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Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: GLORIA-AF Registry

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Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: GLORIA-AF Registry

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Cover Title: GLORIA-AF registry: 2-year follow-up data

WHAT IS KNOWN

- Non- vitamin K antagonist (VKA) anticoagulants (NOACs) are the preferred therapy for prevention of ischemic stroke based on phase 3 trials, but there is insufficient information on their efficacy and safety in daily practice, based on prospectively collected data

WHAT IS NEW

- This study shows that in non-valvular AF patient population, with up to 2 years of follow-up, the use of dabigatran led to a low incidence of ischemic stroke, major bleeding, and myocardial infarction in routine clinical care, confirming the sustained safety and effectiveness of dabigatran in clinical practice over 2 years of follow-up

ABSTRACT

Background and Purpose—GLORIA-AF is a large, global, prospective registry program of newly diagnosed atrial fibrillation (AF) patients with ≥1 stroke risk factors. We describe the effectiveness and safety of dabigatran etexilate over 2 years from routine clinical practice in nearly 3000 patients from GLORIA-AF who are newly diagnosed with non-valvular AF and at risk of stroke.

Methods—Consecutive enrollment into phase II of GLORIA-AF was initiated following approval of dabigatran for stroke prevention in non-valvular AF. Within this Phase II, 2937 dabigatran patients completed 2-year follow-up by May 2016 and were eligible for analysis. Patients who took at least 1 dose of dabigatran (n=2932) were used to estimate incidence rates.

Results—Overall incidence rates per 100 person-years of 0.63 (95% confidence interval [CI], 0.42–0.92) for stroke, 1.12 (0.83–1.49) for major bleeding, 0.47 (0.29–0.72) for myocardial infarction, and 2.69 (2.22–3.23) for all-cause death were observed. For patients taking 150 mg dabigatran twice daily (BID), corresponding rates (95% CI) were 0.56 (0.30–0.94), 1.00 (0.64–1.47), 0.48 (0.25–0.83), and 2.07 (1.55–2.72), respectively. For patients taking 110 mg dabigatran BID, event rates (95% CI) were 0.67 (0.33–1.20), 1.16 (0.70–1.80), 0.43 (0.17–0.88), and 3.16 (2.36–4.15).

Conclusions—These global data confirm the sustained safety and effectiveness of dabigatran over 2 years of follow-up, consistent with the results from clinical trials as well as contemporary real-world studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT01468701, NCT01671007, and NCT01937377.

Introduction

Anticoagulant therapy is indicated to reduce the risk of ischemic stroke in patients with atrial fibrillation (AF). Vitamin K antagonists (VKAs; for example, warfarin) significantly reduce the risk of ischemic stroke and death but increase the risk of major bleeding and intracranial hemorrhage (ICH).[1] Non-VKA oral anticoagulants (NOACs) have been shown to be at least as effective but safer than VKAs in terms of ICH[2] and are now indicated as preferential anticoagulants in most recent guidelines.[3]

While several non-interventional studies based on, for example, claims data or nationwide registries have been published showing the effectiveness and safety of dabigatran etexilate (hereafter "dabigatran") compared with warfarin,[4–8] prospective registries will provide complementary evidence of the effectiveness and safety of dabigatran in daily practice.

The Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry program is a large, global, prospective registry of consecutive newly diagnosed AF patients with ≥1 stroke risk factor.[9] Here, we report a pre-specified interim analysis of 2937 dabigatran patients in phase II of GLORIA-AF who completed 2-year follow-up by May 2016.

Methods

Design

The design of GLORIA-AF, a global, non-interventional registry program with 3 phases, has been described in detail.[9] In phase II, which started in each country upon approval of dabigatran, cross-sectional data, for example, AF disease characteristics, medical conditions including concomitant diseases, and medications, were collected at baseline for all enrolled patients with newly diagnosed AF. No additional procedures, apart from assessments performed as part of routine clinical practice, were required. In patients prescribed dabigatran, 2-year follow-up was performed to describe its safety and effectiveness. Ethical approval was obtained from the Institutional Review Boards as required at participating sites.

