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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

Rates of the primary outcome were 1.69% per year in the warfarin group, as compared with 1.53% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% confidence interval [CI], 0.74 to 1.11; P<0.001 for noninferiority) and 1.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.66; 95% CI, 0.53 to 0.82; P<0.001 for superiority). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group receiving 110 mg of dabigatran (P=0.003) and 3.11% per year in the group receiving 150 mg of dabigatran (P=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with 110 mg of dabigatran (P<0.001) and 0.10% per year with 150 mg of dabigatran (P<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

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Atrial fibrillation increases the risks of stroke and death. Vitamin K antagonists, such as warfarin, reduce the risks of stroke and death but increase the risk of hemorrhage as compared with control therapy.[1] Therefore, warfarin is recommended for patients who have atrial fibrillation and are at risk for stroke.[2]

Vitamin K antagonists are cumbersome to use, because of their multiple interactions with food and drugs, and they require frequent laboratory monitoring. Therefore, they are often not used, and when they are, rates of discontinuation are high.[3,4] Many patients receiving warfarin still have inadequate anticoagulation.[5] Thus, there is a need for new anticoagulant agents that are effective, safe, and convenient to use.

Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin. It has an absolute bioavailability of 6.5%, 80% of the given dose is excreted by the kidneys, its serum half-life is 12 to 17 hours, and it does not require regular monitoring.[6] Dabigatran has been evaluated in a pilot trial involving patients with atrial fibrillation and in a study for the prevention of venous thromboembolism, in which doses of 150 mg twice daily and 220 mg once daily, respectively, were promising.[7,8] We performed a large, randomized trial comparing the use of dabigatran, at doses of 110 mg twice daily and 150 mg twice daily, with warfarin.

METHODS

TRIAL DESIGN

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a randomized trial designed to compare two fixed doses of dabigatran, each administered in a blinded manner, with open-label use of warfarin in patients who had atrial fibrillation and were at increased risk for stroke. The design of this study has been described previously.[9]

The study was funded by Boehringer Ingelheim and was coordinated by the Population Health Research Institute (Hamilton, ON, Canada), which independently managed the database and performed the primary data analyses. An operations committee, with assistance from an international steering committee and with participation by the sponsor, was responsible for the design, conduct, and reporting of the study. The study was approved by all appropriate national regulatory authorities and ethics committees of the participating centers. All the authors vouch for the accuracy and completeness of the data and the analyses.

STUDY PARTICIPANTS

Patients were recruited from 951 clinical centers in 44 countries. In brief, patients were eligible if they had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Reasons for exclusion were the presence of a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a condition that increased the risk of hemorrhage, a creatinine clearance of less than 30 ml per minute, active liver disease, and pregnancy. (Detailed inclusion and exclusion criteria are available in Tables 1 and 2 of the Supplementary Appendix, available with the full text of this article at NEJM.org.)

PROCEDURES

After providing written informed consent, all trial participants were randomly assigned to receive one of two doses of dabigatran, or to receive warfarin, by means of a central, interactive, automated telephone system. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly. The time that the INR was within the therapeutic range was calculated with the use of the method of Rosendaal et al.,[10] excluding INRs from the first week and after discontinuation of the study drug. These data were reported back to the participating centers with advice for optimal INR control. Concomitant use of aspirin (at a dose of <100 mg per day) or other antiplatelet agents was permitted. Quinidine use was

permitted until 2 years after the trial started, when the protocol was amended to prohibit its use, because of its potential to interact with dabigatran.

Follow-up visits occurred 14 days after randomization, at 1 and 3 months, every 3 months thereafter in the first year, and then every 4 months until the study ended. Liver-function testing was performed monthly during the first year of the follow-up period. On the basis of a prespecified evaluation of liver-function tests in at least 6000 patients in the dabigatran group after they had been followed for 6 months or more, the data safety monitoring board recommended that the frequency of liver-function testing be reduced, with such testing performed only at the regular visits.

