ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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ABSTRACT

BACKGROUND

Triple antithrombotic therapy with warfarin plus two antiplatelet agents is the standard of care after percutaneous coronary intervention (PCI) for patients with atrial fibrillation, but this therapy is associated with a high risk of bleeding.

METHODS

In this multicenter trial, we randomly assigned 2725 patients with atrial fibrillation who had undergone PCI to triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). Outside the United States, elderly patients (≥80 years of age; ≥70 years of age in Japan) were randomly assigned to the 110-mg dual-therapy group or the triple-therapy group. The primary end point was a major or clinically relevant nonmajor bleeding event during follow-up (mean follow-up, 14 months). The trial also tested for the noninferiority of dual therapy with dabigatran (both doses combined) to triple therapy with warfarin with respect to the incidence of a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization.

RESULTS

The incidence of the primary end point was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63; P<0.001 for noninferiority; P<0.001 for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; P<0.001 for noninferiority). The incidence of the composite efficacy end point was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for noninferiority). The rate of serious adverse events did not differ significantly among the groups.

CONCLUSIONS

Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. (Funded by Boehringer Ingelheim; RE-DUAL PCI ClinicalTrials.gov number, NCT02164864.)

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In determining the best approach for antithrombotic therapy in patients with atrial fibrillation who are undergoing percutaneous coronary intervention (PCI), it can be difficult to balance the prevention of thrombosis with the risk of bleeding.[1,2] Oral anticoagulation is indicated in patients with atrial fibrillation for the prevention of stroke and systemic embolism, whereas dual antiplatelet therapy with a $P2Y_{12}$ inhibitor plus aspirin is indicated in patients who are undergoing PCI with stent implantation for the prevention of cardiovascular events, including stent thrombosis.[3-5] Until recently, most guidelines recommended both anticoagulation and dual antiplatelet therapy (triple therapy).[3,6-9] However, studies have shown that these regimens are associated with high rates of major bleeding, and such findings have prompted efforts to seek new therapeutic strategies.[10-15]

Two new promising approaches have emerged to reduce the risk of bleeding among patients in whom both oral anticoagulation and antiplatelet therapy are indicated. The first approach is the use of non–vitamin K antagonist oral anticoagulants, the first of which was the oral direct thrombin inhibitor dabigatran. Two doses of this agent were each shown to be effective for stroke prevention among patients with atrial fibrillation, including those receiving either single or dual antiplatelet therapy.[16,17] The second approach is the omission of aspirin from the standard regimen and the use of a single $P2Y_{12}$ inhibitor in combination with an oral anticoagulant. In a moderate-sized trial involving patients who were undergoing PCI and in whom anticoagulation was indicated, the risk of bleeding (and vascular events) was lower with this dual-therapy approach than with standard triple therapy.[18] Data from another trial supported the use of triple therapy for a shortened duration.[19] Most recently, another trial showed that the risk of bleeding was lower with a regimen of reduced-dose rivaroxaban plus a $P2Y_{12}$ inhibitor than with standard triple therapy.[20-22] We conducted the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) to compare the use of two regimens of dual antithrombotic therapy that included dabigatran with the use of triple antithrombotic therapy that included warfarin among patients with atrial fibrillation who had undergone PCI.

Methods

Trial Oversight

The trial was designed and led by an executive steering committee and the sponsor (Boehringer Ingelheim) in collaboration with an international steering committee (for a complete list of committee members, see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol and amendments (available at NEJM.org) were approved by the ethics committee at each participating center. Data were reviewed regularly throughout the trial by an independent data and safety monitoring committee. The trial had an open-label design; however, all primary and secondary endpoint events were adjudicated by an independent committee whose members were unaware of the treatment assignments. The authors vouch for the accuracy and completeness of the data and analyses and the adherence of the trial to the protocol. The first draft of the manuscript was written by the first author and revised in collaboration with all the authors. Assistance with editing of the manuscript before submission was provided by a medical writer funded by Boehringer Ingelheim. All the authors made the decision to submit the manuscript for publication. Boehringer Ingelheim provided dabigatran and warfarin, served as the data coordinating center, performed site monitoring, and performed the statistical analysis (which was reviewed by the executive steering committee).

