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ABSTRACT

BACKGROUND

In patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) with placement of stents, standard anticoagulation with a vitamin K antagonist plus dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin reduces the risk of thrombosis and stroke but increases the risk of bleeding. The effectiveness and safety of anticoagulation with rivaroxaban plus either one or two antiplatelet agents are uncertain.

METHODS

We randomly assigned 2124 participants with nonvalvular atrial fibrillation who had undergone PCI with stenting to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2), or standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (group 3). The primary safety outcome was clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention).

RESULTS

The rates of clinically significant bleeding were lower in the two groups receiving rivaroxaban than in the group receiving standard therapy (16.8% in group 1, 18.0% in group 2, and 26.7% in group 3; hazard ratio for group 1 vs. group 3, 0.59; 95% confidence interval [CI], 0.47 to 0.76; P<0.001; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; P<0.001). The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar in the three groups (Kaplan–Meier estimates, 6.5% in group 1, 5.6% in group 2, and 6.0% in group 3; P values for all comparisons were nonsignificant).

CONCLUSIONS

In participants with atrial fibrillation undergoing PCI with placement of stents, the administration of either low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy. (Funded by Janssen Scientific Affairs and Bayer Pharmaceuticals; PIONEER AF-PCI ClinicalTrials.gov number, NCT01830543.)

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Approximately 5 to 8% of patients who undergo percutaneous coronary intervention (PCI) have atrial fibrillation.[1-3] Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin is superior to oral anticoagulation with a vitamin K antagonist in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent,[4] but oral anticoagulation is superior to DAPT in reducing the risk of ischemic stroke in patients with atrial fibrillation.[5] The treatment strategy for patients with atrial fibrillation who have received stents must balance the risk of stent thrombosis and ischemic stroke with the risk of bleeding. A common guideline-supported practice is to combine all three drugs in a strategy known as triple therapy[6]; however, this approach may result in excessive major bleeding, with rates of 2.2% within the first month and 4 to 12% within the first year of treatment.[7]

Novel oral anticoagulants may provide advantages over vitamin K antagonists. Rivaroxaban, an oral factor Xa inhibitor, has been associated with a lower risk of stroke and systemic embolism than vitamin K antagonists among patients with nonvalvular atrial fibrillation, with similar rates of major bleeding but significantly lower rates of intracranial hemorrhage and fatal bleeding.[8] Rivaroxaban also reduced the risk of death from cardiovascular causes, myocardial infarction, and stroke when administered as secondary prevention after an acute coronary syndrome in the ATLAS ACS 2–TIMI 51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51).[9] We conducted the PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) to compare the safety of the following three treatment strategies after PCI with stent placement in patients with paroxysmal, persistent, or permanent nonvalvular atrial fibrillation: a regimen established in the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting)[10] of low-dose rivaroxaban (15 mg once daily) plus a single $P2Y_{12}$ inhibitor, a regimen established in the ATLAS ACS 2–TIMI 51 trial of very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT, and standard triple therapy with a vitamin K antagonist plus DAPT.

Methods

Trial Oversight

PIONEER AF-PCI was an international, multicenter, randomized, open-label trial. The trial was sponsored by Janssen Scientific Affairs and Bayer Pharmaceuticals. The executive committee was responsible for the design and conduct of the trial. Although the sponsors coordinated the data management, all statistical analyses were performed independently by the PERFUSE study group, whose members used a copy of the complete raw database. The academic members of the executive committee were solely responsible for drafting the manuscript and editing all versions. All the authors made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for adherence to the trial protocol, available with the full text of this article at NEJM.org. The trial was approved by national and institutional regulatory agencies and ethics committees. An independent data and safety monitoring board monitored the scientific integrity and the safety of the trial. Complete lists of the members of the executive committee, PERFUSE study group, and data and safety monitoring board, as well as all investigators, can be found in the Supplementary Appendix, available at NEJM.org. Details of the trial design have been published previously.[11]

Trial Population

Men and women at least 18 years of age who had paroxysmal, persistent, or permanent nonvalvular atrial fibrillation (defined as atrial fibrillation not considered to be caused by a primary valve stenosis) and who had just undergone PCI with stent placement were enrolled. All participants provided written informed consent.

The main inclusion criterion was documented atrial fibrillation that occurred within 1 year before screening; patients with documented atrial fibrillation that occurred more than 1 year before screening were also eligible if the participant had been receiving oral anticoagulation for atrial fibrillation for the 3 months immediately preceding the index PCI. Major exclusion criteria were

a history of stroke or transient ischemic attack, clinically significant gastrointestinal bleeding within 12 months before randomization, a calculated creatinine clearance of less than 30 ml per minute, anemia of an unknown cause with a hemoglobin concentration of less than 10 g per deciliter, or any other condition known to increase the risk of bleeding. The complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix.