OUTCOMES

The primary study outcome was stroke or systemic embolism. The primary safety outcome was major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke. Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy. Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

An international team of adjudicators reviewed documents in local languages after blinding, or documents were translated by an independent group and were centrally blinded. Each primary and secondary outcome event was adjudicated by two independent investigators who were unaware of the treatment assignments. All transient ischemic attacks were reviewed to ensure that strokes had not been missed. To detect possible unreported events, symptom questionnaires were regularly administered to patients, and adverse-event and hospitalization reports were scrutinized for unreported primary or secondary outcomes.

STATISTICAL ANALYSIS

The primary analysis was designed to test whether either dose of dabigatran was noninferior to warfarin, as evaluated with the use of Cox proportional-hazards modeling. To satisfy the noninferiority hypothesis, the upper bound of the one-sided 97.5% confidence interval for the relative risk of an outcome with dabigatran as compared with warfarin needed to fall below 1.46. This noninferiority margin was derived from a meta-analysis of trials of vitamin K antagonists as compared with control therapy in patients with atrial fibrillation, with the margin defined according to the upper bound of the 95% confidence interval for the relative risk of the primary outcome in the control group versus the warfarin group.[11] The margin of 1.46 represents half the 95% confidence interval of the estimated effect of control therapy over warfarin. To account for testing of both dabigatran doses against warfarin, we planned to determine whether the higher of the two one-sided P values for the two doses was less than 0.025, in which case both treatments would be declared to be noninferior. If the higher of the two one-sided P values was 0.025 or greater, the lower of the two was required to be less than 0.0125 to permit a claim of statistical significance. All analyses were based on the intention-to-treat principle. After noninferiority of both doses of dabigatran was established, all subsequent P values were reported for two-tailed tests of superiority. Cox regression was used to calculate relative risks, confidence intervals, and P values. Chi-square testing was used to compare rates of medication discontinuation and adverse events.

We planned to enroll 15,000 patients, an enrollment that we estimated would provide 84% power to evaluate the noninferiority of each dose

of dabigatran. Two protocol changes were made by the operations committee during the enrollment period, without knowledge of emerging treatment effects. These were the enforcement of balanced enrollment of patients who had not received long-term therapy with a vitamin K antagonist (i.e., had a total lifetime use of <61 days) and those who had (i.e., had a total lifetime use of ≥61 days), and an increase in the sample size to 18,000 patients to maintain the statistical power in case of a low event rate. An independent data safety monitoring board reviewed the unblinded study data and performed two prespecified interim analyses of efficacy, with a plan to recommend study termination if the benefit of dabigatran exceeded 3 SD from unity of the parameter estimate and if that benefit persisted on repeat analysis 3 months later.

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

A total of 18,113 patients were enrolled between December 22, 2005, and December 15, 2007. The three treatment groups were well balanced with respect to baseline characteristics (Table 1). The mean age of the patients was 71 years, and 63.6% were men. Half the patients had received long-term therapy with vitamin K antagonists. The mean $CHADS_2$ score was 2.1 (Table 1).

FOLLOW-UP DATA

Final follow-up visits occurred between December 15, 2008, and March 15, 2009. The median duration of the follow-up period was 2.0 years, and complete follow-up was achieved in 99.9% of patients, with 20 patients lost to follow-up. The rates of discontinuation for 110 mg of dabigatran, 150 mg of dabigatran, and warfarin were 14.5%, 15.5%, and 10.2%, respectively, at 1 year and 20.7%, 21.2%, and 16.6% at 2 years. Aspirin was used continuously during the treatment period in 21.1%, 19.6%, and 20.8% of patients receiving 110 mg of dabigatran, 150 mg of dabigatran, and warfarin, respectively. In the warfarin group, the mean percentage of the study period during which the INR was within the therapeutic range was 64%.

