ORIGINAL ARTICLE

Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation

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ABSTRACT

BACKGROUND

Catheter ablation of atrial fibrillation is typically performed with uninterrupted anticoagulation with warfarin or interrupted non–vitamin K antagonist oral anticoagulant therapy. Uninterrupted anticoagulation with a non–vitamin K antagonist oral anticoagulant, such as dabigatran, may be safer; however, controlled data are lacking. We investigated the safety of uninterrupted dabigatran versus warfarin in patients undergoing ablation of atrial fibrillation.

METHODS

In this randomized, open-label, multicenter, controlled trial with blinded adjudicated end-point assessments, we randomly assigned patients scheduled for catheter ablation of paroxysmal or persistent atrial fibrillation to receive either dabigatran (150 mg twice daily) or warfarin (target international normalized ratio, 2.0 to 3.0). Ablation was performed after 4 to 8 weeks of uninterrupted anticoagulation, which was continued during and for 8 weeks after ablation. The primary end point was the incidence of major bleeding events during and up to 8 weeks after ablation; secondary end points included thromboembolic and other bleeding events.

RESULTS

The trial enrolled 704 patients across 104 sites; 635 patients underwent ablation. Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, −5.3 percentage points; 95% confidence interval, −8.4 to −2.2; P<0.001). Dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.

CONCLUSIONS

In patients undergoing ablation for atrial fibrillation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin. (Funded by Boehringer Ingelheim; RE-CIRCUIT ClinicalTrials.gov number, NCT02348723.)

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Catheter ablation of atrial fibrillation is a well-established treatment for symptomatic atrial fibrillation. Guidelines have incorporated catheter ablation of symptomatic atrial fibrillation as a class 1 or 2 indication, depending on previous antiarrhythmic treatment and type of atrial fibrillation.[1-3] The most important complications associated with ablation of atrial fibrillation are periprocedural stroke or transient ischemic attack (TIA) and cardiac tamponade.[3]

Systemic anticoagulation before, during, and after ablation is important in reducing the risk of periprocedural cerebrovascular events.[3] To minimize these risks, heparin should be administered during ablation to maintain an activated clotting time of more than 300 seconds. However, there is less consensus on preprocedural and postprocedural anticoagulation management.[3] Uninterrupted vitamin K antagonism during the time of ablation of atrial fibrillation is associated with a lower risk of periprocedural bleeding and stroke than stopping vitamin K antagonism and bridging with low-molecular-weight heparin.[4,5]

Preliminary safety data are available from observational studies of cohorts of patients undergoing catheter ablation with uninterrupted non–vitamin K antagonist oral anticoagulant therapy[6-17]; these data are supported by recent meta-analyses comparing periprocedural non–vitamin K antagonist oral anticoagulant therapy with uninterrupted vitamin K antagonists.[18,19] The limited systematic, prospective clinical data for non–vitamin K antagonist oral anticoagulants in the context of catheter ablation of atrial fibrillation poses a management challenge.[3,4,6-20] One exploratory controlled trial involving 248 patients showed that the uninterrupted use of a factor Xa inhibitor was feasible; the incidences of thromboembolic events and major bleeding events were low and were similar to those with uninterrupted dose-adjusted vitamin K antagonist therapy.[21]

Dabigatran etexilate (dabigatran) has efficacy and safety outcomes similar or superior to those of warfarin for stroke prevention in patients with atrial fibrillation.[22,23] The favorable safety and efficacy profile of dabigatran has been consistently confirmed by practice-based evidence from multiple sources, including two Food and Drug Administration studies and several independent scientific groups.[24-27] The RE-CIRCUIT (Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy) trial was a prospective, randomized trial investigating the safety and efficacy of a periprocedural anticoagulation regimen with uninterrupted dabigatran as compared with uninterrupted warfarin in patients undergoing ablation of atrial fibrillation.