TREATMENT

Randomization occurred within 72 hours after sheath removal, once the international normalized ratio (INR) was 2.5 or lower. Before randomization, the investigator prespecified the intended duration of DAPT (1, 6, or 12 months) and the intended $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor); the participants were stratified according to the intended inhibitor type and duration of DAPT and were then randomly assigned, in a 1:1:1 ratio, to group 1, 2, or 3.

Participants in group 1 were assigned to receive rivaroxaban at a dose of 15 mg once daily (or a dose of 10 mg once daily if they had moderate renal impairment, indicated by a creatinine clearance of 30 to 50 ml per minute) plus background single antiplatelet therapy with clopidogrel at a dose of 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) for 12 months. Although aspirin could be administered up to 24 hours before the first dose of the trial drugs, aspirin at all doses was to be withheld after randomization.

Participants in group 2 were assigned to receive rivaroxaban at a dose of 2.5 mg twice daily plus background DAPT with low-dose aspirin (75 to 100 mg per day) and clopidogrel at a dose of 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) for a prespecified duration of 1, 6, or 12 months. Participants who received the treatment for 1 or 6 months then received rivaroxaban at a dose of 15 mg once daily (or 10 mg once daily if they had moderate renal impairment) plus background single antiplatelet therapy with low-dose aspirin (75 to 100 mg per day) for the remainder of the 12-month treatment period.

Participants in group 3 were assigned to receive the vitamin K antagonist warfarin once daily (with dose adjustment to achieve a target INR of 2.0 to 3.0) plus background DAPT with low-dose aspirin (75 to 100 mg per day) and clopidogrel at a dose of 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) for a prespecified duration of 1, 6, or 12 months. Participants who received the treatment for 1 or 6 months then received warfarin once daily (with dose adjustment to achieve a target INR of 2.0 to 3.0) plus background single antiplatelet therapy with low-dose aspirin (75 to 100 mg per day) for the remainder of the 12-month treatment period.

Rivaroxaban was provided to all participants free of charge. The antiplatelet drugs were considered to be standard therapy and were not paid for by the trial. Warfarin was provided to participants in all countries except those in which it is considered to be standard therapy (Canada, Chile, England, the Netherlands, Sweden, and the United States).

END POINTS

The primary safety end point was the occurrence of clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention; for details, see the Supplementary Appendix) during the treatment period (which was defined as the time from the first administration of a trial drug to 2 days after the trial drugs were discontinued, through 12 months of therapy). Secondary end points included the incidence of each component of the primary safety end point, as well as the following efficacy end points: the occurrence of a major adverse cardiovascular event (a composite of death from cardiovascular causes, myocardial infarction, or stroke), each component of the major adverse cardiovascular event end point, and stent thrombosis. Exploratory end points included the occurrence of major bleeding defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria and the occurrence of severe bleeding defined according to the Global Utilization of Streptokinase and Tissue Plasminogen Factor for Occluded Coronary Arteries (GUSTO) criteria.

All efficacy events included in the secondary end points were adjudicated by an independent clinical events committee whose members were

