ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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ABSTRACT

BACKGROUND

Dabigatran is an oral direct thrombin inhibitor that has been shown to be an effective alternative to warfarin in patients with atrial fibrillation. We evaluated the use of dabigatran in patients with mechanical heart valves.

METHODS

In this phase 2 dose-validation study, we studied two populations of patients: those who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier. Patients were randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. The selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

RESULTS

The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in 7 patients (4%) and 2 patients (2%), respectively. All patients with major bleeding had pericardial bleeding.

CONCLUSIONS

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. (Funded by Boehringer Ingelheim; ClinicalTrials.gov numbers, NCT01452347 and NCT01505881.)

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Prosthetic heart-valve replacement is recommended for many patients with severe valvular heart disease and is performed in several hundred thousand patients worldwide each year.[1] Mechanical valves are more durable than bioprosthetic valves[2] but typically require lifelong anticoagulant therapy. The use of vitamin K antagonists provides excellent protection against thromboembolic complications in patients with mechanical heart valves[3] but requires restrictions on food, alcohol, and drugs and lifelong coagulation monitoring. Because of the limitations of vitamin K antagonists, many patients opt for a bioprosthesis rather than a mechanical valve, despite the higher risk of premature valve failure requiring repeat valve-replacement surgery with bioprostheses.

Dabigatran etexilate (dabigatran) is an oral direct thrombin inhibitor that was shown to be effective as an anticoagulant in the treatment of patients with atrial fibrillation in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.[4-6] Prompted by these data and the promising results of studies in animals, which showed the efficacy of dabigatran in preventing valve thrombosis,[7-9] we conducted the Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN). The primary aim of RE-ALIGN was to validate a new regimen for the administration of dabigatran to prevent thromboembolic complications in patients with mechanical heart valves.[10]

Methods

Study Design and Oversight

RE-ALIGN was a prospective, randomized, phase 2, open-label trial with blinded end-point adjudication. The trial was conducted at 39 centers in 10 countries. The study design, which has been described previously,[10] was developed by the steering committee together with the sponsor, Boehringer Ingelheim. The trial protocol was approved by the ethics committee at each participating site. An independent data and safety monitoring board closely monitored the trial. The data were collected and analyzed by Boehringer Ingelheim, U.K. All drafts of the manuscript were written by all the authors, who collectively vouch for the accuracy and completeness of the results and for the fidelity of this report to the trial protocol, which is available with the full text of this article at NEJM.org.

Patients and Randomization

Trial enrollment began on November 2, 2011. Patients were eligible for inclusion if they were between the ages of 18 and 75 years and were undergoing implantation of a mechanical bileaflet valve in the aortic or mitral position or both (population A) or if they had undergone implantation of a mechanical bileaflet mitral valve (with or without mechanical bileaflet aortic-valve replacement) more than 3 months before randomization (population B). Exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. All patients provided written informed consent before enrollment.

Patients were randomly assigned to receive dabigatran or warfarin in a ratio of 2:1. Randomization was performed with the use of a 24-hour automated voice-response system.

Study-Drug Regimen

For patients in the dabigatran group, the dosing algorithm that we tested was based on a pharmacokinetic model developed in the RE-LY trial and on studies of the characteristics of dabigatran in other populations.[11-14] On the basis of these studies, we determined that a trough plasma level of 50 ng of dabigatran per milliliter or higher was desirable to prevent valve thrombosis. The starting dose of dabigatran was based on renal function, with an initial dose of 150 mg twice daily in patients with a creatinine clearance of less than 70 ml per minute, 220 mg twice daily in those with a creatinine clearance of 70 to 109 ml per minute, and 300 mg twice daily in those with a clearance of 110 ml per minute or more. We measured trough plasma levels of dabigatran at prespecified intervals and adjusted the dose to ensure a level of 50 ng per milliliter or higher (see the Supplementary Appendix for details).

Patients who had a plasma level of dabigatran that was less than 50 ng per milliliter at the highest dose of dabigatran were switched to a nonstudy vitamin K antagonist. In addition, renal function was serially monitored, and if the creatinine clearance fell below 30 ml per minute or if there was a decrease of 50% or more from the

baseline creatinine clearance, dabigatran was discontinued and a nonstudy anticoagulant was administered.

