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The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study

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Background—During follow-up of between 1 and 3 years in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, 2 doses of dabigatran etexilate were shown to be effective and safe for the prevention of stroke or systemic embolism in patients with atrial fibrillation. There is a need for longer-term follow-up of patients on dabigatran and for further data comparing the 2 dabigatran doses.

Methods and Results—Patients randomly assigned to dabigatran in RE-LY were eligible for the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the double-blind dabigatran dose received in RE-LY, for up to 28 months of follow up after RE-LY (median follow-up, 2.3 years). There were 5851 patients enrolled, representing 48% of patients originally randomly assigned to receive dabigatran in RE-LY and 86% of RELY-ABLE–eligible patients. Rates of stroke or systemic embolism were 1.46% and 1.60%/y on dabigatran 150 and 110 mg twice daily, respectively (hazard ratio, 0.91; 95% confidence interval, 0.69–1.20).

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Rates of major hemorrhage were 3.74% and 2.99%/y on dabigatran 150 and 110 mg (hazard ratio, 1.26; 95% confidence interval, 1.04–1.53). Rates of death were 3.02% and 3.10%/y (hazard ratio, 0.97; 95% confidence interval, 0.80–1.19). Rates of hemorrhagic stroke were 0.13% and 0.14%/y.

Conclusions—During 2.3 years of continued treatment with dabigatran after RE-LY, there was a higher rate of major bleeding with dabigatran 150 mg twice daily in comparison with 110 mg, and similar rates of stroke and death.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00808067. **(*Circulation*. 2013;128:237–243.)**

Key Words: atrial fibrillation ■ dabigatran ■ hemorrhage ■ stroke

Atrial fibrillation (AF) is a common condition that increases the risk of thrombus in the left atrial appendage and that is strongly associated with an increased risk of ischemic stroke.[1] Antithrombotic medications, which inhibit either platelet activity or coagulation, reduce this risk.[2] Until recently, the most effective antithrombotic agents were the vitamin K antagonists, such as warfarin, although a narrow therapeutic window, high intra- and interpatient variability, need for therapeutic monitoring, and concern about bleeding have limited their use.[3] Recently, the direct thrombin inhibitor dabigatran and inhibitors of Factor Xa have been evaluated in large phase III clinical trials with an average follow-up of ≈2 years.[4–7]

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Dabigatran etexilate is a prodrug with rapid conversion to the active metabolite, dabigatran, in the circulation. It has a half-life or 12 to 17 hours and has 80% renal elimination. There are few drug–drug interactions, and it has a broad therapeutic window at fixed doses and no need for anticoagulant monitoring. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial randomly assigned 18 113 patients with AF and with at least 1 risk factor for stroke to receive either of 2 blinded fixed doses of dabigatran (110 mg or 150 mg twice daily) or unblinded, adjusted-dose warfarin. RE-LY demonstrated that dabigatran 150 mg twice daily was superior to warfarin for the prevention of stroke or systemic embolism and that dabigatran 110 mg twice daily was noninferior.[4] Both doses greatly reduced hemorrhagic stroke, and dabigatran 110 mg twice daily significantly reduced major bleeding in comparison with warfarin. These findings led to the regulatory approval of dabigatran for patients with AF in 81 countries. The mean duration of follow-up in RE-LY was 2.0 years with a maximum follow-up of up to 3 years. Little is known of the consistency of effects of dabigatran during longer periods of follow-up.

Regulatory agencies in different countries have taken different positions regarding the approval of dabigatran 150 and 110 mg and their use in specific patient subgroups.[8] Further information comparing the 2 doses of dabigatran would be useful.

The Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) study was designed to provide additional information on the long-term effects of the 2 doses of dabigatran in patients completing RE-LY by extending the follow-up of patients on dabigatran from a mean of 2 years at the end of RE-LY by an additional 2.25 years.

Methods

Patient Eligibility

Patients were eligible for RELY-ABLE if they were participating in RE-LY, randomly assigned to double-blinded dabigatran study medication, and not permanently discontinued from study medication at the time of the final RE-LY study visit. Exclusion criteria reassessed at the time of enrollment into RELY-ABLE included the need for anticoagulant treatment for disorders other than AF, a plan to perform pulmonary vein ablation or surgery for AF, documented gastrointestinal ulcer disease in the 30 days before the start of the trial, estimated creatinine clearance ≤30 mL/min, anemia (hemoglobin <100 g/L), thrombocytopenia (platelet count $<100\times10^9$/L). Patients provided written informed consent. After enrollment in RELY-ABLE, patients continued to receive the same dose of dabigatran, double-blind, that they had received during RE-LY. Patients randomly assigned to warfarin in RE-LY were not eligible for RELY-ABLE.

Patient Follow-Up

The final RE-LY study visits occurred between December 15, 2008 and March 15, 2009. It was intended that patients would begin study treatment in RELY-ABLE without interruption at their final RE-LY study visit; however, the protocol allowed for an interruption of dabigatran treatment for up to 8 weeks after the final RE-LY study, during which time they would be treated with other anticoagulation therapy. The RELY-ABLE study follow-up visits occurred at 4, 8, 13, 18, and 23 months, and the final visit occurred at 28 months after their study enrollment visit. In some countries where dabigatran was not yet approved at the time of the 28-month visit, the trial was extended, and continued follow-up information was collected in patients (n=2188) who continued to receive blinded study medication. Follow-up beyond the 28-month visit is not included in this analysis. Patients who permanently discontinued study medication in RELY-ABLE were scheduled for a final visit, at which point follow-up was stopped (vital status, however, was collected at study conclusion in all patients). Laboratory sampling was performed at the 0-, 8-, 18-, and 28-month visits and included the evaluation of liver and kidney function. Patients discontinued therapy if, during the trial, their estimated creatinine clearance decreased to <30 mL/min; but they could have it restarted if the estimated creatinine clearance returned to ≥30 mL/min.