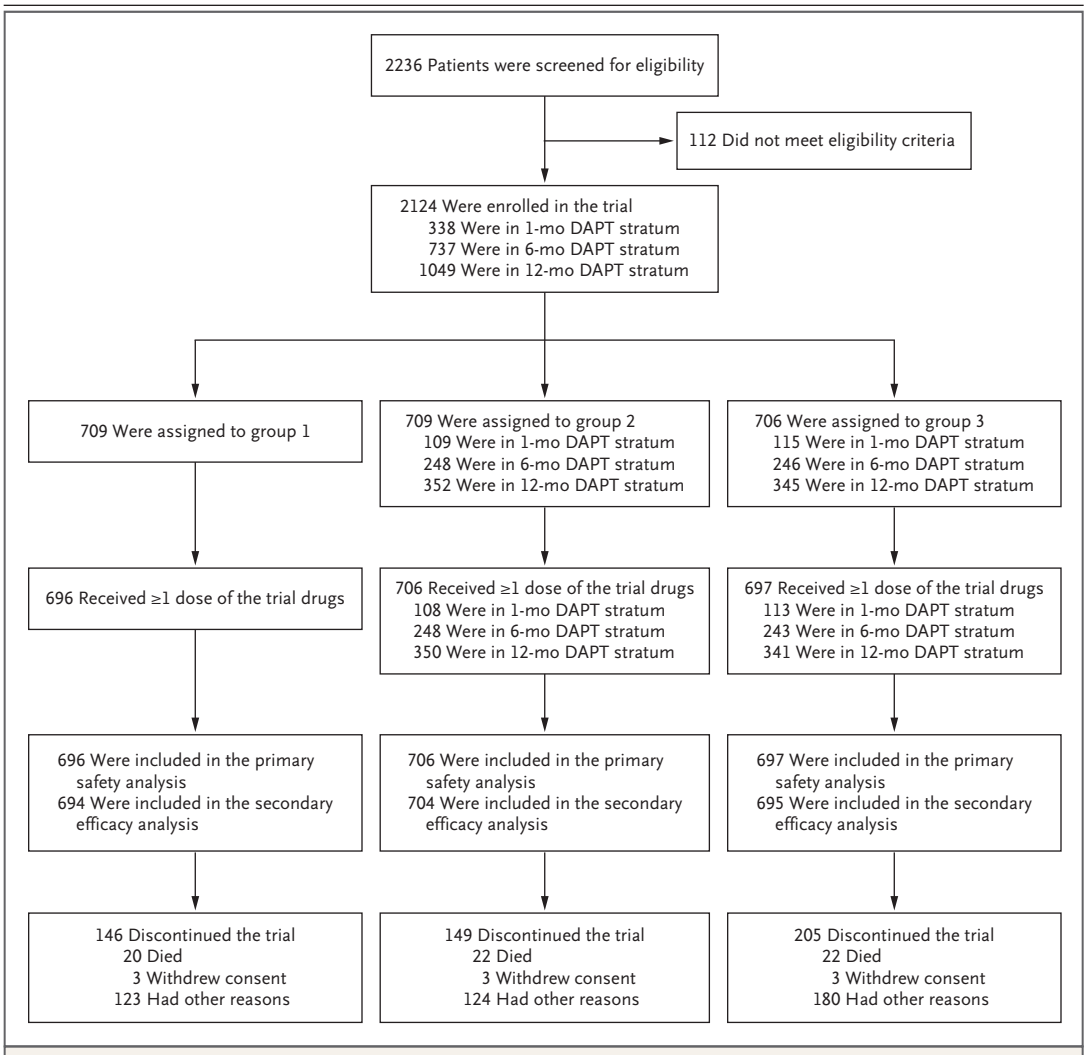


Figure 1. Stratification, Randomization, and Follow-up.

Participants were stratified according to the intended duration (1 month, 6 months, or 12 months, as specified by the investigators) of dual antiplatelet therapy (DAPT), after which they were randomly assigned to one of three groups. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. Six participants from one site (two in each group) were excluded from all secondary efficacy analyses because of violations of Good Clinical Practice guidelines.

unaware of the treatment assignments. Data on bleeding events were entered into an electronic data-capture system and were subsequently classified by type of bleeding with the use of a computer-generated algorithm that was based on 100% source-verified data. Major and minor bleeding events were adjudicated by the clinical events committee, as were 15% of bleeding events requiring medical attention; the remaining 85% were classified with the use of the algorithm only. The concordance of the algorithm with the outcomes adjudicated by the clinical events committee was monitored by the data and safety monitoring committee on an ongoing basis (Fig. S2 in the Supplementary Appendix).

STATISTICAL ANALYSIS

All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). Analyses were based on pooled data across all

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Group 1 (N=709)	Group 2 (N=709)	Group 3 (N=706)
Age — yr	70.4±9.1	70.0±9.1	69.9±8.7
≥65 Yr of age — no. (%)	523 (73.8)	516 (72.8)	526 (74.5)
≥75 Yr of age — no. (%)	254 (35.8)	245 (34.6)	230 (32.6)
Female sex — no. (%)	181 (25.5)	174 (24.5)	188 (26.6)
Race or ethnic group — no. (%)†			
White	662 (93.4)	671 (94.6)	664 (94.1)
Black	7 (1.0)	3 (0.4)	1 (0.1)
Asian	25 (3.5)	28 (3.9)	33 (4.7)
American Indian or Alaska Native	1 (0.1)	0	0
Other or unknown	14 (2.0)	7 (1.0)	8 (1.1)
Current smoker — no. (%)	37 (5.2)	56 (7.9)	48 (6.8)
Creatinine clearance — ml/min‡	78.3±31.3	77.5±31.8	80.7±30.0
Creatinine clearance of 30 to <60 ml/min — no./total no. (%)‡	194/674 (28.8)	196/680 (28.8)	175/668 (26.2)
Creatinine clearance of <30 ml/min — no./total no. (%)‡	8/674 (1.2)	7/660 (1.1)	2/668 (0.3)
$P2Y_{12}$ inhibitor at baseline — no. (%)			
Clopidogrel	660 (93.1)	664 (93.7)	680 (96.3)
Prasugrel	12 (1.7)	11 (1.6)	5 (0.7)
Ticagrelor	37 (5.2)	34 (4.8)	21 (3.0)
Type of index event — no./total no. (%)§			
NSTEMI	130/701 (18.5)	129/703 (18.3)	123/691 (17.8)
STEMI	86/701 (12.3)	97/703 (13.8)	74/691 (10.7)
Unstable angina	145/701 (20.7)	148/703 (21.1)	164/691 (23.7)
Type of stent — no./total no. (%)			
Drug-eluting stent	464/709 (65.4)	471/705 (66.8)	468/704 (66.5)
Bare-metal stent	231/709 (32.6)	220/705 (31.2)	224/704 (31.8)
Drug-eluting and bare-metal stents	14/709 (2.0)	14/705 (2.0)	12/704 (1.7)
Type of atrial fibrillation — no./total no. (%)			
Persistent	146/708 (20.6)	146/709 (20.6)	149/705 (21.1)
Permanent	262/708 (37.0)	238/709 (33.6)	243/705 (34.5)
Paroxysmal	300/708 (42.4)	325/709 (45.8)	313/705 (44.4)
CHA_2DS_2-VASc score — no. (%)¶			
0	11 (1.6)	10 (1.4)	7 (1.0)
1	66 (9.3)	65 (9.2)	44 (6.2)
2	112 (15.8)	93 (13.1)	96 (13.6)
3	125 (17.6)	122 (17.2)	148 (21.0)
4	138 (19.5)	153 (21.6)	174 (24.6)
5	140 (19.7)	163 (23.0)	125 (17.7)
6	93 (13.1)	85 (12.0)	91 (12.9)
7	24 (3.4)	18 (2.5)	21 (3.0)