For patients in the warfarin group, the target range for the international normalized ratio (INR) was 2 to 3 in those deemed to be at low thromboembolic risk (patients who had a mechanical aortic valve with no additional risk factors) and 2.5 to 3.5 in those deemed to be at intermediate or high risk (patients who had a mechanical aortic valve with additional risk factors or a mechanical mitral valve),[15] according to local practice. The INR was monitored at prespecified intervals, with the dose of warfarin adjusted as required (see the Supplementary Appendix for details).

FOLLOW-UP AND OUTCOMES

RE-ALIGN was a 12-week trial. At the end of 12 weeks, trial participants could choose to stop the study drug and switch to a nonstudy vitamin K antagonist or they could choose to enroll in an extension trial (RE-ALIGN-EX). Participants in the extension trial continued to receive the assigned study drug for a planned interval of up to 84 months.

The primary outcome of this phase 2 trial was the trough plasma level of dabigatran, as determined on high-performance liquid chromatography–tandem mass spectrometry (see the Supplementary Appendix). Additional efficacy and safety outcomes included stroke, systemic embolism, transient ischemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death.

Valve thrombosis was defined according to the criteria of the Valve Academic Research Consortium.[16] All echocardiograms were centrally analyzed by investigators who were unaware of the study-group assignments. The definition of major bleeding was based on the criteria of the International Society on Thrombosis and Hemostasis.[17] All clinical events were defined in the study protocol and were adjudicated by an independent committee whose members were unaware of the study-group assignments.

STATISTICAL ANALYSIS

The sample-size calculation was based on validation of the dosing regimen. The trial was designed to test a dosing regimen that would result in less than 10% of patients having a dabigatran trough level below 50 ng per milliliter. On the assumption that the pharmacokinetic model of dabigatran in the RE-LY trial was applicable to patients with a mechanical heart valve, this would require a sample of 405 patients randomly assigned to receive dabigatran or warfarin in a ratio of 2:1. No formal stopping rules were specified.

Clinical outcomes were analyzed according to the intention-to-treat principle, with all patients who underwent randomization included in the analysis. Events that occurred after randomization and until November 28, 2012 (the day on which investigators were instructed to switch patients to a nonstudy vitamin K antagonist), were included in the primary analysis of clinical outcomes. Baseline data are reported as means and standard deviations for continuous data and as numbers and percentages for categorical data. Cox proportional-hazards modeling was used for efficacy and safety analyses. A P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

STUDY DISCONTINUATION

On the basis of an interim unblinded review of safety data, the data and safety monitoring board recommended discontinuation of the study for population A on October 11, 2012, and for population B on November 28, 2012, because of excess thromboembolic and bleeding events among patients in the dabigatran group. After consultation with the steering committee, the sponsor decided to terminate the trial. All participating patients discontinued the assigned study drug and were switched to a nonstudy vitamin K antagonist.

PATIENTS

Of the 252 patients who underwent randomization, 168 were assigned to receive dabigatran and 84 were assigned to receive warfarin. Baseline characteristics are summarized in Table 1. The majority of the patients (199, or 79%) were in population A. Valve location was aortic in 172 patients (68%), mitral in 71 (28%), and both in 9 (4%). A total of 74 patients (29%) were deemed to be at low risk for thromboembolic complications, and

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dabigatran (N=168)	Warfarin (N=84)
Male sex — no. (%)	107 (64)	56 (67)
Age		
Mean — yr	56.0±9.4	55.7±10.4
<50 yr — no. (%)	34 (20)	20 (24)
Creatinine clearance — ml/min	107.8±39.9	106.4±34.4
Use of aspirin or clopidogrel after surgery — no. (%)		
One agent or both	51 (30)	25 (30)
Both agents	3 (2)	1 (1)
Geographic region — no. (%)		
North America (Canada only)	15 (9)	9 (11)
Western Europe	98 (58)	42 (50)
Central Europe	55 (33)	33 (39)
Type of valve-replacement surgery — no. (%)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)
Baseline thromboembolic risk — no. (%)†		
Low	51 (30)	23 (27)
Intermediate or high	117 (70)	61 (73)
Population group — no. (%)		
Population A (surgery during current hospital stay)	133 (79)	66 (79)
Population B (≥3 mo after surgery)	35 (21)	18 (21)
Medical and surgical history — no. (%)		
Coronary artery disease	39 (23)	24 (29)
Previous myocardial infarction	9 (5)	7 (8)
Previous CABG	5 (3)	4 (5)
Atrial fibrillation	37 (22)	22 (26)
Atrial flutter	7 (4)	5 (6)
New York Heart Association class ≥II	62 (37)	29 (35)
Left ventricular ejection fraction ≤40%	11 (7)	4 (5)
Hypertension	101 (60)	53 (63)
Diabetes mellitus	27 (16)	13 (15)
Hyperlipidemia	75 (45)	42 (50)
Previous stroke	5 (3)	5 (6)
Previous transient ischemic attack	4 (2)	3 (4)
Hypercoagulable condition	3 (2)	2 (2)
Logistic EuroSCORE‡	2.3±1.9	2.3±1.8
Society of Thoracic Surgeons risk score§	2.0±2.3	1.8±1.7