Patients

Consecutive adult patients with ≥1 risk factor for stroke [CHA_2DS_2-VASc scores ≥1, based on the presence of congestive heart failure; hypertension; age ≥75 years (doubled); diabetes; stroke (doubled); vascular disease; age 65–74 years; and sex category (female)], and newly diagnosed with non-valvular AF (that is AF diagnosed within 3 months of the first visit [[documented by 12-lead electrocardiogram (ECG), ECG rhythm strip, pacemaker/implantable cardioverter defibrillator ECG, or Holter ECG] were included between November 2011 and December 2014. Patients with mechanical heart valves, prior VKA therapy for >60 days, life expectancy ≤ 1 year at enrollment, a medical condition other than AF for which chronic use of VKAs is indicated and AF due to a generally reversible cause were excluded. Bleeding risk was assessed by the HAS-BLED bleeding score, which includes the presence of hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years, and drugs and/or alcohol concomitantly.[10] Patients were recruited from outpatient settings including university hospitals, community hospitals,

specialist offices, and general practice offices. Centers were selected to reflect physicians who typically identify and manage new AF cases in a given country.

Medication

Dabigatran was prescribed at the discretion of the treating physician, and according to available doses (150, 110, and 75 mg twice daily [BID] depending on the country and local label); patients who took at least 1 dose of dabigatran were included in the outcome event analysis.

Follow-up and Outcomes

Follow-up visits took place at 3, 6, 12, and 24 months post baseline. Two-year outcomes included stroke (ischemic or hemorrhagic), systemic embolism, major bleeding, life-threatening bleeding, myocardial infarction (MI), vascular death, all-cause death (including death of unknown cause), as well as the composite end point of stroke, systemic embolism, MI, life-threatening bleeding, and vascular death. The analysis for estimation of incidence rates includes only the dabigatran treatment period as prespecified in the analysis plan. Data collected after permanent discontinuation of dabigatran (defined as treatment discontinued for >30 days or switch to another OAC) were not included in the analysis.

Data Collection and Quality Control

Clinical data were collected using a validated web-based system to ensure confidentiality and integrity. Study staff at each site entered data over a secure network and study physicians electronically signed the case report form to confirm accuracy and completeness of the information. Data quality and queries were addressed during bimonthly telephone calls to all sites, by periodic site monitoring, and independent audits. Additional data quality measures

included automatic programmed data checks, bimonthly manual data reviews, and quarterly medical quality reviews of aggregate data to address any systematic data issues identified (for example, trends for missing data).

Statistical Analysis

Data are summarized by means or medians and standard deviation (SD) or quartiles (Q1, Q3) for continuous variables, and by frequencies and percentages for categorical variables. Incidence rates are shown per 100 person-years and two-sided 95% confidence intervals (CIs), based on the Poisson distribution and its relation to the χ^2-distribution,[11] and are based on the period from commencement of dabigatran until permanent treatment cessation (that is, treatment stop +3 days, switch to another treatment, or study completion/discontinuation). Treatment interruptions of <30 days were disregarded for the analyses. Kaplan-Meier plots for time-to-event data are provided. Descriptive results are presented and no statistical hypothesis tests were performed. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of 15 641 patients enrolled in 44 countries, 2937 were prescribed dabigatran and were eligible for this interim analysis of 2-year follow-up data; 2932 took dabigatran at least once and were included in the outcome analysis.

Dabigatran was prescribed mostly by cardiologists (91.1%). Other treating physicians included general practitioners (3.5%), internists (2.1%), and neurologists (1.6%). The

majority of patients were followed at a specialist office (36.4%), community hospital (29.5%), university hospital (21.7%), and the remainders were treated at a primary care center (7.7%), outpatient or anticoagulation clinics (4.0%), or "other" (0.8%). Participating countries per region and regional contributions are summarized in Figure 1.