* Plus–minus values are means ±SD. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. There were no significant differences among the three groups.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was calculated with the use of the Cockcroft–Gault equation.
§ NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
¶ A higher CHA_2DS_2-VASc score indicates a higher risk of stroke.

strata of DAPT durations (1, 6, or 12 months) within each treatment group. Modified intention-to-treat analyses were based on data for all participants who underwent randomization and received at least one dose of a trial drug during the treatment period. Intention-to-treat analyses were based on data obtained through follow-up for all participants who underwent randomization. The comparisons of group 1 versus group 3 and group 2 versus group 3 were performed simultaneously, with no adjustment to the type I error rate of 0.05. The time from the first dose of a trial drug to the first occurrence of a primary safety end-point event was analyzed with the use of a Cox proportional-hazards model, with treatment group as a covariate and with stratification according to the intended DAPT duration for the comparison of group 2 with group 3 (no stratification for the comparison of group 1 with group 3), to provide a point estimate (hazard ratio) and a two-sided 95% confidence interval. Cumulative event rates were estimated at 360 days with the use of the Kaplan–Meier method, and P values were calculated with the use of the two-sided log-rank test. Before the data were unblinded, six participants from one site (two in each group) were excluded from all secondary efficacy analyses because of violations of Good Clinical Practice guidelines but were included in the primary safety analysis. P values of less than 0.05 were considered to indicate statistical significance.

Figure 2 (facing page). Cumulative Incidence of the Primary Safety End Point and a Secondary Efficacy End Point.

Panel A shows the cumulative incidence of the primary safety end point of clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention), and Panel B shows the cumulative incidence of the secondary efficacy end point of major adverse cardiovascular events (a composite of death from cardiovascular causes, myocardial infarction, or stroke) during the treatment period (from the time of the first administration of a trial drug up to 2 days after the trial treatment was discontinued) in the three treatment groups. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. In each panel, the inset shows the same data on an expanded y axis.