* Plus–minus values are means ±SD. There were no significant differences between the two study groups. CABG denotes coronary-artery bypass grafting.

† Patients who underwent aortic-valve replacement and had no additional risk factors were classified as being at low thromboembolic risk; those who underwent aortic-valve replacement and had additional risk factors (i.e., atrial fibrillation or flutter, left ventricular dysfunction, previous thromboembolism, or a hypercoagulable condition) and those who underwent mitral-valve replacement, regardless of whether they had additional risk factors, were classified as being at intermediate or high risk.[15]

‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. A score of more than 20 indicates a very high surgical risk.

§ The Society of Thoracic Surgeons score measures risk at the time of cardiovascular surgery. A score of more than 10 indicates a very high surgical risk.

178 patients (71%) were deemed to be at intermediate or high risk.

STUDY-DRUG EXPOSURE

Nine patients (six in the dabigatran group and three in the warfarin group) did not receive a study drug. In population A, the median time to the administration of the first dose of a study drug after surgery was 6 days (interquartile range, 4 to 7) for patients in the dabigatran group and 5 days (interquartile range, 3 to 6) for those in the warfarin group. The median interval from the administration of the first dose of warfarin to achievement of the target INR was 7 days (overall interquartile range, 5 to 11; population A, 5 to 12; population B, 1 to 8). In the dabigatran group, the median time to reach the target plasma level of at least 50 ng of dabigatran per milliliter was 8 days (overall interquartile range, 7 to 12; population A, 7 to 23; population B, 7 to 8).

A total of 99 patients in the dabigatran group and 59 in the warfarin group participated in the extension trial and continued to receive the assigned study drug after 12 weeks. The mean duration of treatment with the assigned study drug in population A was 143 days in the dabigatran group and 152 days in the warfarin group. The corresponding mean durations in population B were 136 days and 143 days.

STUDY-DRUG DOSES AND BLOOD LEVELS

The initial dose of dabigatran was 150 mg twice daily in 15% of patients, 220 mg twice daily in 54%, and 300 mg twice daily in 31%. The dose of dabigatran was increased in 39 of 162 patients (24%), and discontinuation of dabigatran therapy was required per protocol in 13 patients (8%) who had a trough plasma level of less than 50 ng per milliliter despite treatment with dabigatran at a dose of 300 mg twice daily (Table 2).

On the basis of a linear interpolation method similar to that reported by Rosendaal et al.[18] for calculating the time in the therapeutic range for warfarin, patients in the dabigatran group had a targeted plasma level of 50 ng per milliliter for an average of 86% of the time, with a mean percentage of time above this level of 84% in population A and 96% in population B (Table 2). During the first 4 weeks of therapy, plasma levels of dabigatran were lower in population A than in population B (Table 3). In the warfarin group, the time in the therapeutic range was lower in population A than in population B (49% vs. 51%). The relationship between observed trough levels of dabigatran and those predicted by dose modeling is shown in Figure S1 in the Supplementary Appendix.

CLINICAL OUTCOMES

In the dabigatran group, stroke occurred in 9 patients (5%) and myocardial infarction occurred in 3 patients (2%); there were no cases of stroke or myocardial infarction in the warfarin group (Table 4). One patient in the dabigatran group and 2 patients in the warfarin group died (<1% vs. 2%) (see the Supplementary Appendix for de-

Table 2. Patients Requiring Dose Escalation or Discontinuation of Dabigatran and Mean Percentage of Time above the Target Trough Plasma Level of Dabigatran.*

Dabigatran Dose	Population A (N=127)		Population B (N=35)		All Patients (N=162)	
	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡
All doses	47/127 (37)	84	5/35 (14)	96	52/162 (32)	86
150 mg twice daily	4 /11 (36)	99	2/13 (15)	98	6/24 (25)	98
220 mg twice daily	32/71 (45)	84	1/16 (6)	100	33 /87 (38)	87
300 mg twice daily	11/45 (24)	79	2/6 (33)	83	13/51 (25)	79

* Shown are the numbers of all patients who received at least one dose of dabigatran who required a dose escalation or discontinuation, divided by the total number of patients receiving the initial dose level. The target trough plasma level of dabigatran was 50 ng per milliliter or more. Data are from the initial 12-week treatment period.