Outcome Events

The study outcomes of RELY-ABLE were the same as those of RE-LY[4]: stroke (ischemic or hemorrhagic), systemic embolism, myocardial infarction, pulmonary embolism, vascular death, and total mortality. Safety outcomes included major, life-threatening, minor, and total bleeding, and deep vein thrombosis. Net clinical benefit was defined as a composite of the following events: stroke, systemic embolism, myocardial infarction, pulmonary embolism, death, or major bleeding. Major bleeding was defined as bleeding associated with a reduction in hemoglobin of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells or symptomatic bleeding into a critical area or organ. Major bleeds were classified as life-threatening if they met any of the following criteria: fatal, symptomatic, intracranial, hemoglobin reduction ≥50 g/L, transfusion ≥ 4

U, associated with hypotension requiring intravenous inotropic agents or necessitating surgical intervention. Minor bleeds were any other clinical bleeds that did not fill the criteria for major bleeds. There was no adjudication of outcome events occurring in RELY-ABLE.

Statistical Analysis

There was no primary outcome for RELY-ABLE because the study was descriptive. The statistical analysis describes the outcomes of patients on the 2 doses of dabigatran and compares their efficacy and safety. Cox proportional hazards modeling was used to compare the outcomes between patients receiving dabigatran 110 and 150 mg. Data analysis included only patients enrolled in RELY-ABLE from the time of enrollment in RELY-ABLE until the 28-month visit.

A total of 5891 patients were entered in RELY-ABLE, of whom 8 did not receive a single study dose, and 32 others were excluded from the analysis because of serious protocol violations during RELY-ABLE at their clinical centers. The data set for the analysis of the RELY-ABLE cohort included 5851 patients. There were 695 patients enrolled into RELY-ABLE after the RE-LY final visit was completed (342 and 353 on dabigatran 110 and 150 mg, respectively). Of these, 369 patients were enrolled in RELY-ABLE within 4 weeks and 326 others between 4 and 8 weeks beyond the RE-LY final visit. No strokes or deaths and 3 major bleeds occurred in these patients during the interim period between the 2 studies. This period is not included in the RELY-ABLE analysis. Baseline characteristics of RE-LY patients enrolled and not enrolled in RELY-ABLE receiving dabigatran 110 mg or 150 mg were compared by using the Student t test or χ^2 tests as appropriate; in addition, the probability value for RE-LY treatment interaction was calculated.

Study Conduct

The study was sponsored by Boehringer-Ingelheim and was coordinated at the Population Health Research Institute at McMaster University in Hamilton, Ontario, which independently managed the database and performed the primary data analysis. An operations group 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. The study was approved by an institutional review committee at each site, and all subjects gave informed consent. The authors had complete access to the primary clinical trial data. The trial was registered at clinicaltrials.gov (unique identifier: NCT00808067).

Results

Table 1 shows the disposition of patients randomly assigned to dabigatran from the beginning of RE-LY to the 28-month visit in RELY-ABLE. There were 403 (13.8%) patients on dabigatran 110 mg and 429 (14.6%) patients on dabigatran 150 mg twice daily who permanently discontinued their study medication before the 28-month study visit of RELY-ABLE. The Kaplan-Meier estimates of the time to permanent study medication discontinuation at 2 years were 11.0% (95% confidence interval [CI], 9.9%–12.2%) for dabigatran 110 mg and 11.9% (95% CI, 10.8%–13.2%) on dabigatran 150 mg (Figure II in the online-only Data Supplement). There were 2188 patients who continued to receive study medication and to participate in RELY-ABLE beyond the 28-month visit. (This was done to continue safety follow-up in countries where the drug was not yet available commercially.) The median duration of follow-up for RELY-ABLE patients (up to the 28-month visit) was 2.3 years. The longest duration of follow-up of any patient receiving dabigatran, from the beginning of RE-LY to the 28-month visit of RELY-ABLE, was 5.5 years. During RELY-ABLE, there were temporary interruptions of study medication in 1244 (43%) patients receiving dabigatran 110 mg and in 1294 (44%) patients receiving dabigatran 150 mg. The most common reasons for these interruptions were surgery and hospitalization (48% and 18% of interruptions, respectively).

Patient Characteristics

The RE-LY baseline clinical characteristics of patients participating in RELY-ABLE, in general, were similar to those of patients not participating in RELY-ABLE, but there were some significant differences (Table 2). Patients who enrolled in RELY-ABLE were more likely to be male and to have paroxysmal rather than permanent AF and less likely to have a history of heart failure, but they had rates of diabetes mellitus and documented coronary disease similar to other RE-LY patients. The evaluation of baseline clinical characteristics of enrolled and not enrolled patients according to dabigatran dose (Table 2) showed no systematic differences between doses for any of the baseline clinical characteristics. Patients who were enrolled in RELY-ABLE were also less likely to have had a major clinical event during the RE-LY study in comparison with patients who participated in RE-LY but did not continue in RELY-ABLE. Table I in the online-only Data Supplement shows baseline characteristics that were reassessed at the time of enrollment into RELY-ABLE (1–3 years after enrollment into RE-LY).