Patient Population

Men and women who were at least 18 years of age were eligible for inclusion in the trial if they had nonvalvular atrial fibrillation and had successfully undergone PCI with a bare-metal or drug-eluting stent within the previous 120 hours.[23] Nonvalvular atrial fibrillation could be paroxysmal, persistent, or permanent, but it could not be secondary to a reversible disorder unless long-term treatment with an oral anticoagulant was anticipated. Patients who had been receiving treatment with an oral anticoagulant before PCI and those who had not received oral anticoagulation were eligible. The indication for PCI could be either an acute coronary syndrome or stable

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coronary-artery disease. Key exclusion criteria were the presence of bioprosthetic or mechanical heart valves, severe renal insufficiency (creatinine clearance, <30 ml per minute), or other major coexisting conditions. A complete list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. Written informed consent was obtained from all the patients.

TREATMENTS

Patients had received standard antithrombotic treatment for the PCI procedure. After PCI, patients who were eligible for enrollment in the trial were randomly assigned to receive one of three treatments: dual therapy with dabigatran etexilate (110 mg twice daily) plus either clopidogrel or ticagrelor (110-mg dual-therapy group), dual therapy with dabigatran etexilate (150 mg twice daily) plus either clopidogrel or ticagrelor (150-mg dual-therapy group), or triple therapy with warfarin plus aspirin (≤100 mg daily) and either clopidogrel or ticagrelor (triple-therapy group). In the triple-therapy group, aspirin was discontinued after 1 month in patients in whom a bare-metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted (Fig. S1 in the Supplementary Appendix).

Randomization was performed with the use of permuted blocks, with stratification according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]) and region (United States, Japan, or other countries). All patients in the United States and nonelderly patients in other countries were randomly assigned to the 110-mg dual-therapy group, the 150-mg dual-therapy group, or the triple-therapy group in a 1:1:1 ratio. Elderly patients outside the United States were randomly assigned to the 110-mg dual-therapy group or the triple-therapy group in a 1:1 ratio; they were not eligible to be assigned to the 150-mg dual-therapy group, in accordance with the recommendations of the dabigatran label in those countries (Fig. 1).

All the patients were to receive either clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) for at least 12 months after randomization; the choice of agent was at the discretion of the investigator. The dose of warfarin was adjusted to ensure that the patient's international normalized ratio (INR) was within a range of 2.0 to 3.0. Follow-up was performed every 3 months. All the patients had an end-of-treatment visit when the trial anticoagulant (dabigatran or warfarin) was discontinued; a follow-up visit took place 4 weeks thereafter. The trial continued until all the patients had a minimum of 6 months of follow-up and the target number of end-point events was anticipated to be reached.

END POINTS

The primary end point was the first major or clinically relevant nonmajor bleeding event, as defined by the International Society on Thrombosis and Hemostasis (ISTH; detailed definitions are provided in Table S2 in the Supplementary Appendix), in a time-to-event analysis.[24] A main secondary end point was a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization (PCI or coronary-artery bypass grafting). Other secondary end points included a combined end point of thromboembolic events or death, as well as the individual thromboembolic events and definite stent thrombosis. For detailed definitions of the end points and a list of other safety end points, see Tables S3 and S4 in the Supplementary Appendix. All clinical end-point events were adjudicated by an independent committee whose members were unaware of the treatment assignments. Subgroup analyses were planned across major subgroups.

STATISTICAL ANALYSIS

The trial was designed to test the two safety hypotheses that dual therapy with dabigatran at a dose of 110 mg twice daily and dual therapy with dabigatran at a dose of 150 mg twice daily would be noninferior to triple therapy with warfarin with respect to the primary end point. A noninferiority margin of 1.38 for the upper boundary of the 95% confidence interval was used by the Food and Drug Administration for registration trials of non–vitamin K antagonist anticoagulants to evaluate the risk of stroke or systemic embolism.[25] The same noninferiority margin was used to evaluate the risk of bleeding and thromboembolic events in this trial, because it was considered to be the most clinically relevant available reference in the absence of any other type of data.[23] The incidence of the primary end point was compared between the 110-mg dual-therapy group and the triple-therapy group with the use of a stratified Cox proportional-