RESULTS

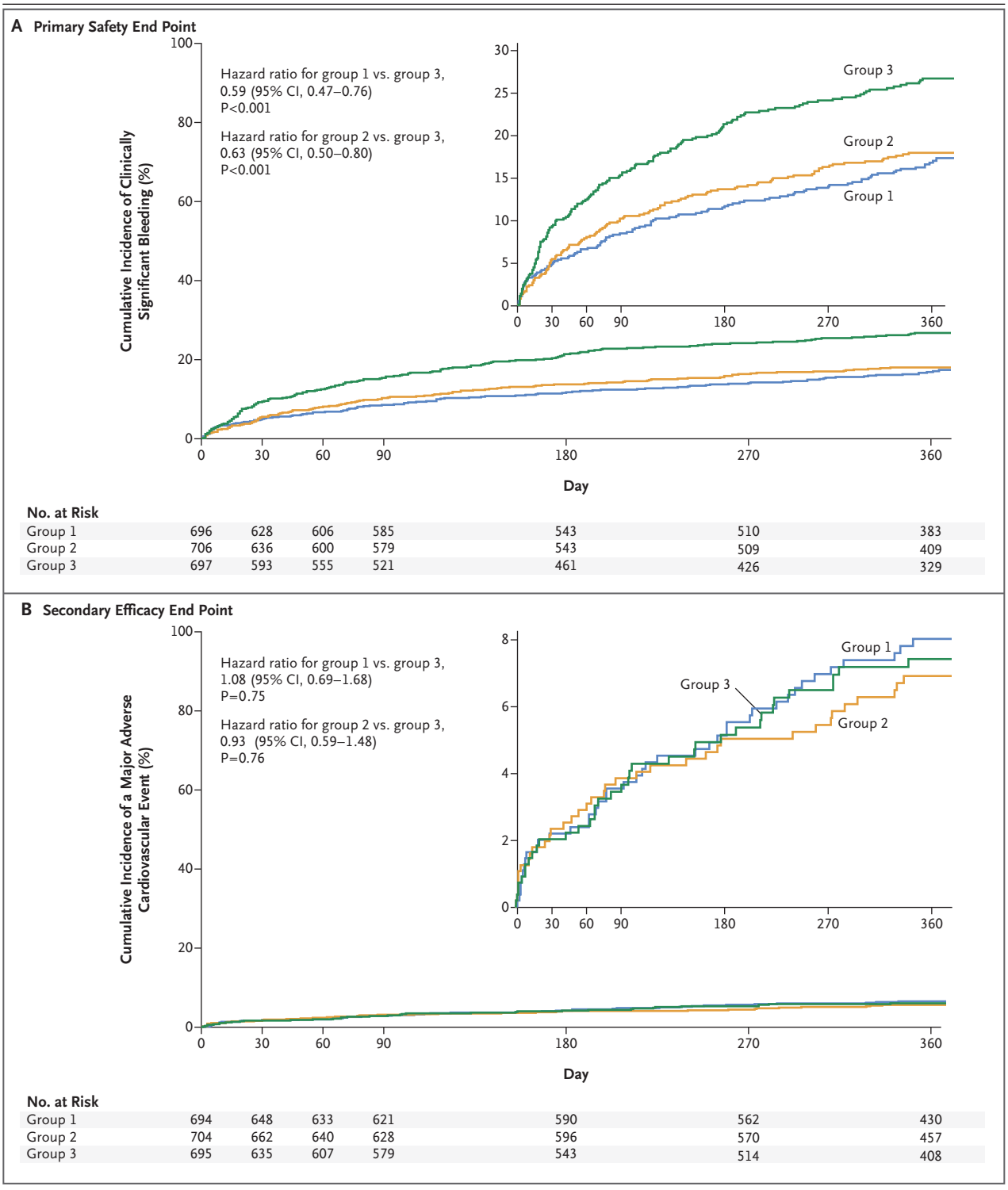
PARTICIPANTS

From May 2013 through July 2015, a total of 2124 participants were stratified according to intended DAPT duration and were then randomly assigned to one of three treatment groups (Fig. 1). Among the participants who received at least one dose of the trial treatment, 21.0% of the participants in group 1, 21.1% in group 2, and 29.4% in group 3 permanently discontinued the treatment before the scheduled termination date (P<0.001 for both comparisons [group 1 vs. group 3 and group 2 vs. group 3]) (Table S6 in the Supplementary Appendix). The rate of withdrawal of consent for continued participation in the trial was 0.4% (3 participants in each group) (P>0.99 for both comparisons). No participants were lost to follow-up.

The baseline characteristics were well matched across the treatment groups (Table 1). Most of the trial participants were white men. Less than 10% of the participants were enrolled in North America. The intended $P2Y_{12}$ inhibitor for the majority of participants was clopidogrel, with that drug chosen for a greater proportion of participants in group 3 than in group 1 or 2. Among participants who received a vitamin K antagonist (group 3), the time in the therapeutic range (INR range of 2.0 to 3.0) was 65.0% and did not differ by country or region (Table S7 and Fig. S4 in the Supplementary Appendix).

SAFETY END POINTS

At 12 months, the primary safety end point of clinically significant bleeding had occurred in 16.8% of participants in group 1, 18.0% in group 2, and 26.7% in group 3 (hazard ratio for group 1 vs. group 3, 0.59; 95% confidence interval [CI], 0.47 to 0.76; P<0.001; hazard ratio for group 2 vs. group 3, 0.63; 95% CI, 0.50 to 0.80; P<0.001) (Fig. 2A and Table 2). The lower rate of bleeding in the two groups receiving rivaroxaban than in the group receiving the vitamin K antagonist was consistent across multiple subgroups (Figs. S5 and S6 in the Supplementary Appendix). The results of the intention-to-treat analysis did not differ significantly from the results of the



modified intention-to-treat analysis (Table S8 in the Supplementary Appendix).

Both groups receiving rivaroxaban had significantly lower rates of bleeding requiring medical attention than did the group receiving standard therapy, across all strata of DAPT durations (hazard ratio for group 1 vs. group 3, 0.61; 95% CI, 0.47 to 0.80; P<0.001; hazard ratio for group 2 vs.