PRIMARY OUTCOME

Stroke or systemic embolism occurred in 182 patients receiving 110 mg of dabigatran (1.53% per year), 134 patients receiving 150 mg of dabigatran (1.11% per year), and 199 patients receiving warfarin (1.69% per year) (Table 2 and Fig. 1). Both doses of dabigatran were noninferior to warfarin (P<0.001). The 150-mg dose of dabigatran was also superior to warfarin (relative risk, 0.66; 95% confidence interval [CI], 0.53 to 0.82; P<0.001), but the 110-mg dose was not (relative risk, 0.91; 95% CI, 0.74 to 1.11; P=0.34). Rates of hemorrhagic stroke were 0.38% per year in the warfarin group, as compared with 0.12% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.31; 95% CI, 0.17 to 0.56; P<0.001) and 0.10% per year in the group that received 150 mg of dabigatran (relative risk, 0.26; 95% CI, 0.14 to 0.49; P<0.001).

OTHER OUTCOMES

Rates of death from any cause were 4.13% per year with warfarin, as compared with 3.75% per year with 110 mg of dabigatran (relative risk with dabigatran, 0.91; 95% CI 0.80 to 1.03; P=0.13) and 3.64% per year with 150 mg of dabigatran (relative risk, 0.88; 95% CI, 0.77 to 1.00; P=0.051). The rate of myocardial infarction was 0.53% per year with warfarin and was higher with dabigatran: 0.72% per year in the 110-mg group (relative risk, 1.35; 95% CI, 0.98 to 1.87; P=0.07) and 0.74% per year in the 150-mg group (relative risk, 1.38, 95% CI, 1.00 to 1.91; P=0.048).

BLEEDING

The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.80; 95% CI, 0.69 to 0.93; P=0.003) and 3.11% per year in the group that received 150 mg of dabigatran (relative risk, 0.93; 95% CI, 0.81 to 1.07; P=0.31) (Table 3). Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (1.80%, 0.74%, and 18.15%, respectively) than with either the 110-mg dose of dabigatran (1.22%, 0.23%, and 14.62%, respectively) or the 150-mg dose of dabigatran (1.45%, 0.30%, and 16.42%, respectively) (P<0.05 for all comparisons of dabigatran with warfarin). There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin.

The net clinical benefit outcome consisted of major vascular events, major bleeding, and death. The rates of this combined outcome were 7.64% per year with warfarin and 7.09% per year with 110 mg of dabigatran (relative risk with dabiga-

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Dabigatran, 110 mg	Dabigatran, 150 mg	Warfarin
Age — yr	71.4±8.6	71.5±8.8	71.6±8.6
Weight — kg	82.9±19.9	82.5±19.4	82.7±19.7
Blood pressure — mm Hg			
Systolic	130.8±17.5	131.0±17.6	131.2±17.4
Diastolic	77.0±10.6	77.0±10.6	77.1±10.4
Male sex — no./total no. (%)	3865/6015 (64.3)	3840/6076 (63.2)	3809/6022 (63.3)
Type of atrial fibrillation — no./total no. (%)			
Persistent	1950/6011 (32.4)	1909/6075 (31.4)	1930/6021 (32.0)
Paroxysmal	1929/6011 (32.1)	1978/6075 (32.6)	2036/6021 (33.8)
Permanent	2132/6011 (35.4)	2188/6075 (36.0)	2055/6021 (34.1)
$CHADS_2$ score†	2.1±1.1	2.2±1.2	2.1±1.1
0 or 1 — no./total no. (%)	1958/6014 (32.6)	1958/6076 (32.2)	1859/6022 (30.9)
2 — no./total no. (%)	2088/6014 (34.7)	2137/6076 (35.2)	2230/6022 (37.0)
3–6 — no./total no. (%)	1968/6014 (32.7)	1981/6076 (32.6)	1933/6022 (32.1)
Previous stroke or transient ischemic attack — no./total no. (%)	1195/6015 (19.9)	1233/6076 (20.3)	1195/6022 (19.8)
Prior myocardial infarction — no./total no. (%)	1008/6015 (16.8)	1029/6076 (16.9)	968/6022 (16.1)
Heart failure — no./total no. (%)	1937/6015 (32.2)	1934/6076 (31.8)	1922/6022 (31.9)
Diabetes mellitus — no./total no. (%)	1409/6015 (23.4)	1402/6076 (23.1)	1410/6022 (23.4)
Hypertension — no./total no. (%)	4738/6015 (78.8)	4795/6076 (78.9)	4750/6022 (78.9)
Medications in use at baseline — no./total no. (%)			
Aspirin	2404/6013 (40.0)	2352/6075 (38.7)	2442/6017 (40.6)
ARB or ACE inhibitor	3987/6013 (66.3)	4053/6075 (66.7)	3939/6017 (65.5)
Beta-blocker	3784/6013 (62.9)	3872/6075 (63.7)	3719/6017 (61.8)
Amiodarone	624/6013 (10.4)	665/6075 (10.9)	644/6017 (10.7)
Statin‡	2698/6013 (44.9)	2667/6075 (43.9)	2673/6017 (44.4)
Proton-pump inhibitor	812/6013 (13.5)	847/6075 (13.9)	832/6017 (13.8)
H_2-receptor antagonist	225/6013 (3.7)	241/6075 (4.0)	256/6017 (4.3)
Long-term VKA therapy	3011/6015 (50.1)	3049/6076 (50.2)	2929/6022 (48.6)