Mean age at enrollment was 70.3 years (SD, 10.2), median 71.0 (Q1–Q3, 64.0–78.0). Table 1 shows patient demographic and baseline characteristics. The most prevalent comorbidities were history of hypertension (78.9%), hyperlipidemia (44.5%), congestive heart failure (24.9%), diabetes mellitus (22.7%), left ventricular hypertrophy (25.0%), coronary artery disease (20.2%), and history of stroke (10.1%). Paroxysmal AF was present in 50.6% of patients, 36.2% had persistent AF, and 13.2% had permanent AF. AF was symptomatic in 26.5%, and minimally symptomatic or asymptomatic in 73.5% of patients. The median CHA_2DS_2-VASc score was 3.0 (SD, 1.4), and 88.2% had CHA_2DS_2-VASc score ≥ 2. Median HAS-BLED score was 1.0 (SD, 0.8), with scores <3 in most patients (83.5%).

Dabigatran Treatment

Dabigatran 150 mg BID was prescribed to 1748 (59.5%), dabigatran 110 mg BID to 1106 (37.7%), and dabigatran 75 mg BID to 73 (2.5%) patients. Mean duration of on-treatment follow-up in the initial treatment period was 17.7 months (SD, 9.3). The probability that of remaining on dabigatran therapy for at least 24 months was ~70% based on Kaplan-Meier estimates. Among patients who discontinued dabigatran (n = 828, 28.2%), approximately one third stopped dabigatran primarily due to dyspepsia or other AEs or SAEs. The majority of respondents cited "other" reason(s) (without further details) as the primary reason for discontinuation (n = 495, 59.8%). As expected, patients taking lower doses of dabigatran were older and had lower

creatinine clearances, higher CHA_2DS_2-VASc and HAS-BLED scores, and more often a past stroke event or MI (Table 1).

Clinical Outcomes

During follow-up the incidence rate per 100 person-years for stroke was 0.63 (95% CI, 0.42–0.92; Table 2), for major bleeding 1.12 (95% CI, 0.83–1.49), for life-threatening bleeding 0.54 (95% CI, 0.34–0.81), and for fatal bleeding 0.12 (95% CI, 0.04–0.27). Incidence rates per 100 person-years for MI, overall death, and vascular death were 0.47 (95% CI, 0.29–0.72), 2.69 (95% CI, 2.22–3.23), and 0.91 (95% CI, 0.65–1.25), respectively. The rate of the composite end point—stroke, systemic embolism, MI, life-threatening bleed, or vascular death—was 2.24 (95% CI, 1.81–2.73) per 100 person-years. Figure 2 shows the estimated cumulative probabilities based on the Kaplan-Meier estimates for major bleeding, stroke, and MI.

Table 3 shows outcomes by subtype. Among strokes, most were ischemic. Primary hemorrhagic strokes occurred in only 0.07 cases per 100 patient-years. Only 10.7% of stroke events were classified as hemorrhagic strokes. Gastrointestinal was the most prevalent bleeding location (upper 29%, lower 31%, not further specified 6%).

Clinical Outcome by Different Doses of Dabigatran

For patients taking 150 mg dabigatran BID, incidence rates per 100 patient-years were 0.56 (95% CI, 0.30–0.94) for stroke, 1.00 (95% CI, 0.64–1.47) for major bleeding, 0.48 (95% CI, 0.25–0.83) for MI, and 2.07 (95% CI, 1.55–2.72) for all-cause death. For patients taking 110 mg dabigatran BID, corresponding event rates were 0.67 (0.33–1.20) for stroke, 1.16 (0.70–1.80) for major bleeding, 0.43 (0.17–0.88) for MI, and 3.16 (2.36–4.15) for all-cause death

(Table 4). Data on 75 mg dabigatran BID were not included in this analysis due to limited patient numbers.

Discussion

This is the first global prospective study to follow a large cohort of consecutive, newly diagnosed AF patients treated with dabigatran in daily clinical practice. After up to 2 years of follow-up the overall incidence rate for stroke (ischemic or hemorrhagic) was 0.63 per 100 person-years (0.56 and 0.67 for patients taking dabigatran 150 and 110 mg BID, respectively) and for major bleeding was 1.12 per 100 person-years (1.16 for dabigatran 110 mg BID and 1.00 for dabigatran 150 mg BID).