METHODS

TRIAL DESIGN

The RE-CIRCUIT trial was a randomized, open-label, multicenter, controlled trial with blinded adjudicated end-point assessments involving patients with nonvalvular atrial fibrillation undergoing ablation of atrial fibrillation. The trial was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.[28,29] The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board or independent ethics committee at each participating center. Written informed consent was obtained from all the patients before trial entry. The trial was conducted under the guidance of a steering committee, and data (both adjudicated and nonadjudicated) were scrutinized by an independent data and safety monitoring committee. All primary and secondary end points were adjudicated by an independent committee whose members were unaware of the trial-group assignments. The trial was designed by the authors in collaboration with the sponsor (Boehringer Ingelheim). The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The development of the manuscript was led by the first author, in collaboration with all the authors. All the authors made the decision to submit the manuscript for publication. Assistance with manuscript preparation was provided by a medical writer funded by the sponsor.

TRIAL POPULATION

Full inclusion and exclusion criteria are listed in the protocol. Patients 18 years of age or older were included in the trial if they had paroxysmal or persistent nonvalvular atrial fibrillation with planned ablation of atrial fibrillation, had documented atrial fibrillation within 24 months before screening, and were eligible for treatment with dabigatran (150 mg twice daily) according to the local prescribing information. Key exclusion criteria were permanent atrial fibrillation, atrial fibrillation secondary to an obvious reversible cause, and valvular atrial fibrillation.

TREATMENT

Patients were randomly assigned in blocks (1:1 ratio) to receive either dabigatran (150 mg twice daily) or warfarin (combination of 1, 3, and 5 mg, with dose adjustment for a target international normalized ratio [INR] of 2.0 to 3.0), with no stratification. The Rosendaal method was used to evaluate the percentage of time that a patient's INR was in the therapeutic range.[30] Patients who had previously taken a vitamin K antagonist and were assigned to the warfarin group started the trial medication when the INR was less than 3.0 (<2.6 in patients at Japanese sites ≥70 years of age); dabigatran treatment was initiated when a patient's INR was less than 2.0.

The trial consisted of four sequential periods: a screening period of 0 to 2 weeks; a preablation treatment period of 4 to 8 weeks, to achieve the desired stable anticoagulation range in patients receiving warfarin; a postablation treatment period of 8 weeks (starting with the ablation procedure); and a follow-up period of 1 week (Fig. S1 in the Supplementary Appendix, available at NEJM.org). All the patients were to undergo preablation transesophageal echocardiography to rule out left atrial thrombi. The morning dose of dabigatran was taken on the day of the ablation at the patient's usual scheduled time. Ablation was performed with uninterrupted anticoagulation treatment, and anticoagulation was continued for 8 weeks after the procedure. Unfractionated heparin was administered after the placement of femoral sheaths before or immediately after transseptal puncture. During the ablation procedure, achieving and maintaining an activated clotting time of more than 300 seconds was recommended. Dabigatran administration was continued in the evening of the procedure at the scheduled time, with a minimum delay of 3 hours after sheath removal and achievement of hemostasis.

The procedure for ablation of atrial fibrillation was performed according to the recommendations and guidelines of a 2012 expert consensus statement.[3] Patients underwent ablation at the discretion of the attending electrophysiologist; the procedure included pulmonary-vein isolation and any additional substrate-modification approach typically performed in that laboratory. Radiofrequency energy was typically used; however, other energy sources such as cryoablation or laser ablation were allowed.

All the patients were to have a follow-up visit 1 week after the treatment with trial medication ended, which was 8 weeks after the ablation procedure. Any decision to continue anticoagulation with nontrial medication after the follow-up period was based on the recommendations and guidelines[1,3] and at the treating physician's discretion.

TRIAL END POINTS

Primary End Point

The primary end point was the incidence of adjudicated major bleeding events as defined by the International Society on Thrombosis and Hemostasis (ISTH).[31] Major bleeding events were considered from the start of the ablation procedure, from the first femoral puncture to up to 8 weeks after ablation. Prespecified subgroups were analyzed with the use of descriptive statistics (exploratory testing). Information on major bleeding events requiring medical attention (e.g., compression of a puncture site, the use of vitamin K or prothrombin complex concentrates, or a procedure or surgical intervention) was also collected.

Secondary End Points

The secondary efficacy and safety end points were the incidence of the following events during and up to 8 weeks after ablation: a composite of stroke, systemic embolism, or TIA; minor bleeding events; and a composite of major bleeding events and thromboembolic events (stroke, systemic embolism, or TIA). Minor bleeding events were defined as clinical bleeding events that did not fulfill ISTH criteria for major bleeding events.