* Plus-minus values are means ±SD. ARB denotes angiotensin-receptor blocker, and ACE angiotensin-converting enzyme.
† The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.[12]
‡ Statins are defined here as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.
§ Long-term therapy with a vitamin K antagonist (VKA) denotes a total lifetime use of a VKA of 61 or more days.

tran, 0.92; 95% CI, 0.84 to 1.02; P=0.10) and 6.91% per year with 150 mg of dabigatran (relative risk, 0.91; 95% CI, 0.82 to 1.00; P=0.04).

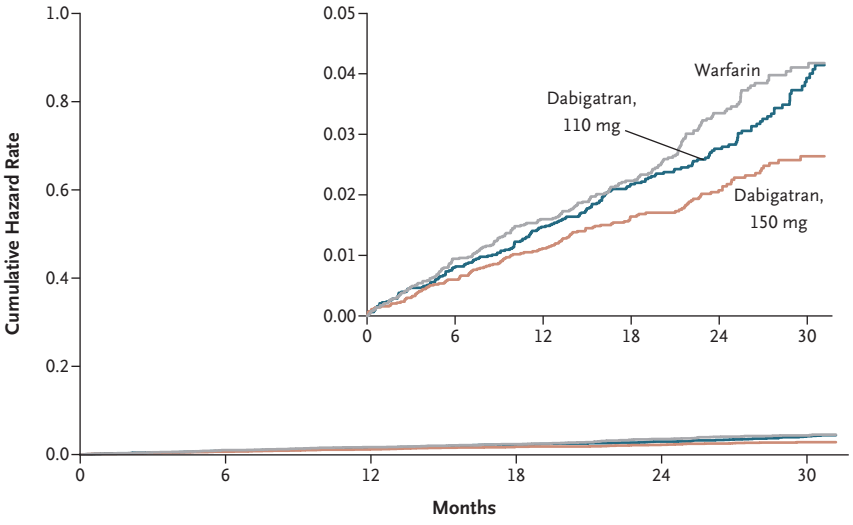
COMPARISON OF DABIGATRAN DOSES

As compared with the 110-mg dose, administration of the 150-mg dose of dabigatran reduced the risk of stroke or systemic embolism (P=0.005). This difference was driven mostly by a decrease in the rate of stroke with ischemic or unspecified cause, whereas rates of hemorrhagic stroke were similar in the two dabigatran groups. There was no significant difference in the rates of death from either vascular causes or any cause between the two doses. On the other hand, as compared with the 110-mg dose, the 150-mg dose of dabigatran

Table 2. Efficacy Outcomes, According to Treatment Group.