Table 2. Cumulative Incidence of the Primary Safety End Point and Its Components, with Stratification According to Intended Duration of DAPT.*

Cohort and End Point	Group 1	Group 2	Groups 1 and 2	Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3		Groups 1 and 2 vs. Group 3	
	No. of Participants with Events (Kaplan–Meier Event Rate)				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	696	706	1402	697						
Clinically significant bleeding	109 (16.8)	117 (18.0)	226 (17.4)	167 (26.7)	0.59 (0.47–0.76)	<0.001	0.63 (0.50–0.80)	<0.001	0.61 (0.50–0.75)	<0.001
Major bleeding	14 (2.1)	12 (1.9)	26 (2.0)	20 (3.3)	0.66 (0.33–1.31)	0.23	0.57 (0.28–1.16)	0.11	0.61 (0.34–1.09)	0.09
Minor bleeding	7 (1.1)	7 (1.1)	14 (1.1)	13 (2.2)	0.51 (0.20–1.28)	0.14	0.50 (0.20–1.26)	0.13	0.51 (0.24–1.08)	0.07
Bleeding requiring medical attention	93 (14.6)	102 (15.8)	195 (15.2)	139 (22.6)	0.61 (0.47–0.80)	<0.001	0.67 (0.52–0.86)	0.002	0.64 (0.51–0.80)	<0.001
Participants assigned to DAPT for 1 mo — no.		108		113						
Clinically significant bleeding		19 (19.4)		27 (25.7)			0.68 (0.38–1.23)	0.20		
Major bleeding		1 (1.1)		5 (5.0)			0.19 (0.02–1.66)	0.10		
Minor bleeding		1 (1.2)		2 (2.0)			0.48 (0.04–5.27)	0.54		
Bleeding requiring medical attention		18 (18.4)		21 (20.4)			0.85 (0.45–1.59)	0.60		
Participants assigned to DAPT for 6 mo — no.		248		243						
Clinically significant bleeding		39 (17.5)		68 (31.2)			0.51 (0.34–0.75)	<0.001		
Major bleeding		7 (3.3)		9 (4.4)			0.74 (0.28–2.00)	0.56		
Minor bleeding		1 (0.5)		6 (2.9)			0.16 (0.02–1.32)	0.05		
Bleeding requiring medical attention		32 (14.5)		56 (26.0)			0.51 (0.33–0.79)	0.002		
Participants assigned to DAPT for 12 mo — no.		350		341						
Clinically significant bleeding		59 (17.9)		72 (23.9)			0.74 (0.52–1.04)	0.08		
Major bleeding		4 (1.3)		6 (2.1)			0.60 (0.17–2.14)	0.43		
Minor bleeding		5 (1.5)		5 (1.8)			0.91 (0.26–3.14)	0.88		
Bleeding requiring medical attention		52 (15.9)		62 (20.9)			0.75 (0.52–1.09)	0.13		

* Data are for all participants who underwent randomization and received at least one dose of the trial regimen during the treatment period. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. The primary safety end point of clinically significant bleeding was a composite of major bleeding or minor bleeding, defined according to Thrombolysis in Myocardial Infarction (TIMI) criteria, or bleeding requiring medical attention. Only one event for each participant could be included in the analysis of the composite end point and in the analyses of each component of the composite end point. If a participant had more than one type of event, the first event that occurred is the event that was included in the analysis of the composite end point, but the first occurrence of each type of event was included in the analyses for each component of the composite end point. Cumulative event rates were estimated with the use of the Kaplan–Meier method, hazard ratios and 95% confidence intervals were calculated with the use of the Cox proportional-hazards model, and P values were calculated with the use of the two-sided log-rank test.

group 3, 0.67; 95% CI, 0.52 to 0.86; P=0.002). There was a lower incidence in groups 1 and 2 than in group 3 of major bleeding defined according to ISTH criteria and severe bleeding defined according to GUSTO criteria (Tables S2 and S11 in the Supplementary Appendix).

EFFICACY END POINTS

A major adverse cardiovascular event (a composite of death from cardiovascular causes, myocardial infarction, or stroke) occurred in 6.5% of the participants in group 1, 5.6% in group 2, and 6.0% in group 3 (P>0.05 for both comparisons) (Fig. 2B and Table 3). The power to detect at least a 15-percentage-point lower risk of the composite end point of a major adverse cardiovascular event with rivaroxaban than with a vitamin K antagonist with 700 participants per group was 11.4% (Table S1 in the Supplementary Appendix). The rates for each component of the end point did not differ significantly among the three treatment groups. The rates of stent thrombosis were low and similar among the three groups. The results were homogeneous across multiple subgroups, and there was no evidence of a significant modulation or interaction with respect to treatment effect (Figs. S7 and S8 in the Supplementary Appendix). The results of the intention-to-treat analysis did not differ significantly from the results of the modified intention-to-treat analysis (Table S12 in the Supplementary Appendix).

DISCUSSION

In participants with atrial fibrillation who had undergone PCI with stent placement, treatment that included either low-dose or very-low-dose rivaroxaban was associated with a lower risk of clinically significant bleeding than was standard triple therapy that included a vitamin K antagonist. The rates of major adverse cardiovascular events were similar but had broad confidence intervals among the three treatment groups.