ADVERSE EVENTS

All adverse events throughout the trial period were recorded and analyzed. An adverse event was defined as any untoward medical occurrence in a patient administered a trial treatment. A severe adverse event was defined as an event that was incapacitating or caused an inability to work or perform usual activities. Data on adverse events were collected from the time of signing of the informed consent, and events were further classified as serious or nonserious during the course of the trial. Efficacy and safety end points were reported only as adverse events. Because efficacy and safety end points could also be serious adverse events, these events were not reported as serious adverse events on the serious-adverse-event form to the sponsor and consequently were not reported in an expedited manner to the competent authorities.

STATISTICAL ANALYSIS

The trial had a planned enrollment of at least 290 patients per treatment group undergoing ablation across 114 international sites. Calculations were performed with the use of nQuery Advisor, version 7.0 (Statistical Solutions). The trial was exploratory because the sample required to provide sufficient power to establish formal noninferiority with an acceptable upper limit of the 95% confidence interval (e.g., 1.5) would have made the trial unfeasible (>2000 patients per group). On the basis of multiple scenarios, it was decided that a minimum of 290 patients who could be evaluated per treatment group would be enough to provide clinically meaningful information. Under the assumption of no difference in absolute rates of major bleeding events between the two treatment groups, the chosen total sample of 580 would produce a confidence interval for the difference between dabigatran and warfarin with an upper limit of 2.48%, if the absolute rate of major bleeding events were 0.59%. If the absolute rate of major bleeding events were 4.55%, the upper limit of the confidence interval of the difference would have been 4.98%.[32] To minimize any potential bias, a central randomization strategy using computer-generated sequences was implemented through an interactive computerized response system.

To provide a statistical framework to identify differences between the treatment groups, nominal P values were determined. The primary and secondary end point analyses were based on the ablation set. The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure. Point estimates for the incidence of major bleeding events and their two-sided 95% confidence intervals, based on the normal approximation of independent binomial distribution without stratification, were determined. The risk difference between dabigatran and warfarin was calculated, and the two-sided 95% confidence interval and corresponding P value were estimated. In general, adverse events were analyzed descriptively. The treated set (all randomly assigned patients who had taken ≥1 dose of trial drug) were included in the safety analysis, and the summaries were based on the actual treatment received. Statistical analysis and reporting of adverse events concentrated on events that emerged during treatment.

RESULTS

TRIAL PARTICIPANTS

The trial enrolled 704 patients across 104 sites in 11 countries from April 2015 through July 2016, of whom 678 patients underwent randomization. The ablation set included 635 patients (317 in the dabigatran group and 318 in the warfarin group) (Fig. 1). Demographic and clinical characteristics were well balanced between the treatment groups at baseline (Table 1). Dabigatran adherence was calculated on the basis of the number of capsules taken; nonadherence was recorded when adherence was not between 80% and 120% of the expected dose. Warfarin adherence was monitored with the use of the INR. The mean adherence with dabigatran was 97.6%, and patients receiving INR-adjusted warfarin were within the guideline-defined target INR range (2.0 to 3.0) for 66% of the time overall. The majority of patients (86.1% in the dabigatran group and 84.3% in the warfarin group) received trial medication for at least 8 weeks after ablation, and more than 98% received trial medication for at least 6 weeks, with no meaningful difference between the treatment groups (Table S1 in the Supplementary Appendix).

PRIMARY END POINT

There were 27 patients overall with adjudicated major bleeding events during and up to 8 weeks after ablation. The percentage of patients with major bleeding events was significantly lower in the dabigatran group than in the warfarin group (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, −5.3 percentage points; 95% confidence interval [CI], −8.4 to −2.2; P<0.001). The relative risk reduction versus warfarin was 77.2%. The robustness of the primary end point was supported by a Cox proportional-hazards analysis showing a hazard ratio of 0.22 for dabigatran versus warfarin (95% CI, 0.08 to 0.59)