During RELY-ABLE (Table 3 and Figure 1), the annual rates of stroke or systemic embolism were 1.46% and 1.60%/y

Table 1. Patient Disposition in RE-LY and RELY-ABLE

	Dabigatran 150 mg	Dabigatran 110 mg
Randomized to dabigatran in RE-LY	6076	6015
Completed RE-LY alive and still receiving study dabigatran	4519	4492
Patient followed at site participating in RELY-ABLE	3397	3395
Patient enrolled in RELY-ABLE *	2937	2914
Completed RELY-ABLE still receiving study medication†	2508	2511
Continued in RELY-ABLE beyond the 28-month visit‡	1102	1086

The study was performed in 35 countries at 598 clinical centers. The geographic distribution of patients was 38% from Canada or United States, 33% from Western Europe, 12% from Asia, 11% from Central Europe, 6% from Australia and Israel, and 1% from Brazil. RE-LY indicates Randomized Evaluation of Long-term Anticoagulation Therapy; and RELY-ABLE, Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation.

*Does not include 8 patients who received no dose of study medication in RELY-ABLE and 32 patients treated at sites with serious Good Clinical Practice violations.

†Either patient died or completed 28-month RELY-ABLE visit without permanent study medication discontinuation.

‡Available for patients in countries where the RELY-ABLE trial was extended beyond the 28-month visit'

Table 2. RE-LY Baseline Patient Characteristics and Clinical Events During RE-LY

	RE-LY Patients Not Enrolled in RELY-ABLE		RE-LY Patients Enrolled in RELY-ABLE		*P*-Values	
	150 mg (n=3139)	110 mg (n=3101)	150 mg (n=2937)	110 mg (n=2914)	Enrolled vs Not Enrolled	110 vs 150 mg
Age, y, mean (SD)	72 (9)	72 (9)	71 (8)	71 (8)	0.001	0.55
Systolic BP-sitting, mm Hg; mean (SD)	131 (18)	131 (18)	131 (18)	131 (18)	0.20	0.46
Heart rate, beats/min; mean (SD)	74 (15)	75 (15)	73 (15)	73 (15)	<0.001	0.08
Male, n (%)	1929 (62)	1951 (63)	1911 (65)	1914 (66)	0.03	0.64
AF diagnosed >2 y; nr (%)	1503 (48)	1463 (47)	1373 (47)	1380 (47)	0.89	0.47
Persistent AF, n (%)	1004 (32)	1017 (33)	905 (31)	933 (32)	0.52	0.81
Paroxysmal AF, n (%)	912 (29)	905 (29)	1066 (36)	1024 (35)	<0.001	0.47
Permanent AF, n (%)	1222 (39)	1177 (38)	966 (33)	955 (33)	<0.001	0.64
Prior stroke or TIA, n (%)	611 (20)	614 (20)	622 (21)	581 (20)	0.89	0.28
Vitamin K antagonist experienced, n (%)	1524 (49)	1475 (48)	1525 (52)	1536 (53)	<0.001	0.33
History of hypertension, n (%)	2505 (80)	2417 (78)	2290 (78)	2321 (80)	0.11	0.02
History of myocardial infarction, n (%)	551 (18)	542 (18)	478 (16)	466 (16)	0.12	0.87
History of heart failure, n (%)	1121 (36)	1147 (37)	813 (28)	790 (27)	<0.001	0.29
History of diabetes mellitus, n (%)	765 (24)	734 (24)	637 (22)	675 (23)	0.64	0.15
History of CAD, n (%)	878 (28)	868 (28)	832 (28)	793 (27)	0.50	0.49
$CHADS_2$ risk score, mean (SD)	2.2 (1.1)	2.2 (1.1)	2.1 (1.1)	2.1 (1.1)	<0.001	0.32
Baseline use of β-blocker, n (%)	1892 (60)	1853 (60)	1980 (67)	1931 (66)	<0.001	0.68
Baseline use of statin, n (%)	1293 (41)	1292 (42)	1374 (47)	1406 (48)	<0.001	0.60
Baseline use of ARB or ACE inhibitor, n (%)	2118 (68)	2043 (66)	1935 (66)	1944 (67)	0.52	0.16
Events occurring during RE-LY						
Major bleed, event number (rate/y)	309 (5.3)	251 (4.3)	91 (1.5)	91 (1.5)	<0.001	0.21
Stroke, event number (rate/y)	106 (1.8)	140 (2.4)	17(0.3)	31 (0.5)	<0.001	0.33
Myocardial infarction, event number (rate/y)	67 (1.1)	60 (1.0)	22 (0.3)	28 (0.5)	<0.001	0.29

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; $CHADS_2$; RE-LY, Randomized Evaluation of Long-term Anticoagulation Therapy; RELY-ABLE, Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation; SD, standard deviation; and TIA, transient ischemic attack.

on dabigatran 150 and 110 mg, respectively (hazard ratio [HR], 0.91; 95% CI, 0.69–1.20). Annual rates of ischemic stroke (including stroke of uncertain cause) were 1.15% and 1.24%/y on dabigatran 150 and 110 mg, respectively (HR, 0.92; 95% CI, 0.67–1.27). Annual rates of hemorrhagic stroke were similar in the 2 treatment arms and were very low at 0.13% and 0.14%/y on dabigatran 150 and 110 mg, respectively. Annual rates of myocardial infarction were also low and similar between the 2 groups at 0.69% and 0.72%/y.