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority, unless otherwise indicated. The modified Rankin scale (on which scores can range from 0 [no neurologic disability] to 5 [severe disability], with 6 indicating a fatal stroke) was used to categorize stroke: nondisabling stroke was defined by a score of 0 to 2, and disabling or fatal stroke, a score of 3 to 6.



No. at Risk

Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

was associated with a trend toward an increased risk of major bleeding (P=0.052) and also with increased risks of gastrointestinal, minor, and any bleeding. The net clinical benefit was almost identical for the two doses.

ADVERSE EVENTS AND LIVER FUNCTION

The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia (Table 4). Dyspepsia occurred in 348 patients (5.8%) in the warfarin group and in 707 patients (11.8%) and 688 patients (11.3%) in the 110-mg and 150-mg dabigatran groups, respectively (P<0.001 for both comparisons) (Table 4). Elevations in the serum aspartate aminotransferase or alanine aminotransferase level of more than 3 times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin.

SUBGROUP ANALYSES

For the subgroups shown in Figure 2, no significant interaction was seen with the treatment effect of dabigatran (at either dose). There was no significant interaction between the treatment effect of dabigatran and presence or absence of long-term therapy with a vitamin K antagonist. Although 80% of the dabigatran dose is renally excreted, there was no significant interaction in the treatment effect of dabigatran across levels of the baseline calculated creatinine clearance.

DISCUSSION

We compared two fixed-dose regimens of dabigatran (110 mg twice daily and 150 mg twice daily), administered in a blinded fashion, with adjusted-dose warfarin, administered in an unblinded fashion, in patients who had atrial fibrillation and were at risk for stroke. Both dabigatran doses were noninferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding.

Previous studies seeking to identify a safe and effective alternative to warfarin for patients with atrial fibrillation have all had specific limitations. The combination of clopidogrel and aspirin was more effective than aspirin alone[13] but less effective than warfarin.[14] Subcutaneous idraparinux was more effective than warfarin but was associated with a substantially higher risk of bleeding.[15]

Table 3. Safety Outcomes, According to Treatment Group.*

Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Table 4. Discontinuation of the Study Drug, Adverse Events, and Liver Function According to Treatment Group.*

Variable	Dabigatran, 110 mg (N=6015)	Dabigatran, 150 mg (N=6076)	Warfarin (N=6022)
		number of patients (percent)	
Study-drug discontinuation			
Discontinued at 1 yr†	862 (15)	935 (16)	608 (10)
Discontinued at 2 yr†	1161 (21)	1211 (21)	902 (17)
Reason for discontinuation			
Patient's decision	440 (7.3)	474 (7.8)	375 (6.2)
Outcome event	192 (3.2)	164 (2.7)	130 (2.2)
Serious adverse event‡	163 (2.7)	166 (2.7)	105 (1.7)
Gastrointestinal symptoms§	134 (2.2)	130 (2.1)	38 (0.6)
Gastrointestinal bleeding	58 (1.0)	80 (1.3)	54 (0.9)
Adverse events¶			
Dyspepsia‡‖	707 (11.8)	688 (11.3)	348 (5.8)
Dizziness	486 (8.1)	506 (8.3)	568 (9.4)
Dyspnea	557 (9.3)	580 (9.5)	586 (9.7)
Peripheral edema	473 (7.9)	478 (7.9)	468 (7.8)
Fatigue	399 (6.6)	401 (6.6)	372 (6.2)
Cough	344 (5.7)	348 (5.7)	364 (6.0)
Chest pain	312 (5.2)	377 (6.2)	357 (5.9)
Back pain	316 (5.3)	314 (5.2)	337 (5.6)
Arthralgia	270 (4.5)	335 (5.5)	346 (5.7)
Nasopharyngitis	337 (5.6)	330 (5.4)	336 (5.6)
Diarrhea	377 (6.3)	397 (6.5)	346 (5.7)
Atrial fibrillation	330 (5.5)	357 (5.9)	349 (5.8)
Urinary tract infection	273 (4.5)	289 (4.8)	335 (5.6)
Upper respiratory tract infection	288 (4.8)	285 (4.7)	313 (5.2)
Liver function			
ALT or AST >3× ULN	124 (2.1)	117 (1.9)	132 (2.2)
ALT or AST >3× ULN with concurrent bilirubin >2× ULN	13 (0.2)	13 (0.2)	21 (0.3)
Hepatobiliary disorder**			
Serious adverse event	33 (0.5)	34 (0.6)	33 (0.5)
Non–serious adverse event	101 (1.7)	109 (1.8)	112 (1.9)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.
† Rates of discontinuation at 1 and 2 years were higher with dabigatran than with warfarin (P<0.001). The rates are based on Kaplan–Meier estimates.
‡ P<0.001 for the comparison of either dose of dabigatran with warfarin.
§ Gastrointestinal disorders included pain, vomiting, and diarrhea.
¶ The adverse events listed are those that were reported in more than 5% of patients in any of the three treatment groups.
‖ Dyspepsia was defined to include the coding terms abdominal pain upper, abdominal pain, abdominal discomfort, and dyspepsia.
** Hepatobiliary disorders were classified as serious adverse events if they consisted of clinical or biochemical liver dysfunction requiring hospitalization, most frequently cholelithiasis or cholecystitis. Hepatobiliary disorders classified as adverse events were most frequently cholelithiasis, cholecystitis, abnormal hepatic function, and jaundice.