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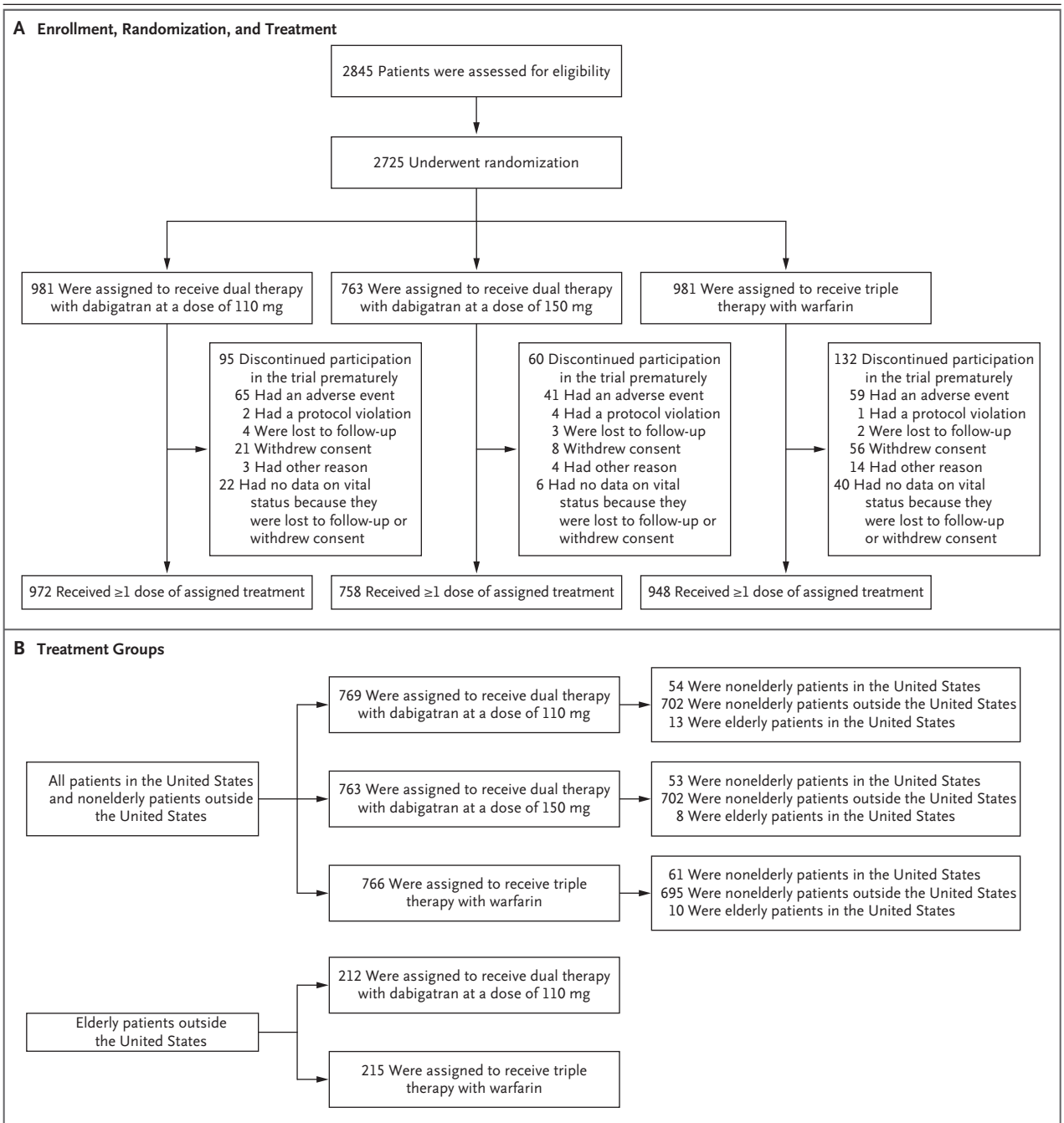


Figure 1. Enrollment, Randomization, and Treatment.

Shown is the distribution of patients during enrollment, randomization, and treatment (Panel A) and within the treatment groups according to country and age group (Panel B). Elderly was defined as 80 years of age or older (≥70 years of age in Japan), and nonelderly younger than 80 years of age (<70 years of age in Japan). Elderly patients outside the United States were not eligible to be assigned to the 150-mg dual-therapy group, in accordance with the recommendations of the dabigatran label in those countries.

hazards regression model, with stratification according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]) (see the Supplementary Appendix). The incidence of the primary end point was compared between the 150-mg dual-therapy group and the triple-therapy group with the use of an unstratified Cox proportional-hazards model. For com-

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parisons between the 150-mg dual-therapy group and the triple-therapy group, we used a corresponding triple-therapy group that included only patients who had been eligible to be assigned to the 150-mg dual-therapy group (i.e., did not include elderly patients outside the United States). Therefore, the sample sizes for the 150-mg dual-therapy group and the corresponding triple-therapy group are smaller than those for the 110-mg dual-therapy group and the complete triple-therapy group (Fig. 1). The primary analysis, which was performed on an intention-to-treat basis, included all patients who underwent randomization, regardless of whether they received treatment. A sensitivity analysis, which was performed on an on-treatment basis, included all patients who had received at least one dose of the trial anticoagulant; data on events that occurred more than 7 days after the trial anticoagulant was permanently discontinued were censored.