† Doses were increased from 150 mg twice daily to 220 mg twice daily and from 220 mg twice daily to 300 mg twice daily if the steady-state trough level of dabigatran was less than 50 ng per milliliter. Among patients receiving an initial dose of 300 mg twice daily, dabigatran was discontinued if repeated measurement of the trough level was less than 50 ng per milliliter.

‡ The percentage of time above the target level was calculated with the use of the Rosendaal method on the basis of trough levels of dabigatran, as measured on high-performance liquid chromatography–tandem mass spectrometry. Excluded from this calculation were three patients for whom no measurements were available during the initial study period.

Table 3. Trough Plasma Levels of Dabigatran, According to Treatment Duration and Population.*

Treatment Duration	Population A			Population B			All Patients		
	No. of Patients	Geometric Mean Trough Dabigatran Level	Geometric Coefficient of Variation	No. of Patients	Geometric Mean Trough Dabigatran Level	Geometric Coefficient of Variation	No. of Patients	Geometric Mean Trough Dabigatran Level	Geometric Coefficient of Variation
		ng/ml	%		*ng/ml*	%		*ng/ml*	%
1 wk	105	66	73	27	123	55	132	75	76
2 wk	18	69	71	7	115	33	25	79	67
4 wk	100	98	62	27	125	45	127	103	60
End of treatment	50	107	102	11	125	75	61	110	97

* Data are from the initial 12-week treatment period. Trough plasma levels of total dabigatran were measured 10 to 16 hours after the last dose was administered. Plasma levels of dabigatran after alkaline cleavage of conjugates were determined on high-performance liquid chromatography–tandem mass spectrometry. The lower limit of quantitation for the assay was 1.0 ng per milliliter. The accuracy and precision of the assay were within 9.1% and 13.8%, respectively.

Table 4. Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.*

Outcome	Population A		Population B		All Patients		Hazard Ratio (95% CI)†	P Value‡
	Dabigatran (N=133)	Warfarin (N=66)	Dabigatran (N=35)	Warfarin (N=18)	Dabigatran (N=168)	Warfarin (N=84)		
	number of patients (percent)							
Death	1 (1)	2 (3)	0	0	1 (1)	2 (2)	0.25 (0.02–2.72)	0.26
Stroke	9 (7)	0	0	0	9 (5)	0	NA	NA
Systemic embolism	0	0	0	0	0	0	NA	NA
Transient ischemic attack	2 (2)	2 (3)	1 (3)	0	3 (2)	2 (2)	0.75 (0.13–4.49)	0.75
Myocardial infarction	1 (1)	0	2 (6)	0	3 (2)	0	NA	NA
Death, stroke, systemic embolism, or myocardial infarction	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)	3.37 (0.76–14.95)	0.11
Death, stroke, transient ischemic attack, systemic embolism, or myocardial infarction	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)	1.94 (0.64–5.86)	0.24
Valve thrombosis without symptoms	2 (2)	0	3 (9)	0	5 (3)	0	NA	NA
Bleeding								
Any	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23–4.86)	0.01
Major	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.37–8.46)	0.48
Major with pericardial location	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.36–8.45)	0.48

* NA denotes not applicable.
† Hazard ratios are for all the patients in the dabigatran group as compared with all those in the warfarin group.
‡ P values were calculated with the use of the Wald chi-square test.

tails). Valve thrombosis without clinical symptoms was detected in 5 patients, all of whom were in the dabigatran group (3%). The composite of stroke, transient ischemic attack, systemic embolism, myocardial infarction, or death occurred in 15 patients (9%) in the dabigatran group and 4 patients (5%) in the warfarin group (hazard ratio in the dabigatran group, 1.94; 95% confidence interval [CI], 0.64 to 5.86; P=0.24) (Table 4 and Fig. 1A). Most thromboembolic events among patients in the dabigatran group occurred in population A.