Ximelagatran, an earlier direct thrombin inhibitor, appeared to be similar to warfarin with respect to efficacy and safety but was found to be hepatotoxic.[16] In our serial measurement of liver function, we did not find evidence of hepatotoxicity with dabigatran.

The rate of myocardial infarction was higher with both doses of dabigatran than with warfarin. An explanation might be that warfarin provides better protection against coronary ischemic events than dabigatran, and warfarin is known to reduce the risk of myocardial infarction.[17] However, rates of myocardial infarction were similar between patients with atrial fibrillation who were receiving warfarin and those who were receiving ximelagatran, another direct thrombin inhibitor.[16] The explanation for this finding is therefore uncertain.

The most devastating complication of warfarin therapy is intracranial hemorrhage, especially hemorrhagic stroke. As compared with aspirin, warfarin doubles the risk of intracranial hemorrhage.[1] Thus, our finding that the rate of this complication with both doses of dabigatran was less than one third the rate with warfarin, without a reduction in the efficacy against ischemic stroke, suggests an important advantage of dabigatran. The rate of major bleeding with warfarin was higher in our study than in some previous trials.[11,13,14] This is partly explained by the more inclusive definition of major bleeding in our study. There was an increase in the rate of gastrointestinal bleeding with the higher dabigatran dose, despite the overall lower rates of bleeding at other sites. To enhance absorption of dabigatran, a low pH is required. Therefore, dabigatran capsules contain dabigatran-coated pellets with a tartaric acid core. This acidity may partly explain the increased incidence of dyspeptic symptoms with both dabigatran doses and the increased risk of gastrointestinal bleeding with the 150-mg dose.

The benefit of dabigatran may be explained in part by the twice-daily dosing regimen. Since dabigatran has an elimination half-life of 12 to 17 hours, twice-daily dosing reduces variability in the anticoagulation effect, especially as compared with the anticoagulation effect of warfarin, which is difficult to control. Warfarin broadly inhibits coagulation (inhibiting factors II, VII, IX, and X and proteins C and S). By selectively inhibiting only thrombin, dabigatran may have antithrombotic efficacy while preserving some other hemostatic mechanisms in the coagulation system and thus potentially mitigating the risk of bleeding.

Figure 2 (facing page). Relative Risk of the Primary Outcome of Stroke or Systemic Embolism with Dabigatran versus Warfarin, According to Subgroup.