Annual rates of major bleeding (Table 4 and Figure 2) were 3.74% and 2.99%/y on dabigatran 150 and 110 mg twice daily, respectively (HR, 1.26; 95% CI, 1.04–1.53). Annual rates of

Table 3. Stroke, Ischemic Outcomes, and Hospitalizations

	150 mg n (%/y)	110 mg n (%/y)	HR (150 mg vs 110 mg)	95% CI
Stroke or systemic embolism	93 (1.46)	102 (1.60)	0.91	0.69–1.20
All stroke	79 (1.24)	88 (1.38)	0.89	0.66–1.21
Ischemic or type uncertain	73 (1.15)	79 (1.24)	0.92	0.67–1.27
Hemorrhagic	8 (0.13)	9 (0.14)	0.89	0.34–2.30
Nondisabling (modified Rankin score 0–2)	36 (0.57)	49 (0.77)	0.73	0.48–1.13
Disabling (modified Rankin score 3–5) or fatal	40 (0.63)	39 (0.61)	1.03	0.66–1.59
Myocardial infarction	44 (0.69)	46 (0.72)	0.96	0.63–1.45
Pulmonary embolism	8 (0.13)	7 (0.11)	1.14	0.41–3.15
Cardiovascular hospitalization	634 (9.96)	619 (9.74)	1.03	0.92–1.15
Any hospitalization	1204 (18.9)	1170 (18.4)	1.04	0.96–1.12

CI indicates confidence interval; HR, hazard ratio; and %/y, rate per 100 patient-years of follow-up.

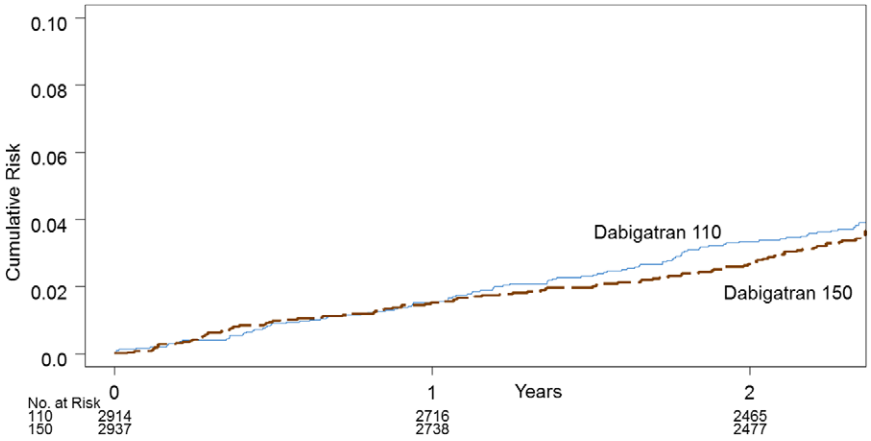

Figure 1. Stroke or systemic embolism.

major gastrointestinal bleeding were similar between treatments at 1.54% and 1.56%/y for dabigatran 150 and 110 mg, respectively. Mortality rates were similar for the 2 dabigatran doses (3.10% and 3.02%/y for 110 and 150 mg, respectively) with a hazard ratio very close to unity (HR=0.97) (Figure 3).

During RELY-ABLE, serious adverse events occurred in 1067 (36.3%) and 982 (33.7%) patients receiving dabigatran 150 and 110 mg, respectively. Dyspeptic symptoms were reported in 141 (4.8%) and 156 (5.3%) of patients receiving dabigatran 110 and 150 mg, respectively, during the RELY-ABLE follow-up (see Figure I and Table II in the online-only Data Supplement, showing time to first serious adverse event and serious adverse events by organ class, respectively). Elevation of the aspartame aminotransferase or of the alanine aminotransferase >3 times the upper limit of normal, together with elevation of the total bilirubin >2 times the upper limit of normal occurred during RELY-ABLE in 4 and 1 patients receiving dabigatran 110 and 150 mg, respectively.

Discussion

For both dabigatran 110 mg and 150 mg twice daily, the rates of major ischemic, hemorrhagic, and fatal outcomes that occurred during an additional period of 2.3 years following RE-LY are not inconsistent with those seen during RE-LY. The mean period of follow-up for RE-LY and RELY-ABLE receiving dabigatran was 4.3 years; some patients on dabigatran were followed for up to 5.5 years. It is particularly noteworthy that the very low rates of hemorrhagic stroke and intracranial bleeding observed in RE-LY continued to be observed during the extended follow-up period.