Assuming an event rate for the primary end point of 14% in each treatment group, we calculated that 167 patients with events per group would give the trial 83.6% power to detect the noninferiority of dual therapy with dabigatran to triple therapy with warfarin, at a one-sided alpha level of 0.025. This calculation yielded an estimated total sample size of at least 2500 patients. To control the type I error rate, a hierarchical procedure for multiple testing was used to test the major trial hypotheses. For further details, see Table S5 in the Supplementary Appendix.

In the initial protocol, a sample size of 8520 patients had been planned to allow for a coprimary end-point comparison of thromboembolic-event rates in each dual-therapy group versus the triple-therapy group; however, enrollment of this number of patients in a timely fashion was determined to be infeasible. The protocol was amended to specify the current sample size, and the comparison of thromboembolic-event rates in the two dual-therapy groups combined versus the triple-therapy group was changed to a secondary end point.

RESULTS

PARTICIPANTS

Between July 21, 2014, and October 31, 2016, a total of 2725 patients underwent randomization at 414 sites in 41 countries (for a complete list of countries, see the Supplementary Appendix). Details regarding patient disposition are shown in Figure 1. Only 6 patients (0.2%) were lost to follow-up and had no data on vital status. A total of 2.0% of the patients in the 110-mg dual-therapy group, 0.5% in the 150-mg dual-therapy group, and 3.9% in the triple-therapy group withdrew consent and had no data on vital status at the end of the trial. Details regarding the times at which patients withdrew consent are shown in Table S6 in the Supplementary Appendix. Of the patients in each treatment group who completed the trial, 130 (13.3%) in the 110-mg dual-therapy group, 99 (13.0%) in the 150-mg dual-therapy group, and 163 (16.6%) in the triple-therapy group stopped receiving the trial anticoagulant prematurely. The mean duration of treatment with the trial anticoagulant was 12.3 months, and the mean duration of follow-up was 14.0 months.

Baseline characteristics of the patients are shown in Table 1 and in Table S7 in the Supplementary Appendix. The mean age was 70.8 years (16.8% of the patients were in the elderly age group), and the index indication for PCI was an acute coronary syndrome in 50.5% of the patients. Drug-eluting stents alone were used in 82.6% of the patients. Most of the patients received clopidogrel; only 12.0% received ticagrelor. Details regarding the use of concomitant antiplatelet therapies over time are shown in Table S8 in the Supplementary Appendix. In the triple-therapy group, the mean percentage of time in the therapeutic INR range (calculated by means of the method of Rosendaal et al.[26]) was 64%.

PRIMARY END POINT

The incidence of the primary end point (the first major or clinically relevant nonmajor bleeding event) was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63; P<0.001 for noninferiority; P<0.001 for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; P<0.001 for noninferiority) (Fig. 2A and 2B and Table 2). Results of the intention-to-treat analysis were consistent with results of the on-treatment analysis and with results across major subgroups (Table S9 and Fig. S2 in the Supplementary Appendix). The rates of major bleeding alone and

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin† (N=764)
Age — yr	71.5±8.9	71.7±8.9	68.6±7.7	68.8±7.7
Elderly age group — no. (%)‡	225 (22.9)	225 (22.9)	8 (1.0)	8 (1.0)
Male sex — no. (%)	728 (74.2)	750 (76.5)	592 (77.6)	594 (77.7)
Diabetes mellitus — no./total no. (%)	362/981 (36.9)	371/980 (37.9)	260/763 (34.1)	303/763 (39.7)
Previous stroke — no./total no. (%)	74/981 (7.5)	100/980 (10.2)	52/763 (6.8)	77/763 (10.1)
CHA_2DS_2-VASc score§	3.7±1.6	3.8±1.5	3.3±1.5	3.6±1.5
HAS-BLED score¶	2.7±0.7	2.8±0.8	2.6±0.7	2.7±0.8
Creatinine clearance — ml/min‖	76.3±28.9	75.4±29.1	83.7±31.0	81.3±29.6
Previous myocardial infarction — no. (%)	237 (24.2)	268 (27.3)	194 (25.4)	211 (27.6)
Previous PCI — no./total no. (%)	326/981 (33.2)	347/980 (35.4)	239/763 (31.3)	272/763 (35.6)
Previous CABG — no./total no. (%)	97/981 (9.9)	111/980 (11.3)	79/763 (10.4)	87/763 (11.4)
Type of atrial fibrillation — no./total no (%)				
Persistent	174/981 (17.7)	178/980 (18.2)	132/763 (17.3)	149/763 (19.5)
Permanent	320/981 (32.6)	318/980 (32.4)	250/763 (32.8)	238/763 (31.2)
Paroxysmal	487/981 (49.6)	484/980 (49.4)	380/763 (49.8)	376/763 (49.3)
Indication for PCI — no. (%)				
Stable angina or positive stress test	433 (44.1)	429 (43.7)	320 (41.9)	339 (44.4)
Acute coronary syndrome	509 (51.9)	475 (48.4)	391 (51.2)	369 (48.3)
Staged procedure	156 (15.9)	168 (17.1)	138 (18.1)	134 (17.5)
Other	43 (4.4)	62 (6.3)	65 (8.5)	50 (6.5)
Type of stent — no./total no. (%)				
Drug-eluting	804/979 (82.1)	826/976 (84.6)	621/762 (81.5)	638/759 (84.1)
Bare-metal	148/979 (15.1)	133/976 (13.6)	123/762 (16.1)	107/759 (14.1)
Drug-eluting and bare-metal	19/979 (1.9)	12/976 (1.2)	10/762 (1.3)	9/759 (1.2)
Other	8/979 (0.8)	5/976 (0.5)	8/762 (1.0)	5/759 (0.7)