The dose of rivaroxaban used in the management of atrial fibrillation may differ from the dose used in the management of an acute coronary syndrome. The administration of rivaroxaban at a dose of 20 mg once daily without antiplatelet agents in patients with nonvalvular atrial fibrillation was noninferior to dose-adjusted warfarin in reducing the rates of stroke and systemic embolism and of fatal and intracranial bleeding in the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[8] A reduced dose of 15 mg daily in participants with moderate impairment of renal function (i.e., a creatinine clearance of 30 to 49 ml per minute) was associated with efficacy and safety profiles similar to those seen with the 20-mg dose in participants without renal impairment. However, both the 15-mg and 20-mg doses of rivaroxaban for atrial fibrillation were associated with a significantly increased risk of bleeding if administered concomitantly with DAPT in the ATLAS ACS–TIMI 46 trial.[12] Indeed, the addition of rivaroxaban at a daily dose of 10 mg to DAPT in participants with an acute coronary syndrome was associated with excessive bleeding, including a higher risk of fatal bleeding than that associated with a daily dose of 5 mg.[9,12] Thus, patients with an acute coronary syndrome who are receiving DAPT may be unable to safely receive the doses of rivaroxaban that are traditionally administered in patients with atrial fibrillation. In the ATLAS ACS 2–TIMI 51 trial, among participants with an acute coronary syndrome who were receiving DAPT, the addition of a very low dose of rivaroxaban (2.5 mg twice daily) was associated with lower rates of death from cardiovascular causes, myocardial infarction, and stroke than was DAPT alone.[9]

The WOEST trial was a randomized trial that compared the safety and efficacy of clopidogrel plus warfarin with those of clopidogrel plus aspirin and warfarin (triple therapy) among 573 patients undergoing PCI who required anticoagulation. The group receiving clopidogrel plus warfarin had significantly lower rates of any bleeding through 1 year after PCI than did the group receiving triple therapy. The PIONEER and WOEST trials differ in several regards. The PIONEER population is composed entirely of participants with atrial fibrillation, whereas only 69% (162) of the participants in the group receiving standard triple therapy in the WOEST trial had atrial fibrillation.[10] In the PIONEER trial, only 22% of the patients receiving triple therapy were treated for 1 year, whereas in the WOEST trial, 66% of such participants were treated for 1 year.[10] The shorter duration of triple therapy in PIONEER may have made it more difficult to show a reduc-

Table 3. Cumulative Incidence of Secondary Efficacy End Points, with Stratification According to Intended Duration of DAPT.*

Cohort and End Point	Group 1	Group 2	Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3	
	No. of Participants with Events (Kaplan–Meier Event Rate)			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	694	704	695				
Major adverse cardiovascular event	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Death from cardiovascular causes	15 (2.4)	14 (2.2)	11 (1.9)	1.29 (0.59–2.80)	0.52	1.19 (0.54–2.62)	0.66
Myocardial infarction	19 (3.0)	17 (2.7)	21 (3.5)	0.86 (0.46–1.59)	0.62	0.75 (0.40–1.42)	0.37
Stroke	8 (1.3)	10 (1.5)	7 (1.2)	1.07 (0.39–2.96)	0.89	1.36 (0.52–3.58)	0.53
Stent thrombosis	5 (0.8)	6 (0.9)	4 (0.7)	1.20 (0.32–4.45)	0.79	1.44 (0.40–5.09)	0.57
Major adverse cardiovascular event or stent thrombosis	41 (6.5)	36 (5.6)	36 (6.0)	1.08 (0.69–1.68)	0.75	0.93 (0.59–1.48)	0.76
Participants assigned to DAPT for 1 mo — no.		108	112				
Major adverse cardiovascular event		6 (5.8)	5 (5.2)			1.17 (0.36–3.84)	0.79
Death from cardiovascular causes		2 (2.1)	2 (2.2)			0.96 (0.13–6.80)	0.97
Myocardial infarction		3 (2.9)	1 (1.1)			2.93 (0.30–28.16)	0.33
Stroke		2 (1.9)	3 (3.1)			0.65 (0.11–3.91)	0.64
Stent thrombosis		2 (1.9)	1 (1.1)			1.97 (0.18–21.74)	0.57
Major adverse cardiovascular event or stent thrombosis		6 (5.9)	5 (5.2)			1.17 (0.36–3.84)	0.79
Participants assigned to DAPT for 6 mo — no.		248	243				
Major adverse cardiovascular event		16 (7.0)	9 (4.3)			1.72 (0.76–3.88)	0.19
Death from cardiovascular causes		6 (2.8)	4 (1.9)			1.45 (0.41–5.12)	0.57
Myocardial infarction		7 (3.0)	6 (2.9)			1.13 (0.38–3.37)	0.82
Stroke		6 (2.7)	0				0.02
Stent thrombosis		4 (1.7)	1 (0.4)			3.91 (0.44–35.02)	0.19
Major adverse cardiovascular event or stent thrombosis		16 (7.0)	9 (4.3)			1.72 (0.76–3.40)	0.19
Participants assigned to DAPT for 12 mo — no.		348	340				
Major adverse cardiovascular event		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10
Death from cardiovascular causes		6 (1.9)	5 (1.7)			1.08 (0.33–3.55)	0.89
Myocardial infarction		7 (2.3)	14 (4.8)			0.44 (0.18–1.10)	0.07
Stroke		2 (0.6)	4 (1.3)			0.46 (0.08–2.51)	0.36
Stent thrombosis		0	2 (0.8)				0.10
Major adverse cardiovascular event or stent thrombosis		14 (4.5)	22 (7.4)			0.57 (0.29–1.11)	0.10