Rates of stroke or systemic embolism, on dabigatran 150 and 110 mg, were 1.11% and 1.54%/y in RE-LY and 1.46% and 1.60%/y in RELY-ABLE. The slightly higher rates in RELY-ABLE are at least partly because there was no event adjudication in RELY-ABLE. In RE-LY, adjudication either confirmed reported events or rejected them (84% and 87% of reported stroke or systemic emboli on dabigatran 150 and 110 mg, respectively, were confirmed). It may also be, in part, attributable to the increased age of patients during RELY-ABLE follow-up. Rates of major bleeding on dabigatran 150 and 110 mg were 3.32% and 2.87%/y in RE-LY and 3.74% and 2.99%/y in RELY-ABLE (adjudication in RE-LY confirmed 93% of reported major bleeds on both doses). Rates of hemorrhagic stroke and myocardial infarction remained very low in RELY-ABLE, <0.14%/y and <0.71%/y, respectively; very similar to the rates seen in RE-LY. This provides reassurance

Table 4. Bleeding and Net Benefit Outcomes

	150 mg n (%/y)	110 mg n (%/y)	HR (150 mg vs 110 mg)	95% CI
Major bleeding	238 (3.74)	190 (2.99)	1.26	1.04–1.53
Life-threatening	114 (1.79)	100 (1.57)	1.14	0.87–1.49
Gastrointestinal	98 (1.54)	99 (1.56)	0.99	0.75–1.31
Intracranial	21 (0.33)	16 (0.25)	1.31	0.68–2.51
Extracranial	218 (3.43)	179 (2.82)	1.23	1.01–1.49
Fatal	15 (0.24)	16 (0.25)	0.94	0.46–1.89
Minor bleeding	617 (9.70)	521 (8.19)	1.21	1.07–1.36
Net clinical benefit outcomes				
Total mortality	192 (3.02)	197 (3.10)	0.97	0.80–1.19
Vascular mortality	106 (1.67)	103 (1.62)	1.03	0.78–1.35
Disabling stroke, life-threatening bleed, or death	288 (4.53)	283 (4.45)	1.02	0.86–1.20
Stroke, systemic embolism, myocardial infarction, pulmonary embolism, major bleed, or death	468 (7.36)	438 (6.89)	1.07	0.94–1.22

CI indicates confidence interval; and HR, hazard ratio.

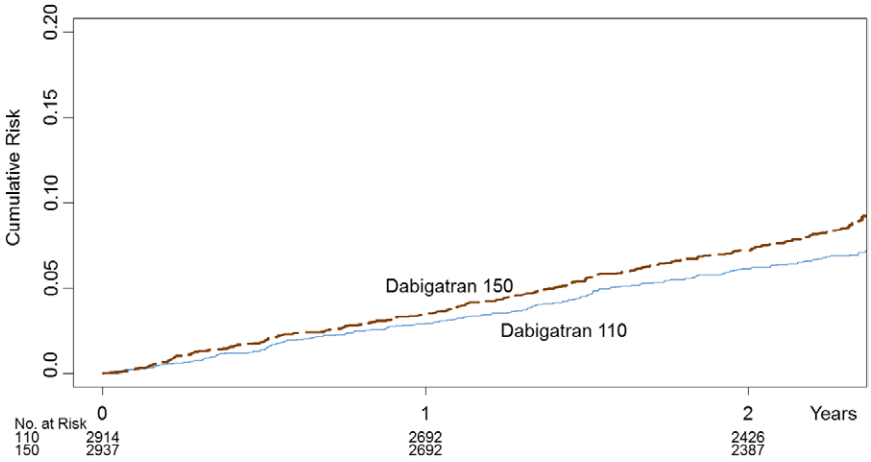

Figure 2. Major bleeding.

that the effects of dabigatran seen during RE-LY are not inconsistent with those seen during longer-term treatment.

Only about half of the dabigatran patients participating in RE-LY were enrolled in RELY-ABLE. Many patients were not eligible owing to medication discontinuation during RE-LY or to nonparticipation of the clinical site. Enrollment rates at participating sites, among eligible patients, were high (86%). There does not appear to be any bias in enrollment for RELY-ABLE based on dabigatran dose. There were almost equal numbers of patients enrolled in RELY-ABLE on each blinded dose, and statistical testing to determine interaction between dabigatran dose and patient characteristics of patients enrolled in RELY-ABLE (versus not enrolled) were not significant. It is not surprising that patients entering RELY-ABLE were less likely to have had either a stroke or bleed (or death) during RE-LY than those who did not enter RELY-ABLE. Patients with major events during RE-LY would be more likely to die or discontinue study medication during RE-LY (making them ineligible for RELY-ABLE). Once enrolled in RELY-ABLE, however, the ischemic and hemorrhagic event rates of these patients were very similar to those of the overall RE-LY population, suggesting the intrinsic risk for events of the RELY-ABLE patients differed little from that of the other RE-LY patients.

In RE-LY, randomized comparison of the 2 doses of dabigatran demonstrated that the 150-mg dose reduced ischemic (or unspecified) stroke in comparison with the 110-mg dose (HR, 0.69; 95% CI, 0.54–0.88; P=0.002), but with a trend to increased major bleeding (HR, 1.16; 95% CI, 1.00–1.34; P=0.04). The mortality (HR, 0.97; 95% CI, 0.85–1.11; P=0.66) and the rate of hemorrhagic stroke, as well, was similar between the dabigatran doses in RE-LY.[4,5] In RELY-ABLE, the relative advantage of the higher dose over the lower dose for ischemic stroke was small (HR, 0.92; 95% CI, 0.67–1.27). There was, however, a higher rate of major bleeding with the higher dose of dabigatran in comparison with the 110 mg twice daily dose (HR, 1.26; 95% CI, 1.04–1.53). There was no difference in mortality between the 2 doses either in RE-LY or in RELY-ABLE. Likewise, analysis of the composite of all major ischemic, hemorrhagic, and fatal events as a measure of net benefit indicates that the 2 doses achieve similar net clinical effects. The similar HRs (150 mg versus 110 mg) for this outcome in RE-LY and RELY-ABLE are 0.97 (95% CI, 0.88–1.07) and 1.07 (95% CI, 0.94–1.22), respectively.