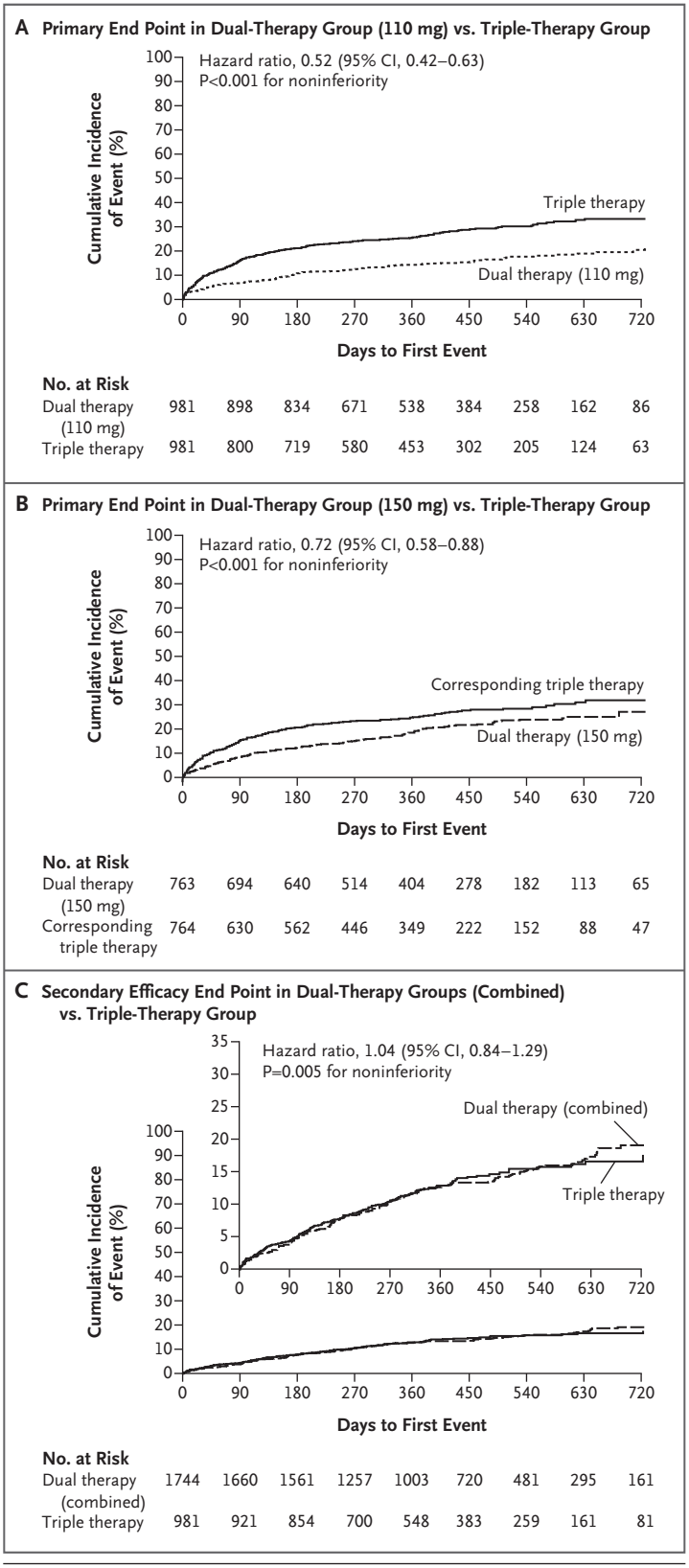
* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
† The corresponding triple-therapy group included only patients who had been eligible to be assigned to the 150-mg dual-therapy group (i.e., did not include elderly patients outside the United States).
‡ Elderly was defined as 80 years of age or older (≥70 years of age in Japan). Stratification according to age group was performed with the use of an interactive voice-response system.
§ The CHA_2DS_2-VASc score reflects the risk of stroke, with values ranging from 0 to 9 and higher scores indicating greater risk.
¶ The HAS-BLED score reflects the risk of major bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk.
‖ Creatinine clearance was calculated with the use of the Cockcroft–Gault equation. Data are missing for 91 patients in the 110-mg dual-therapy group, 80 in the triple-therapy group, 61 in the 150-mg dual-therapy group, and 63 in the corresponding triple-therapy group.

