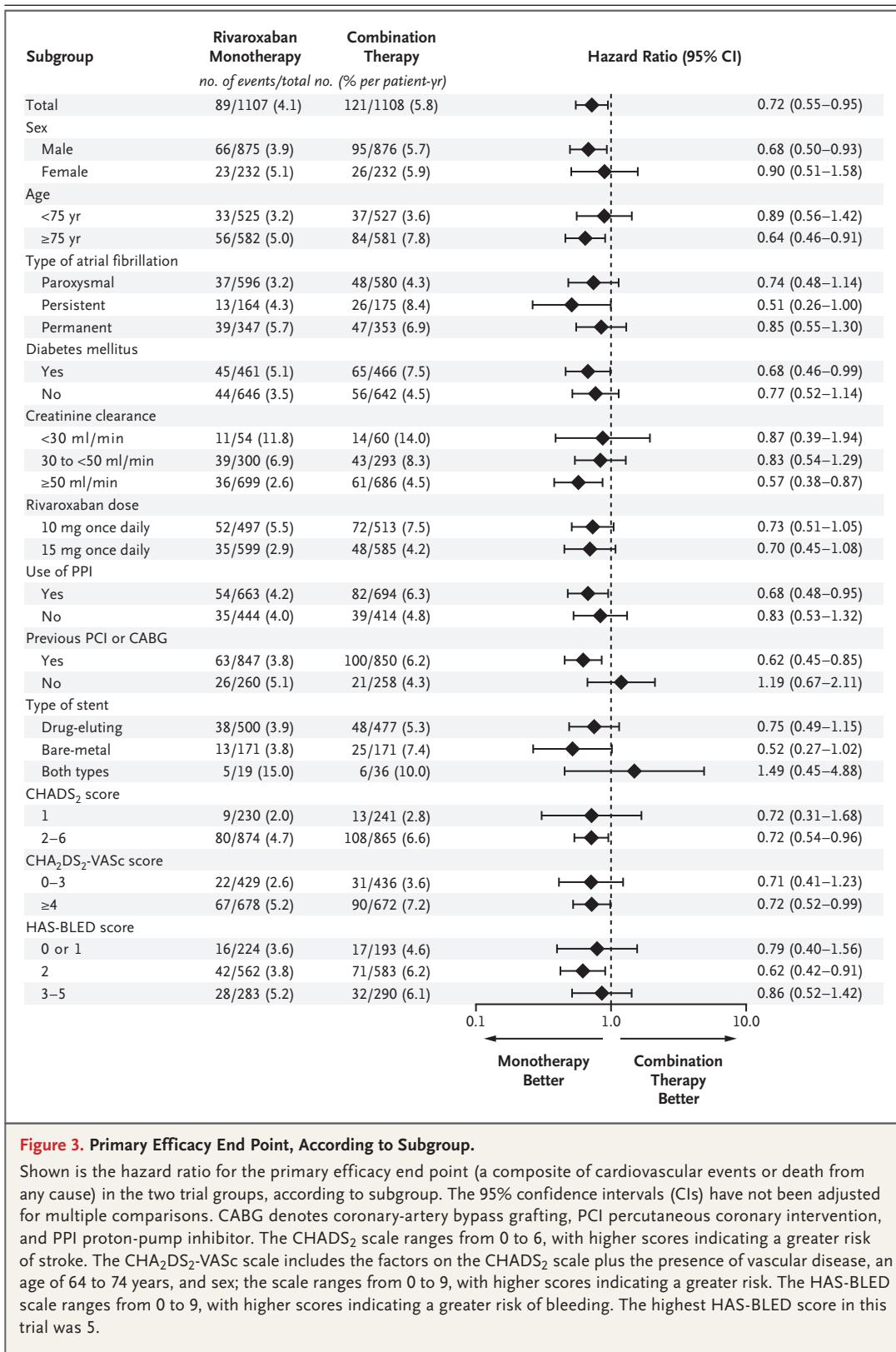
Panel A shows the primary efficacy end point — a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause — in the monotherapy group and the combination-therapy group. Panel B shows the primary safety end point of major bleeding, as defined by the criteria of the International Society on Thrombosis and Hemostasis. The inset graphs show the same data on an expanded y axis.

DISCUSSION

In the AFIRE trial, we evaluated the use of monotherapy with a non-vitamin K antagonist oral anticoagulant for antithrombotic treatment in patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization. The trial met its primary objective of showing the noninferiority of rivaroxaban monotherapy, as compared with combination therapy with rivaroxaban plus antiplatelet therapy, for the composite of cardiovascular events or death from any cause. In an analysis that was not prespecified, monotherapy was superior to combination therapy for this same end point. The trial also met its primary safety end point, with use of monotherapy associated with a significantly lower rate of major bleeding events.

The trial was based on the concept that an antithrombotic regimen for patients with both atrial fibrillation and coronary artery disease should be less intensive than would be required if the regimens for both conditions were combined. This concept was studied in PIONEER AF-PCI,⁵ RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention),⁶ and AUGUSTUS,⁷ which assessed the efficacy and safety of triple therapy versus the two-agent combination of an anticoagulant plus a P2Y₁₂ inhibitor in patients with atrial fibrillation up to 1 year after PCI. All three of these trials were consistent in showing that two-agent combination therapy was at least as effective as triple therapy and was associated with a reduced risk of bleeding events. These trials have shaped current guidelines and consensus documents, which recommend combination therapy with an anticoagulant plus a P2Y₁₂ inhibitor for up to 1 year after PCI in patients with atrial fibrillation.^{8,10,14} After 1 year following PCI, guidelines in western countries recommend oral anticoagulant monotherapy.^{9,10} This recommendation was based on the findings of a national Danish cohort study.^{3,15} However, this recommendation has yet to be supported by evidence from randomized clinical trials.

across all prespecified subgroups, including those defined according to sex, age, stroke and bleeding risk scores, and renal function (Fig. 3). A similar consistency of effect was seen with respect to major bleeding events (Fig. S1 in the Supplementary Appendix).