There are several limitations of RELY-ABLE which include the following: only one-half of the patients continued from RE-LY to RELY-ABLE, no event adjudication was done in RELY-ABLE, and data analysis was not by the intention to treat. Patients enrolled in RELY-ABLE were different from those in RE-LY, and they may have been at lower risk of events. The main strengths are that RELY-ABLE more than doubled the duration of follow-up from that of RE-LY, and patients continued to receive the same dose of dabigatran

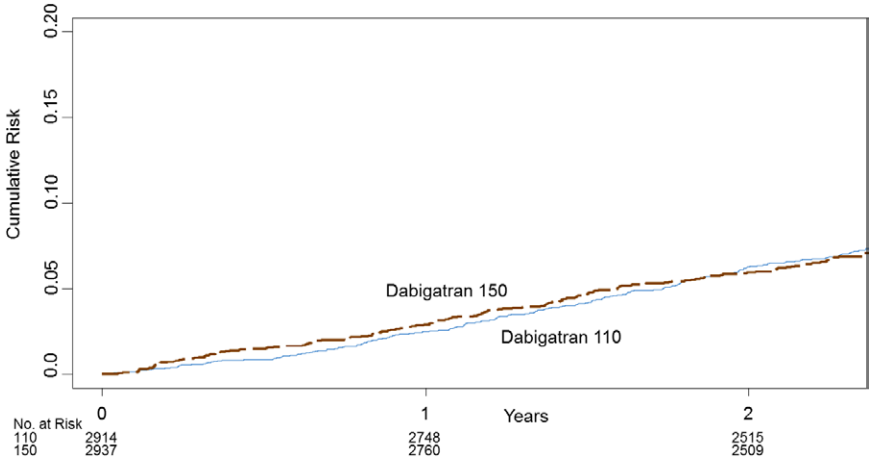

Figure 3. Total mortality.

(double-blind) as they had done in RE-LY. Registries of patients receiving new oral anticoagulants or warfarin also provide useful information about the long-term efficacy and safety of these agents. Once completed, these registries will provide more long-term safety data in populations of real-world patients. One recently published registry reports a rate of intracranial bleeding on dabigatran of 0.3%/y that is consistent with the low intracranial bleeding rates seen in RE-LY and RELY-ABLE with dabigatran 150 mg twice daily.[9]

In summary, the RELY-ABLE study provides additional safety information for a large cohort of patients continuing the same dose of dabigatran as assigned in the RE-LY trial during 2.3 years of additional treatment (total mean follow-up, 4.3 years). During the additional 2.3 years of treatment, the rates of major events were not inconsistent with those seen in RE-LY. In the comparison of the 2 dabigatran doses in RELY-ABLE, there was no significant difference in stroke or mortality, but there was a higher rate of major bleeding with the higher dabigatran dose. There was no difference between the doses in net clinical benefit as estimated by the composite of stroke, bleeding, and death.

Disclosures

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CLINICAL PERSPECTIVE

Patients receiving dabigatran during the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial were eligible to continue their double-blind dose of dabigatran during an additional 2.3 years of follow-up as part of the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial. The purpose of RELY-ABLE was to examine the long-term safety and efficacy of dabigatran. Not all countries or sites participated in RELY-ABLE and ≈25% of eligible patients declined to enroll in RELY-ABLE; thus, just under half of the 12 091 patients receiving dabigatran in RE-LY were entered into the RELY-ABLE long-term extension study. No patients on warfarin were enrolled in RELY-ABLE. RELY-ABLE was an observational study rather than a definitive clinical trial. Patients entering RELY-ABLE were somewhat different from patients enrolled in RE-LY but who did not enter RELY-ABLE. During RELY-ABLE, rates of stroke and systemic embolism on dabigatran were similar to rates observed during RE-LY. This is also true for rates of other important ischemic and thrombotic outcomes and for the safety outcome of major bleeding. Rates of hemorrhagic stroke during RELY-ABLE remained very low as seen during RE-LY. During RELY-ABLE, there was a trend for a lower rate of stroke or systemic embolism on the higher dose of dabigatran and a higher rate of major bleeding on the higher dose of dabigatran. Total mortality on the 2 dabigatran groups was similar. Thus, RELY-ABLE provides some reassurance that the rates of stroke, major bleeding, and death seen during RE-LY on dabigatran are likely to continue during an additional 2-year period of follow-up.