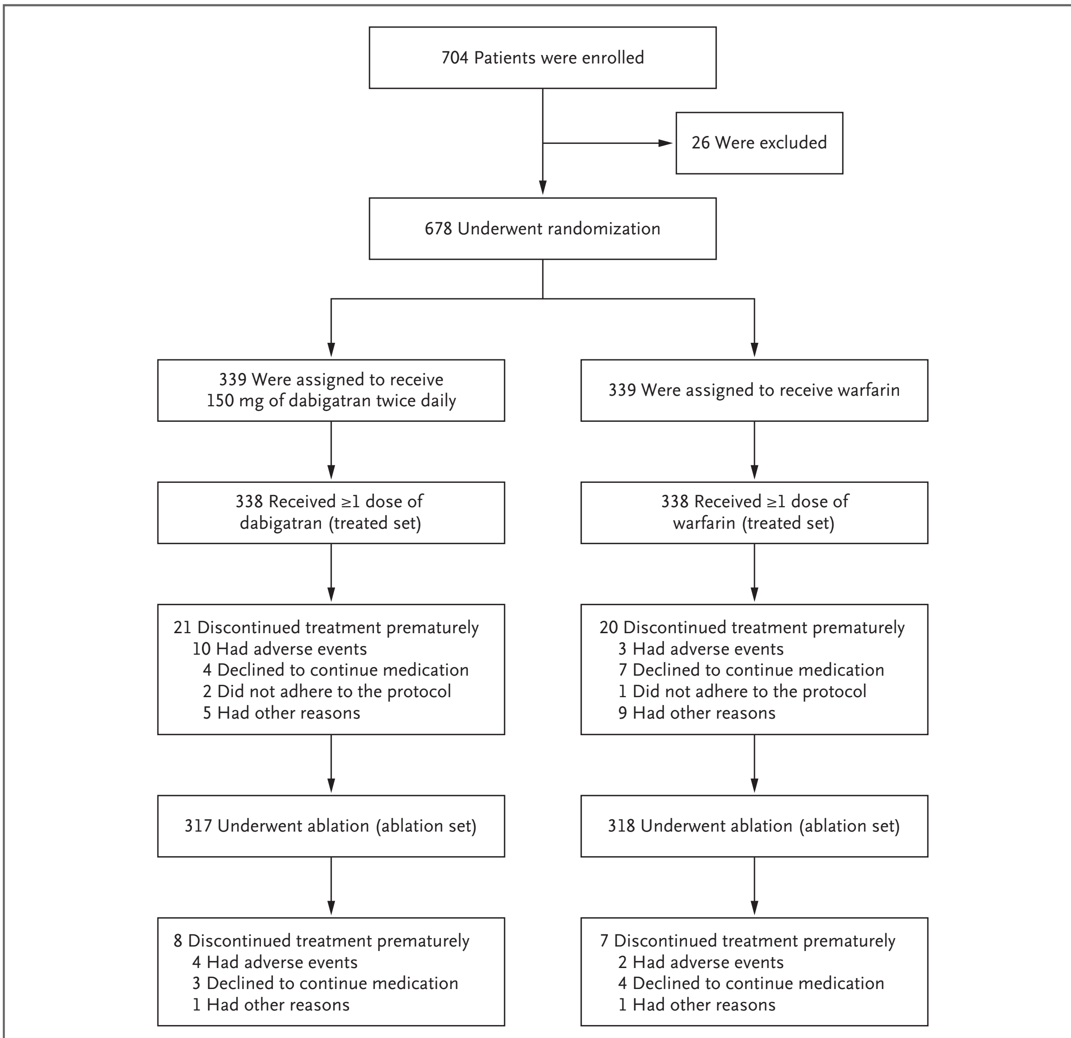


Figure 1. Enrollment, Randomization, and Follow-up.

(Fig. 2). The numbers of major bleeding events in the two groups were as follows: pericardial tamponade, 1 event in the dabigatran group and 6 events in the warfarin group; pericardial effusion, 1 and 0; groin bleeding, 2 and 2; groin hematoma, 0 and 8; intracranial bleeding, 0 and 2; pseudoaneurysm, 0 and 1; gastrointestinal bleeding, 1 and 2; and hematoma, 0 and 2 (Table S2 in the Supplementary Appendix). In particular, dabigatran was associated with fewer major bleeding events than warfarin from the time of ablation to 7 days after ablation (4 vs. 17 major bleeding events) (Table S3 in the Supplementary Appendix).