A major bleeding episode occurred in 7 patients (4%) in the dabigatran group and 2 patients (2%) in the warfarin group, and bleeding of any type occurred in 45 patients (27%) and 10 patients (12%), respectively (hazard ratio, 2.45; 95% CI, 1.23 to 4.86; P=0.01) (Fig. 1B). A consistent pattern of increased bleeding events in the dabigatran group was evident in both population A and population B. However, all major bleeding occurred in patients who underwent randomization within 1 week after cardiac surgery (population A). All patients with major bleeding had pericardial bleeding, which occurred within 2 weeks after surgery in 5 patients in the dabigatran group and 2 patients in the warfarin group.

Clinical outcomes in the as-treated population were consistent with those in the intention-to-treat population (Table S1 in the Supplementary Appendix). Similarly clinical outcomes during the 12-week study period were consistent with those observed during the overall study period, including the extension period (Table S2 in the Supplementary Appendix). Details on the timing of clinical events, doses of dabigatran, and echocardiographic findings (for thromboembolic events) are provided in Tables S2, S3, and S4 in the Supplementary Appendix. There appeared to be no association between plasma levels of dabigatran and the occurrence of thromboembolic events or bleeding (Tables S3 and S4 in the Supplementary Appendix).

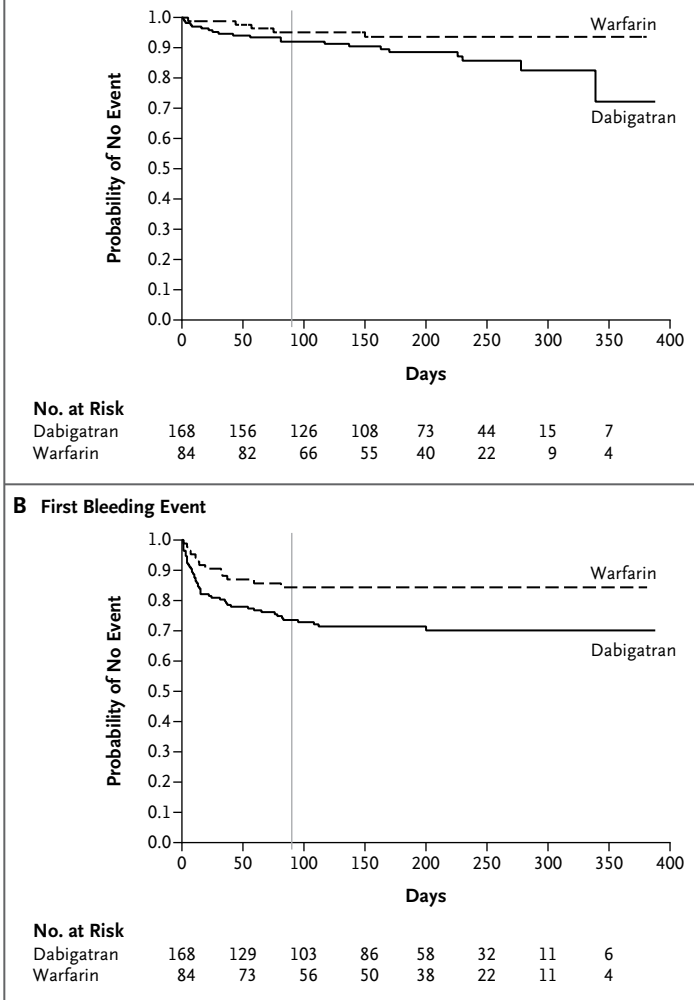

Figure 1. Kaplan–Meier Analysis of Event-free Survival.

Panel A shows event-free survival from the first thromboembolic event (i.e., stroke, systemic embolism, transient ischemic attack, or myocardial infarction) or death (P=0.24). Panel B shows event-free survival from the first bleeding event (P=0.01). In each panel, the vertical line indicates the start of the RE-ALIGN extension trial (RE-ALIGN-EX) and the P value was calculated with the use of the Wald chi-square test.

DISCUSSION

The primary goal of RE-ALIGN was to validate a new dabigatran dosing regimen for the prevention of thromboembolic complications in patients with mechanical heart valves. However, the trial was stopped early because of an excess of thromboembolic and bleeding events in the dabigatran group, as compared with the warfarin group. Most thromboembolic events among patients in the dabigatran group occurred in population A (patients who had started a study drug within 7 days after valve surgery), with fewer occurring in population B (patients who had undergone valve implantation more than 3 months

before randomization). Excess bleeding events among patients receiving dabigatran occurred in the two study populations.