* Data are for all participants who underwent randomization and received at least one dose of the trial regimen during the treatment period; six participants from one site (two in each group) were excluded from all secondary efficacy analyses because of violations of Good Clinical Practice guidelines. Participants in group 1 were assigned to receive low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months, those in group 2 were assigned to receive very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months, and those in group 3 were assigned to receive standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months. The end point of a major adverse cardiovascular event was a composite of death from cardiovascular causes, myocardial infarction, or stroke. Only one event for each participant could be included in the analysis of the composite end point and in the analyses of each component of the composite end point. If a participant had more than one type of event, the first event that occurred is the event that was included in the analysis of the composite end point, but the first occurrence of each type of event was included in the analyses for each component of the composite end point. Cumulative event rates were estimated with the use of the Kaplan–Meier method, hazard ratios and 95% confidence intervals were calculated with the use of the Cox proportional-hazards model, and P values were calculated with the use of the two-sided log-rank test.

tion in the rate of bleeding with the rivaroxaban strategies but is more reflective of current clinical practice.

This trial has several limitations. First, the secondary analyses showed that the efficacy of each of the two doses of rivaroxaban was similar to that of standard therapy. However, the number of secondary efficacy end points in this study was small, and the trial was not powered to definitively establish either superiority or noninferiority. Using the rate for a major adverse cardiovascular event observed in the standard-therapy group of 6.0%, and assuming 90% power to detect a difference between the treatment groups of 15 percentage points at an alpha level of 0.05, we calculate that the sample size needed for a superiority trial would be 13,598 participants per group (a total of 40,794 participants across three groups). Because enrollment and follow-up in this trial involving only 2100 participants at 431 sites required 3 years, the feasibility of enrolling more than 20 times the number of participants over such a protracted period of time is questionable.

Second, the regimen of very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT is indicated in Europe and a number of other countries for the prevention of cardiovascular events in patients with an acute coronary syndrome. However, the rivaroxaban dose of 15 mg once daily (or 10 mg once daily in those with moderate renal impairment) is not currently approved for the management of an acute coronary syndrome or atrial fibrillation.

Third, for one individual component of the composite efficacy end point (stroke) within one stratum of DAPT duration (6 months), the efficacy results were significantly in favor of standard therapy versus therapy with very-low-dose rivaroxaban plus DAPT. For other components of the composite efficacy end point (myocardial infarction and the composite end point) and within another stratum of DAPT duration (12 months), the groups receiving rivaroxaban tended to have results that were superior to those in the standard-therapy group. The overall trial is underpowered, and individual efficacy end points within subgroups are even more underpowered. Even if significant results are observed, type I error or the play of chance could explain the observed results. There was no significant interaction between DAPT duration and the composite efficacy end point, all-cause stroke, or ischemic stroke (Tables S9 through S12 in the Supplementary Appendix), and therefore, evaluation of any one stratum of DAPT duration loses validity. Stratification to 1, 6, or 12 months of DAPT was based on clinician choice, and patients were not randomly assigned to a duration of DAPT. As might be expected, patient characteristics were imbalanced across the strata of DAPT durations and within each stratum of DAPT durations across the three treatment groups (Table S4 in the Supplementary Appendix). Insofar as there are differences in identified confounders, there most likely are also differences in unidentified confounders. The statistical power for all these efficacy end points was quite low, between 5.4 and 13% (Table S1 in the Supplementary Appendix). There was no adjustment for multiplicity in testing all these efficacy end points. There was a lack of consistency in the directionality of the efficacy end-point benefit with standard therapy and therapy containing rivaroxaban, which raises questions regarding the validity of any single observation. Finally, stent thrombosis was not adjudicated by a core laboratory in this trial.[13] As a result of all these limitations, it is inappropriate to draw firm conclusions regarding efficacy from these data.

Among participants with atrial fibrillation who underwent PCI with stenting, administration of either low-dose rivaroxaban (15 mg once daily) plus a $P2Y_{12}$ inhibitor for 12 months or very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months. The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy.

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