In the dabigatran group, 131 patients (41.3%) received the final dose of dabigatran less than 4 hours before the transseptal puncture, 116 patients (36.6%) 4 to less than 8 hours before the puncture, and 62 patients (19.6%) 8 hours or more before the puncture. The information was lacking for 8 patients. Two major bleeding events occurred in the "within 4 hours" group and 3 major bleeding events in the "within 4 to 8 hours" group. In the warfarin group, the mean INR at the time of the ablation was similar in patients with major bleeding events and those without such events (2.4 and 2.3, respectively). The mean intraprocedural activated clotting time in patients with major bleeding events was 374 seconds in the dabigatran group and 314 seconds in the warfarin group; in patients without major bleeding events, the time was 329 seconds in the dabigatran group and 344 seconds in the warfarin group.

Table 1. Baseline Demographic and Clinical Characteristics (Ablation Set).*

Characteristic	Dabigatran, 150 mg Twice Daily (N=317)	Warfarin (N=318)
Age — yr	59.1±10.4	59.3±10.3
Male sex — no. (%)	230 (72.6)	245 (77.0)
Mean body-mass index†	28.5	28.8
Mean CHA_2DS_2-VASc score‡	2.0	2.2
Activated clotting time		
No. of patients analyzed	312	308
Mean — sec	330	342
Medical history — no. (%)		
Congestive heart failure	31 (9.8)	34 (10.7)
Left ventricular dysfunction	25 (7.9)	23 (7.2)
Coronary artery disease	32 (10.1)	48 (15.1)
Percutaneous coronary intervention	16 (5.0)	19 (6.0)
Previous myocardial infarction	10 (3.2)	15 (4.7)
Hypertension	166 (52.4)	177 (55.7)
Previous stroke	10 (3.2)	9 (2.8)
Previous major bleeding or predisposition	3 (0.9)	4 (1.3)
Previous GI bleeding or gastritis	24 (7.6)	21 (6.6)
Renal disease	7 (2.2)	14 (4.4)
Diabetes mellitus	30 (9.5)	34 (10.7)
Atrial fibrillation — no. (%)		
Paroxysmal	213 (67.2)	219 (68.9)
Persistent	86 (27.1)	81 (25.5)
Long-standing persistent	18 (5.7)	18 (5.7)
Medication use — no. (%)§		
Vitamin K antagonists	95 (28.1)	86 (25.4)
Dabigatran	45 (13.3)	36 (10.7)
Rivaroxaban	29 (8.6)	29 (8.6)
Apixaban	21 (6.2)	30 (8.9)
Edoxaban	3 (0.9)	0
NSAIDs	66 (19.5)	78 (23.1)
Proton-pump inhibitors	73 (21.6)	79 (23.4)
Statins	106 (31.4)	101 (29.9)
Beta-blockers	195 (57.7)	204 (60.4)

* Plus–minus values are means ±SD. The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure. GI denotes gastrointestinal, and NSAID nonsteroidal antiinflammatory drug.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The CHA_2DS_2-VASc score reflects the risk of stroke among patients with atrial fibrillation. Scores range from 0 to 9, with higher scores indicating greater risk.

§ Values are for the treated set (338 patients in each group).

Subgroup analyses of the incidence of adjudicated major bleeding events during and up to 8 weeks after ablation were generally consistent with the overall results favoring the dabigatran group. Major bleeding events were, in general, less frequent in the dabigatran group irrespective of sex, age, creatinine clearance, CHA_2DS_2-VASc score (which reflects the risk of stroke among patients with atrial fibrillation), status with respect to previous hypertension, type of ablation, geographic region, and body-mass index (Fig. S2 in the Supplementary Appendix).