Possible explanations for the increase in thromboembolic complications with dabigatran include inadequate plasma levels of the drug and a mechanism of action that differs from that of warfarin. Trough plasma levels of dabigatran in population A were lower during the first few weeks after surgery than they were subsequently, and low drug levels soon after valve surgery may have allowed for early formation of blood clots that were not clinically manifested until later. However, thromboembolic events also occurred among patients with higher trough plasma levels of dabigatran early after surgery and among those in population B who had higher plasma levels than those in population A, suggesting that lower-than-expected drug levels cannot fully explain the increase in the rate of thromboembolic events.

The choice of a target trough plasma level of 50 ng of dabigatran per milliliter was primarily based on data from the RE-LY trial, in which dabigatran at a dose of 150 mg twice daily, as compared with warfarin, had superior efficacy and similar safety in patients with atrial fibrillation. We cannot exclude the possibility that targeting a higher trough level of dabigatran would have been more effective for the prevention of thromboembolic complications. At the same time, it is likely that the use of higher dabigatran doses would have led to unacceptably high bleeding rates, since dabigatran caused excess bleeding at the doses studied. It is also possible that more frequent administration of dabigatran (e.g., three times a day) without an increase in the total daily dose might have resulted in higher trough and lower peak levels, thereby increasing antithrombotic efficacy and reducing bleeding, but this approach was not tested.

Differences in the mechanisms of action of dabigatran and warfarin may also in part explain our findings. In patients with atrial fibrillation, thrombi form in the left atrial appendage under low-flow, low-shear conditions in which thrombin generation is believed to be triggered by stasis and endothelial dysfunction.[19] In contrast, in patients with a mechanical heart valve, coagulation activation and thrombin generation induced by the release of tissue factor from damaged tissues during surgery may partly explain the high risk of early thromboembolic complications. In addition, thrombin generation can be triggered by exposure of the blood to the artificial surface of the valve leaflets and sewing ring, which induce activation of the contact pathway of coagulation. The majority of thrombi in patients with prosthetic heart valves appear to arise from the sewing ring,[20] which does not undergo endothelialization for at least several weeks after surgery. It is thought that the sewing ring becomes less thrombogenic once endothelial tissue has formed around it. Warfarin is likely to be more effective than dabigatran at suppressing coagulation activation because it inhibits the activation of both tissue factor–induced coagulation (by inhibiting the synthesis of coagulation factor VII) and contact pathway–induced coagulation by inhibiting the synthesis of factor IX), as well as inhibiting the synthesis of factor X and thrombin in the common pathway,[21] whereas dabigatran exclusively inhibits thrombin.[22] If contact activation is intense, the resulting thrombin generation may overwhelm local levels of dabigatran, which can lead to thrombus formation on the surface of the valve and related embolic complications.

RE-ALIGN was an open-label trial and thus subject to reporting biases. However, clinical outcomes were prespecified, objectively defined, and independently adjudicated by experts who were unaware of the study-group assignments, all factors that minimize the potential for bias.

The results of our study indicate that dabigatran is not appropriate as an alternative to warfarin for the prevention of thromboembolic complications in patients who require anticoagulation after the implantation of a prosthetic heart valve. The results may also be relevant to studies of other new oral anticoagulants in patients with mechanical heart valves. Like dabigatran, the direct factor Xa inhibitors are effective for stroke prevention in patients with atrial fibrillation,[23,24] but these data cannot be extrapolated to patients with mechanical heart valves because the mechanisms of thrombosis are different. Rivaroxaban has been successfully tested for the prevention of thromboembolic complications associated with mechanical heart valves in preclinical studies,[25] but our study did not provide evidence of the safety and efficacy of the selected dosing algorithm, despite favorable results of preclinical studies.[7-9]

In conclusion, the results of our phase 2 study indicate that at the doses tested, dabigatran was not as effective as warfarin for the prevention of thromboembolic complications in patients with mechanical heart valves and was associated with an increased risk of bleeding. These results might be explained by the relative inability of dabigatran to suppress activation of coagulation that occurs when blood is exposed to the artificial surfaces of the valve prosthesis. The use of dabigatran has no positive value and was associated with excess risk in patients with mechanical heart valves.

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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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