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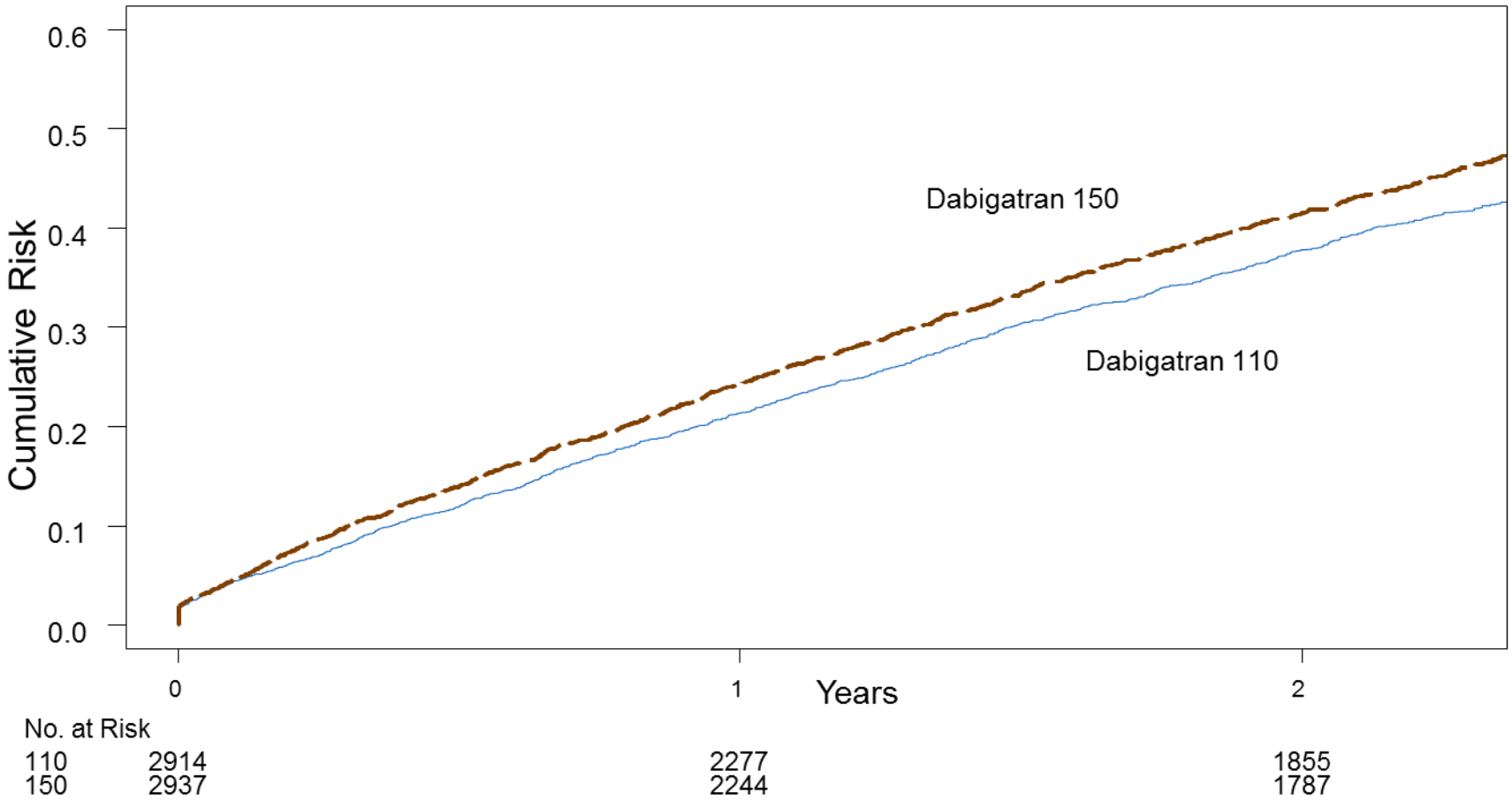
SUPPLEMENTAL MATERIAL

Supplemental Table 1: Selected Baseline Patient Characteristics of RELY-ABLE Patients at time of RELY-ABLE Enrolment