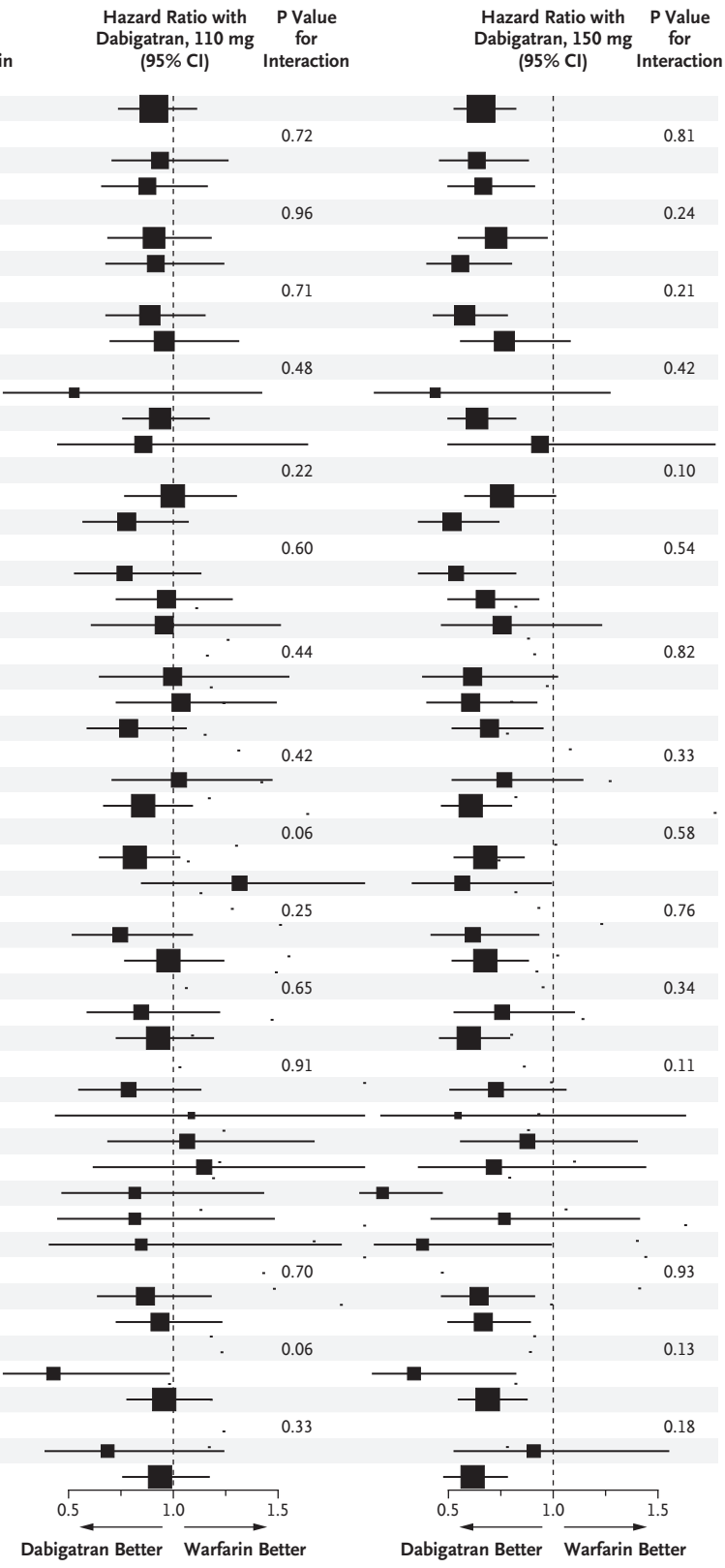
Ethnic group was self-reported. Long-term therapy with a vitamin K antagonist (VKA) denotes a total lifetime use of a VKA of 61 days or more. The body-mass index is the weight in kilograms divided by the square of the height in meters. The $CHADS_2$ score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years or older, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.[12] Creatinine clearance was calculated according to the Cockcroft–Gault method. The squares with horizontal lines are hazard ratios and corresponding 95% confidence intervals; the sizes of squares are proportional to the sizes of the subgroups. PPI denotes proton-pump inhibitor.