of total bleeding were significantly lower in both dual-therapy groups than in the triple-therapy group (Table 2). In addition, when major bleeding was defined according to Thrombolysis in Myocardial Infarction (TIMI) criteria, the rate was lower in both dual-therapy groups than in the triple-therapy group: 1.4% in the 110-mg dual-therapy group as compared with 3.8% in the triple-therapy group (hazard ratio, 0.37; 95% CI, 0.20 to 0.68; P=0.002) and 2.1% in the 150-mg dual-therapy group as compared with 3.9% in the corresponding triple-therapy group (hazard ratio, 0.51; 95% CI, 0.28 to 0.93; P=0.03) (Table 2). Intracranial hemorrhage was rare, but it also occurred at a lower rate in the 110-mg dual-therapy group than in the triple-therapy group (0.3% vs.

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Figure 2. Primary End Point and Secondary Efficacy End Point.

Shown is the cumulative incidence of the primary end point of major or clinically relevant nonmajor bleeding in the group that received dual therapy with dabigatran at a dose of 110 mg versus the group that received triple therapy with warfarin (Panel A) and in the group that received dual therapy with dabigatran at a dose of 150 mg versus the corresponding triple-therapy group (which did not include elderly patients outside the United States) (Panel B). Also shown is the incidence of a secondary efficacy end point of a composite of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization in the two dual-therapy groups combined versus the triple-therapy group (Panel C). In Panel C, the inset shows the same data on an enlarged y axis.



1.0%; hazard ratio, 0.30; 95% CI, 0.08 to 1.07; P=0.06) and at a lower rate in the 150-mg dual-therapy group than in the corresponding triple-therapy group (0.1% vs. 1.0%; hazard ratio, 0.12; 95% CI, 0.02 to 0.98; P=0.047).

SECONDARY EFFICACY END POINTS

The incidence of the composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard ratio, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for noninferiority) (Table 3). The incidence was 15.2% in the 110-mg dual-therapy group as compared with 13.4% in the triple-therapy group (hazard ratio, 1.13; 95% CI, 0.90 to 1.43; P=0.30) and 11.8% in the 150-mg dual-therapy group as compared with 12.8% in the corresponding triple-therapy group (hazard ratio, 0.89; 95% CI, 0.67 to 1.19; P=0.44) (Fig. S3 in the Supplementary Appendix). Results of the intention-to-treat analysis were consistent with results of the on-treatment analysis and with results across multiple subgroups of patients, including those who had an acute coronary syndrome and those who had received a drug-eluting stent (Table S10 and Fig. S5 in the Supplementary Appendix). The rate of the combined end point of thromboembolic events or death was 9.6% in the two dual-therapy groups combined as compared with 8.5% in the triple-therapy group (hazard ratio, 1.17; 95% CI,

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Table 2. Safety End Points.*