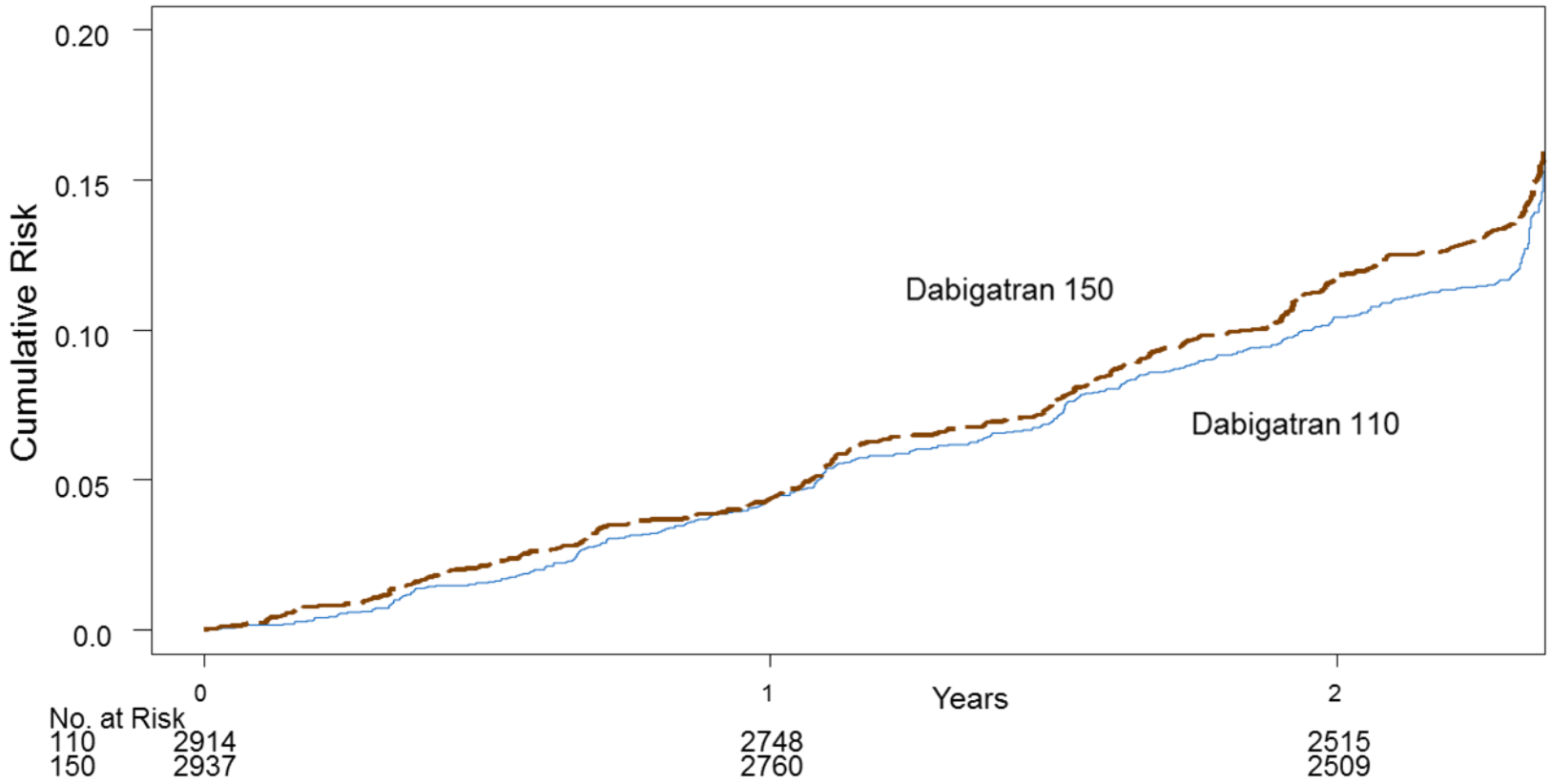
	150 mg	110 mg
Age (years); mean, (SD)	73 (8)	73 (8)
Systolic BP-sitting (mmHg); mean, (SD)	131 (18)	132 (18)
Heart rate, sitting beasts/minute); mean, (SD)	72 (14)	72 (14)
Male; number (%)	1911 (65)	1914(66)
Persistent AF; number (%)	546 (19)	575 (20)
Paroxysmal AF; number (%)	933 (32)	910 (31)
Permanent AF; number (%)	1454 (50)	1424 (49)
History of Hypertension; number (%)	2398 (82)	2384 (82)
History of heart failure	689 (24)	655 (23)
History of diabetes mellitus; number (%)	744 (25)	796 (27)
History of CAD; number (%)	938 (32)	919 (32)
Baseline use of beta blocker; number (%)	1877 (64)	1901 (65)
Baseline use of Statin; number (%)	1515 (52)	1515 (52)

Baseline use of ACE inhibitor; number (%)	1270 (43)	1224 (42)
Baseline use of ARB; number (%)	768 (26)	811 (28)

Supplemental Figure 1 - RELY-ABLE: Time to Serious Adverse Event



Supplemental Figure 2 – RELY-ABLE: time to Permanent Discontinuation of Study Medication



Supplemental Figure 2: Serious Adverse Events in RELY-ABLE by Organ Class

	110 mg		150 mg	
System Organ Class	N	%	N	%
Participants	2914	100.0	2937	100.0
Total Patient with SAE	982	33.7	1067	36.3
Blood and lymphatic system disorders	42	1.4	49	1.7
Cardiac disorders	323	11.1	368	12.5
Congenital, familial and genetic disorders	.	.	1	0.0
Ear and labyrinth disorders	8	0.3	6	0.2
Endocrine disorders	3	0.1	4	0.1
Eye disorders	17	0.6	18	0.6
Gastrointestinal disorders	145	5.0	148	5.0
General disorders and administration site conditions	87	3.0	87	3.0
Hepatobiliary disorders	32	1.1	18	0.6
Immune system disorders	2	0.1	1	0.0
Infections and infestations	225	7.7	240	8.2
Injury, poisoning and procedural complications	108	3.7	115	3.9
Investigations	20	0.7	13	0.4
Metabolism and nutrition disorders	41	1.4	58	2.0
Musculoskeletal and connective tissue disorders	73	2.5	95	3.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	126	4.3	117	4.0
Nervous system disorders	91	3.1	86	2.9
Psychiatric disorders	16	0.5	19	0.6
Renal and urinary disorders	53	1.8	58	2.0
Reproductive system and breast disorders	16	0.5	14	0.5
Respiratory, thoracic and mediastinal disorders	104	3.6	111	3.8
Skin and subcutaneous tissue disorders	12	0.4	5	0.2
Social circumstances	1	0.0	1	0.0
Surgical and medical procedures	3	0.1	2	0.1
Vascular disorders	64	2.2	64	2.2