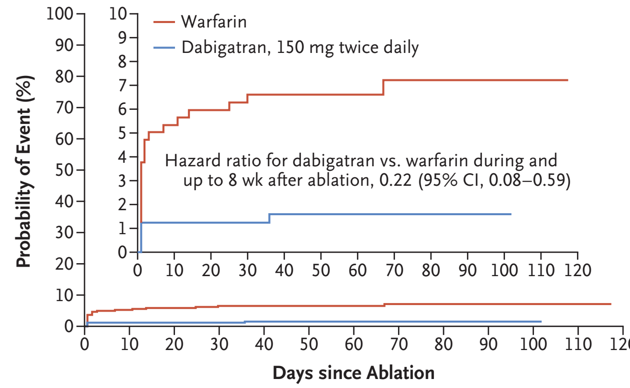
In the dabigatran group, 4 patients with a major bleeding event required medical action; only the pericardial tamponade required procedural intervention (namely, pericardial drainage). Idarucizumab, a specific dabigatran-reversal agent, was not used to treat any of the patients in the dabigatran group who required medical attention. In the warfarin group, 21 patients with a major bleeding event required medical attention, and 11 of these patients required an intervention (6 underwent pericardial drainage, 3 underwent surgical repair of the femoral artery, 1 underwent polyp removal, and 1 received a retroperitoneal intervention) (Table S3 in the Supplementary Appendix).

SECONDARY END POINTS

There were no events of stroke, systemic embolism, or TIA in the dabigatran group and only one event (TIA) in the warfarin group from the time of ablation until 8 weeks after ablation. The incidence of minor bleeding events was similar in the two treatment groups (59 patients [18.6%] in the dabigatran group and 54 patients [17.0%] in the warfarin group). The composite incidence of major bleeding events and thromboembolic events (stroke, systemic embolism, or TIA) was lower in the dabigatran group than in the warfarin group (5 patients [1.6%] vs. 23 patients [7.2%]).

ADVERSE EVENTS

Serious adverse events were reported in 18.6% of the patients in the dabigatran group and 22.2% of the patients in the warfarin group (Table S4 in the Supplementary Appendix). No fatal events were reported in either treatment group. In addition, dabigatran was associated with fewer severe adverse events (3.3% with dabigatran and 6.2% with warfarin). The incidence of adverse events leading to discontinuation of trial treatment was low in both groups (5.6% with dabigatran and 2.4% with warfarin) (Table 2). In 15 patients, the ablation procedure was canceled or postponed for a variety of investigator-identified reasons; a thrombus identified on transesophageal echocardiography was reported in 1 patient (Table S5 in the Supplementary Appendix).



No. at Risk

Dabigatran	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

Figure 2. Kaplan–Meier Plot of Time to First Adjudicated Major Bleeding Event (Ablation Set).

Major bleeding events were defined according to the International Society on Thrombosis and Hemostasis.[31] The hazard ratio was calculated with a Cox proportional-hazards model, with a Wald confidence interval. The inset shows the same data on an expanded y axis.

DISCUSSION

This multicenter, randomized, controlled trial assessed the safety and efficacy of uninterrupted dabigatran as compared with warfarin as a periprocedural anticoagulant in patients undergoing ablation of atrial fibrillation. Dabigatran was associated with a significantly lower rate of major bleeding events than INR-adjusted warfarin, and there were no differences in the incidence of stroke or systemic embolism.

One of the most feared complications of ablation of atrial fibrillation is stroke. Previous clinical trials have shown that continuous vitamin K antagonism is associated with fewer embolic events than interrupted treatment.[3,4] However, data on the use of non–vitamin K antagonist oral anticoagulants around the time of catheter ablation are limited.[15-17,21] Most electrophysiologists have interrupted the dose of non–vitamin K an-

Table 2. Adverse Events during the Treatment Period (Treated Set).*

Event	Dabigatran, 150 mg Twice Daily (N=338)	Warfarin (N=338)	Total (N=676)
		number (percent)	
Any adverse event	225 (66.6)	242 (71.6)	467 (69.1)
Severe adverse event†	11 (3.3)	21 (6.2)	32 (4.7)
Adverse event leading to treatment discontinuation	19 (5.6)	8 (2.4)	27 (4.0)
Serious adverse event	63 (18.6)	75 (22.2)	138 (20.4)
Fatal adverse event	0	0	0
Immediately life-threatening event	1 (0.3)	2 (0.6)	3 (0.4)
Event that resulted in clinically significant or persistent disability or incapacity	0	1 (0.3)	1 (0.1)
Event that required hospitalization	26 (7.7)	34 (10.1)	60 (8.9)
Event that prolonged hospitalization	13 (3.8)	22 (6.5)	35 (5.2)
Other‡	29 (8.6)	27 (8.0)	56 (8.3)

* The treated set included all randomly assigned patients who had taken at least one dose of trial drug. A patient may be counted as having an event that fulfills more than one seriousness criterion. Percentages were calculated with the total number of patients per treatment as the denominator.