End Point	Dual Therapy with Dabigatran, 110 mg (N=981)	Triple Therapy with Warfarin (N=981)	Hazard Ratio (95% CI)	P Value†	Dual Therapy with Dabigatran, 150 mg (N=763)	Corresponding Triple Therapy with Warfarin (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*			
Primary end point: ISTH major or clinically relevant nonmajor bleeding	151 (15.4)	264 (26.9)	0.52 (0.42–0.63)	<0.001 (<0.001 for noninferiority)	154 (20.2)	196 (25.7)	0.72 (0.58–0.88)	0.002 (<0.001 for noninferiority)
ISTH major bleeding	49 (5.0)	90 (9.2)	0.52 (0.37–0.74)	<0.001	43 (5.6)	64 (8.4)	0.64 (0.43–0.94)	0.02
Total bleeding	266 (27.1)	421 (42.9)	0.54 (0.46–0.63)	<0.001	254 (33.3)	316 (41.4)	0.72 (0.61–0.84)	<0.001
Intracranial hemorrhage	3 (0.3)	10 (1.0)	0.30 (0.08–1.07)	0.06	1 (0.1)	8 (1.0)	0.12 (0.02–0.98)	0.047
TIMI major bleeding	14 (1.4)	37 (3.8)	0.37 (0.20–0.68)	0.002	16 (2.1)	30 (3.9)	0.51 (0.28–0.93)	0.03
TIMI major or minor bleeding	29 (3.0)	69 (7.0)	0.41 (0.26–0.63)	<0.001	27 (3.5)	48 (6.3)	0.53 (0.33–0.85)	0.009

* Comparisons between the 110-mg dual-therapy group and the triple-therapy group were stratified according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]). Comparisons between the 150-mg dual-therapy group and the corresponding triple-therapy group were unstratified. All end points other than the primary end point were considered to be descriptive. Details about International Society on Thrombosis and Hemostasis (ISTH) bleeding categories are provided in Table S2 in the Supplementary Appendix. TIMI denotes Thrombolysis in Myocardial Infarction.

† P values for noninferiority were calculated at a one-sided alpha level of 0.025 and are provided only if a noninferiority margin was prespecified. All other P values are for superiority and were calculated at a two-sided alpha level of 0.05.

0.90 to 1.53; P=0.11 for noninferiority). An overall summary of the hierarchical testing is shown in Figure S4 in the Supplementary Appendix.

Rates of additional efficacy end points are shown in Table 3. The absolute number of patients with definite stent thrombosis was low; events occurred in 15 patients (1.5%) in the 110-mg dual-therapy group as compared with 8 (0.8%) in the triple-therapy group (P=0.15) and in 7 patients (0.9%) in the 150-mg dual-therapy group as compared with 7 (0.9%) in the corresponding triple-therapy group (P=0.98).

SERIOUS ADVERSE EVENTS

Analyses of adverse events included patients who had received at least one dose of the trial anticoagulant. Serious adverse events that occurred during treatment were reported in 42.7% of the patients in the 110-mg dual-therapy group, 39.6% in the 150-mg dual-therapy group, and 41.8% in the triple-therapy group (Table S11 in the Supplementary Appendix). Fatal serious adverse events occurred during treatment in 38 patients (3.9%) in the 110-mg dual-therapy group, 24 (3.2%) in the 150-mg dual-therapy group, and 41 (4.3%) in the triple-therapy group. Details regarding the most common serious adverse events and adverse events that led to discontinuation of treatment are shown in Tables S12 and S13 in the Supplementary Appendix.

DISCUSSION

The RE-DUAL PCI trial showed that, among patients with atrial fibrillation who had undergone PCI, two different regimens of full-dose anticoagulation therapy with dabigatran (either 110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) resulted in a risk of major or clinically relevant nonmajor bleeding events that was significantly lower than the risk with triple therapy with warfarin; in addition, dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the composite efficacy end point of thromboembolic events, death, or unplanned revascularization. For the primary end point of major or clinically relevant nonmajor bleeding, the difference in risk between the 110-mg dual-therapy group and the triple-therapy group was 48% (11.5 percentage points) and the difference in risk between the 150-mg dual-therapy group and the correspond-

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Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

* Thromboembolic events were myocardial infarction, stroke, or systemic embolism. Unplanned revascularization was percutaneous coronary intervention or coronary-artery bypass grafting. Comparisons between the 110-mg dual-therapy group and the triple-therapy group and between the combined dual-therapy groups and the triple-therapy group were stratified according to age group (nonelderly or elderly [<80 or ≥80 years of age; <70 or ≥70 years of age in Japan]). Comparisons between the 150-mg dual-therapy group and the corresponding triple-therapy group were unstratified. All end points other than the composite efficacy end point and the combined end point of thromboembolic events or death were considered to be descriptive.

† P values for noninferiority were calculated at a one-sided alpha level of 0.025 and are provided only if a noninferiority margin was prespecified. All other P values are for superiority and were calculated at a two-sided alpha level of 0.05; these P values are provided for descriptive purposes only.