**Figure 3. Primary Efficacy End Point, According to Subgroup.**

Shown is the hazard ratio for the primary efficacy end point (a composite of cardiovascular events or death from any cause) in the two trial groups, according to subgroup. The 95% confidence intervals (CIs) have not been adjusted for multiple comparisons. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, and PPI proton-pump inhibitor. The CHADS₂ scale ranges from 0 to 6, with higher scores indicating a greater risk of stroke. The CHA₂DS₂-VASc scale includes the factors on the CHADS₂ scale plus the presence of vascular disease, an age of 64 to 74 years, and sex; the scale ranges from 0 to 9, with higher scores indicating a greater risk. The HAS-BLED scale ranges from 0 to 9, with higher scores indicating a greater risk of bleeding. The highest HAS-BLED score in this trial was 5.

In one randomized clinical trial, OAC-ALONE (Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stent),¹² investigators evaluated the use of oral anticoagulant monotherapy in patients with atrial fibrillation and stable coronary artery disease at more than 1 year after stenting. However, only one quarter of the patients who were enrolled in OAC-ALONE were treated with non-vitamin K antagonist oral anticoagulants, in contrast to the AFIRE trial, in which all the patients received rivaroxaban. Furthermore, OAC-ALONE was underpowered and inconclusive because of premature termination of enrollment.

The AFIRE trial completed enrollment as planned and had appropriate statistical power to examine the use of monotherapy with a non-vitamin K antagonist oral anticoagulant in this population.¹³ These anticoagulants have several advantages over warfarin, including an improved efficacy and safety profile, a predictable anti-coagulant effect without the need for routine coagulation monitoring, and lower risks of food and drug interactions, intracranial hemorrhage, and death.^{16,17} Our results support the general concept that rivaroxaban monotherapy without anti-platelet therapy is the better approach in this population on the basis of both efficacy and safety.

Some limitations of our trial should be noted. The open-label design had the potential to introduce bias; however, all the events for which medical attention was sought were adjudicated by the members of an independent committee who were unaware of trial-group assignments. There were relatively high rates of withdrawal of consent and loss of patients to follow-up. However, these values were within the 5% rate of discontinuation that was anticipated (Table S12 in the Supplementary Appendix) and were consistent between the two groups. The trial population received the rivaroxaban dose approved in Japan (10 mg or 15 mg once daily, according to the patient's creatinine clearance)¹⁸ rather than the globally approved once-daily dose of 20 mg. However, pharmacokinetic modeling has shown that the level of rivaroxaban in blood samples obtained from Japanese patients who were taking rivaroxaban at the 15-mg dose was similar to the level in white patients who were taking the 20-mg dose.¹⁹ The choice of antiplatelet regimen, either aspirin or a P2Y₁₂ inhibitor, was at the

discretion of the treating physicians, a factor that makes it uncertain whether the benefit of rivaroxaban monotherapy applies equally to the two combination regimens. The early termination of the trial because of an increased risk of death from any cause in the combination-therapy group may overestimate the efficacy data. Finally, the reductions in the rate of ischemic events and death from any cause with rivaroxaban monotherapy were unanticipated and are difficult to explain on the basis of the biologic effects of antithrombotic therapy; these findings may be due to the play of chance.

In conclusion, the AFIRE trial evaluated anti-thrombotic regimens in patients with atrial fibrillation and stable coronary artery disease more than 1 year after revascularization or in those with angiographically confirmed coronary artery disease not requiring revascularization. We found that rivaroxaban monotherapy was noninferior to combination therapy with rivaroxaban plus anti-platelet therapy with respect to cardiovascular events and death from any cause and superior with respect to major bleeding.

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REFERENCES

- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998;339:1665-71.
- Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a North American perspective — 2016 update. *Circ Cardiovasc Interv* 2016;9(11):e004395.
- van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Canegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation* 2019;139:775-86.
- Dewilde WJ, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107-15.
- Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-34.
- Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513-24.
- Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;380:1509-24.
- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2019;16(8):e66-e93.
- Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60.
- Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol* 2018;34:214-33.
- Ancedy Y, Lecoq C, Saint Etienne C, et al. Antithrombotic management in patients with atrial fibrillation undergoing coronary stent implantation: what is the impact of guideline adherence? *Int J Cardiol* 2016;203:987-94.
- Matsumura-Nakano Y, Shizuta S, Komasa A, et al. Open-label randomized trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease beyond 1 year after coronary stent implantation. *Circulation* 2019;139:604-16.
- 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;265:108-12.
- Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation* 2018;138:527-36.
- Lamberts M, Gislason GH, Lip GYH, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation* 2014;129:1577-85.
- Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open Heart* 2016;3(1):e000279.
- Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330-93.
- Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation — the J-ROCKET AF Study. *Circ J* 2012;76:2104-11.
- 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;28:59-70.

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