The use of open-label warfarin could have introduced a bias in the reporting or adjudication of events. This risk was reduced by the implementation of several validated procedures, including blinded evaluation of outcome events. The unexpectedly different rates of myocardial infarction and gastrointestinal bleeding among the three treatment groups support an absence of bias. Control of anticoagulation with warfarin in our study was similar to that in previous international clinical trials, even though half our patients had not previously had extensive treatment with warfarin.[10,17]

The net clinical benefit outcome, which is a measure of the overall benefit and risk, was similar between the two doses of dabigatran, owing to the lower risk of ischemia with the 150-mg dose and the lower risk of hemorrhage with the 110-mg dose. These findings suggest that the dose of dabigatran could potentially be tailored to take into consideration the risk characteristics of a specific patient, although this concept was not specifically tested in our trial.

In conclusion, we compared two doses of dabigatran with warfarin in patients who had atrial fibrillation and who were at risk for stroke. As compared with warfarin, the 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major

Subgroup	Patients *total no.*	Dabigatran 110 mg *% per yr*	Dabigatran 150 mg *% per yr*	Warfarin *% per yr*	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
All patients	18,113	1.53	1.11	1.69				
Long-term VKA therapy						0.72		0.81
No	9,123	1.57	1.07	1.67				
Yes	8,989	1.49	1.15	1.70				
Sex						0.96		0.24
Male	11,514	1.35	1.10	1.49				
Female	6,598	1.86	1.14	2.03				
Body-mass index						0.71		0.21
<28	9,131	1.78	1.17	2.01				
≥28	8,962	1.28	1.04	1.34				
Weight						0.48		0.42
<50 kg	376	2.58	2.24	5.04				
50–99 kg	14,629	1.66	1.14	1.77				
≥100 kg	3,099	0.80	0.87	0.94				
Ethnic group						0.22		0.10
European or Arab	12,679	1.35	1.03	1.35				
Other	5,433	1.97	1.32	2.52				
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50–79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				
$CHADS_2$ score						0.44		0.82
0 or 1	5,775	1.06	0.65	1.05				
2	6,455	1.43	0.84	1.38				
≥3	5,882	2.12	1.88	2.68				
Symptomatic heart failure						0.42		0.33
Yes	4,904	1.90	1.44	1.85				
No	13,203	1.40	1.00	1.63				
Hypertension						0.06		0.58
Yes	14,283	1.46	1.20	1.78				
No	3,829	1.79	0.78	1.36				
Diabetes						0.25		0.76
Yes	4,221	1.76	1.46	2.32				
No	13,891	1.46	1.01	1.50				
Stroke or TIA						0.65		0.34
Yes	3,623	2.32	2.07	2.74				
No	14,489	1.33	0.87	1.43				
Region						0.91		0.11
North America	6,533	1.19	1.11	1.51				
South America	1,134	1.82	0.91	1.68				
Western Europe	3,941	1.53	1.26	1.43				
Central Europe	2,829	1.22	0.78	1.06				
South Asia	1,134	3.35	0.84	4.00				
East Asia	1,648	1.87	1.77	2.28				
Other	1,072	1.95	0.88	2.27				
Aspirin use at baseline						0.70		0.93
Yes	7,198	1.66	1.26	1.92				
No	10,910	1.44	1.03	1.53				
Amiodarone use at baseline						0.06		0.13
Yes	1,933	0.66	0.54	1.55				
No	16,174	1.63	1.18	1.70				
PPI use at baseline						0.33		0.18
Yes	2,491	1.22	1.63	1.77				
No	15,616	1.58	1.03	1.67				



hemorrhage; the 150-mg dose of dabigatran was associated with lower rates of stroke and systemic embolism but with a similar rate of major hemorrhage.

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APPENDIX

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