† A severe adverse event was defined as an event that is incapacitating or causes an inability to work or perform usual activities.

‡ The "other" category included events deemed to be serious by the investigator in that they were important medical events that, after appropriate medical judgment, may have required medical or surgical intervention to prevent any of the outcomes mentioned previously.

tagonist oral anticoagulants before catheter ablation, out of concern that bleeding complications could lead to worse outcomes in the presence of an "irreversible" anticoagulant. High-risk patients receiving non–vitamin K antagonist oral anticoagulants often had their treatment changed over to vitamin K antagonists periprocedurally, so that ablation could be performed with continuous anticoagulation, and then were switched back to a non–vitamin K antagonist oral anticoagulant 1 to 2 months after ablation. This is because higher-risk patients, such as older patients with persistent atrial fibrillation, would have had a period of time before ablation and after sheath removal during which there was no anticoagulant present, which could increase the risk of an embolic event. However, the practice of switching anticoagulants is cumbersome for patients and physicians, and the growing use of non–vitamin K antagonist oral anticoagulants has made this approach impractical.

Cohort data suggest that interrupted and continuous non–vitamin K antagonist oral anticoagulants have similar safety and effectiveness in the context of ablation of atrial fibrillation.[33] Interpretation of the available data is limited by small samples, small numbers of events, and nonrandomized or retrospective study designs.[15-17] A recent meta-analysis including 7996 patients from 19 observational studies showed that non–vitamin K antagonist oral anticoagulants did not differ significantly from interrupted or continuous warfarin treatment with respect to the prevention of thromboembolic events but may be associated with a lower risk of overall bleeding and minor bleeding complications.[18] The only prospective, randomized clinical trial performed to date was the VENTURE-AF trial.[21] This controlled trial involving 248 patients undergoing ablation of atrial fibrillation showed that the uninterrupted use of a factor Xa inhibitor is feasible, with no meaningful difference in thromboembolic events or major bleeding events as compared with uninterrupted vitamin K antagonists. The major limitation of this trial was the small sample and low numbers of major bleeding events and thromboembolic events.

The major concern of performing catheter ablation with uninterrupted non–vitamin K antagonist oral anticoagulant therapy is the risk of bleeding, particularly life-threatening bleeding such as pericardial tamponade. In the present trial, the rate of major bleeding events was significantly lower in the dabigatran group than in the warfarin group. In particular, the rates of pericardial bleeding and groin hematoma were lower with dabigatran. The mechanism of reducing major bleeding events with dabigatran may be related to the more specific mechanism of action (direct thrombin inhibition rather than a decrease in the production of several coagulation factors) and shorter half-life of dabigatran as compared with warfarin, as well as the presence of normal levels of factor VII and a stable anticoagulation effect. Another potential advantage of the periprocedural use of dabigatran is the availability of idarucizumab, a dabigatran-specific reversal agent that can achieve an immediate and complete reversal of the anticoagulant effect.[1] However, even though this agent became available during the RE-CIRCUIT trial, all the bleeding events in the dabigatran group were managed without the need for dabigatran reversal, which is reassuring. These outcomes are consistent with the results of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial,[23] showing superiority of dabigatran (150 mg twice daily) versus a vitamin K antagonist, and of several robust and independent real-world studies that support the findings of the RE-LY trial.[34,35]

A potential limitation of our trial was the open-label design. The different dosing schedule of dabigatran, need for blood testing, and adjustments in the dose of warfarin made blinding clinically impractical. However, all outcome events were independently adjudicated by a blinded events committee. The sample size that would have been required for a formal noninferiority trial was prohibitive. However, the results observed, and the fact that dabigatran was ultimately superior to warfarin with respect to the primary end point, made our observations clinically relevant. We found that periprocedural anticoagulation with uninterrupted dabigatran (150 mg twice daily) was associated with fewer bleeding events than uninterrupted vitamin K antagonism.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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