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ing triple-therapy group was 28% (5.5 percentage points) during approximately 1 year of treatment. Rates of ISTH and TIMI major bleeding were significantly lower in both dual-therapy groups than in the triple-therapy group, findings that reaffirmed the safety of dabigatran in these regimens, even at a dose of 150 mg. In the 110-mg dual-therapy group, the rate of major bleeding was significantly lower (by 4.2 percentage points) and the rate of major thromboembolic events was nonsignificantly higher (by 1.8 percentage points) than the rates in the triple-therapy group, findings that suggest a balance of the risk of bleeding with the prevention of thromboembolism. In the 150-mg dual-therapy group, the rate of major bleeding was significantly lower (by 2.8 percentage points) and the rate of major thromboembolic events was nonsignificantly lower (by 1.0 percentage point) than the rates in the corresponding triple-therapy group. These findings indicate a net clinical benefit of each of the two dual-therapy regimens, and clinicians could potentially select one of these two regimens on the basis of a patient's risk of bleeding and risk of thromboembolic events.

The strategies for dual therapy with dabigatran that we tested incorporated two changes relative to the previous standard of care (triple therapy with warfarin). First, we evaluated two doses of dabigatran, each of which has been approved worldwide for stroke prevention and has been shown to be safe and efficacious.[16] The benefits with respect to lower rates of bleeding parallel those seen previously in the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)[16] but appear to be amplified in this population of patients, who had a particularly high risk of bleeding and in whom aspirin was discontinued after PCI, at the time of randomization. As such, the RE-DUAL PCI trial is a large randomized trial that validates the concept put forth in the WOEST trial (What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting),[18] but with greater statistical power.

In the group that received triple therapy with warfarin, the duration of aspirin therapy was just 1 to 3 months; we adopted this approach in accordance with evolutions in practice and guidelines.[27,28] In effect, triple therapy shifted to dual therapy for most of the trial period; despite this factor, we found that the risk of bleeding was approximately one half and one quarter lower in the 110-mg and 150-mg dual-therapy groups, respectively, than in the triple-therapy group. The results of 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) showed that the rates of clinically significant bleeding associated with dual therapy with three-quarter-dose rivaroxaban, as well as the rates associated with triple therapy with very-low-dose rivaroxaban, were lower than the rates with triple therapy with warfarin.[20] The doses of rivaroxaban that were used in the PIONEER AF-PCI trial were lower than the dose used for stroke prevention 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).[29]

With respect to the composite efficacy end point, our prespecified criterion for noninferiority was met. This trial, which involved 2725 patients, was not powered to allow for comparisons of individual components of this end point. We thus have to exercise caution in examining the nonsignificant small numerical excesses in some components of this end point. It is important to note that we studied dabigatran doses that have previously been shown (in the RE-LY trial,[16] which involved 18,000 patients) to each provide stroke prevention in patients with atrial fibrillation. In choosing any antithrombotic regimen, it is necessary to balance the risk of bleeding with prevention of thromboembolic events. During recent years, clinical guidelines[4] and consensus statements[1,3] have evolved and now suggest that dual antithrombotic therapy is an option in this patient population (class IIb recommendation). Our findings in evaluating two regimens of dual therapy with dabigatran provide evidence that supports these changes in the guidelines for the treatment of this patient population.

There are limitations to our trial. First, we amended the protocol and enrolled a smaller number of patients than we had originally planned to enroll, and this limits the power of the trial to examine efficacy according to dabigatran dose. For the comparison of the composite efficacy end point, we combined the dual-therapy groups,

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which gave the analysis reasonable power (83.6%), and we prespecified that the comparison was part of formal hierarchical testing. Second, although our noninferiority boundary was based on previous studies of atrial fibrillation, it was used for a different end point. Finally, with respect to the results for both the bleeding and thromboembolic-event end points, we may only speculate on the relative contributions of the omission of aspirin and the type of oral anticoagulant in the dual-therapy groups and the triple-therapy group. A trial conducted with a formal 2-by-2 factorial design would be able to discern these contributions, and one such trial is ongoing (ClinicalTrials.gov number, NCT02415400).

In summary, we found that, among patients with atrial fibrillation who had undergone PCI, dual therapy with dabigatran and a $P2Y_{12}$ inhibitor resulted in a risk of bleeding events that was significantly lower than the risk with triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin; in addition, dual therapy with dabigatran was noninferior to triple therapy with warfarin with respect to the rate of thromboembolic events. In the dual-therapy regimens, each of the two doses of dabigatran led to a balance between the risk of bleeding and the prevention of thromboembolic events, which offers clinicians two additional options for the treatment of patients with varying risks of thromboembolic events and bleeding.

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APPENDIX

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