Comparison With Other Non-Interventional Studies

Direct comparisons with other published incidence rates are misleading unless adjusted for differences in patient characteristics. Standardizing the compared incidence rates addresses this problem[12], but the data needed for standardization are seldom published. One exception was the US Food and Drug Administration (FDA)-sponsored Medicare claims database study (FDA/Medicare), which included patients aged ≥65 years taking dabigatran 150 or 75 mg BID and reported age- and sex-specific incidence rates.[4] Consequently, we were able to standardize the results of this study to the age and sex distribution of GLORIA-AF for the population aged ≥65 years taking dabigatran 150 and 75 mg BID. In GLORIA-AF, for this specific population, incidence rates per 100 patient-years were 0.66 for ischemic stroke, 0.18 for ICH, and 0.95 for major gastrointestinal bleeding. The corresponding incidence rates per 100 patient-years in the FDA/Medicare study, standardized to the GLORIA-AF age and sex distribution, are 0.95, 0.26, and 2.66, respectively. Before standardization, the FDA/Medicare rates were 1.13, 0.33, and 3.42, respectively, which are higher because the age distribution of

the FDA/Medicare population was also higher. We emphasize that standardization by age and sex reduces bias in the comparison, but other differences in baseline characteristics (for example, stroke and bleeding risks) or study design (for example, duration of on-treatment follow-up, which was much shorter in the FDA/Medicare study) may remain.

Other studies of incidence rates of outcomes for patients treated with dabigatran did not report data that would allow for standardization. The overall stroke (ischemic or hemorrhagic) incidence rate was 0.92 in a US Department of Defense claims database[7] and 0.77 in a combined analysis from 2 US health insurance databases (both studies including patients taking dabigatran 150 or 75 mg BID).[8] The major bleeding rates were 3.08 and 4.42 per 100 person-years, respectively.[7,8] In a study performed in Danish registries, for VKA naïve patients, when considering outcomes occurring during dabigatran treatment, the major bleeding rates were 4.4 per 100 person-years for patients taking dabigatran 110 mg BID and 2.3 per 100 person-years for patients taking dabigatran 150 mg BID.[5]

Stroke and bleeding risks varied across studies: 72% of patients had a $CHADS_2$ score of ≥2.0 in the FDA/Medicare analysis (the mean score was not reported).[4] The proportion of GLORIA-AF patients with a history of stroke (10%) was also higher than in the FDA/Medicare study (3%). In the US database analysis, the CHA_2DS_2-VASc score (3.9) was higher than in GLORIA-AF,[7] whereas Seeger et al reported a slightly lower CHA_2DS_2-VASc score (2.8) and similar $CHADS_2$ score (1.9).[8] Mean HAS-BLED scores were not reported for most of these database analyses, but the proportion of patients with low HAS-BLED score (<3) was higher in GLORIA-AF (83%) than in the FDA/Medicare analysis (59%),[4] the pooled commercial health insurance databases analysis (65%),[8] and the Department of Defense analysis (23%).[7] In the Danish registry study, the mean HAS-BLED scores of the

VKA naïve patients were 2.32 and 1.70 for patients taking dabigatran 110 and 150 mg BID, respectively, compared with 1.4 and 1.1 in GLORIA-AF. In a routine clinical practice setting, one prospective study evaluating rivaroxaban found comparable stroke rates of 0.7 (95% CI, 0.5–0.9) per 100 person-years but somewhat higher major bleeding rates of 2.1 (1.8–2.5) per 100 person-years.[13] Although the mean HAS-BLED scores were not reported, the mean CHA_2DS_2-VASc score (3.4; SD, 1.7) was similar to that in GLORIA-AF.

In the Context of Clinical Trial Data (RE-LY®)

In the RE-LY® trial, stroke incidence rates per 100 person-years were 1.01 and 1.44 for dabigatran 150 and 110 mg BID, respectively.[14] The corresponding figures for major bleeding were 3.11 and 2.71 per 100 person-years.[14] Event rates in RE-LY, however, should not be compared with the present findings because of differences in the study design, study populations, and stroke and bleeding risk profiles of patients; for example, GLORIA-AF was conducted in a newly diagnosed AF population while the RE-LY[14] study was not. In addition, the baseline CHA_2DS_2-VASc score in GLORIA-AF was 3.2 and the mean $CHADS_2$ score was 1.9, whereas in the RE-LY study[14] the mean $CHADS_2$ score was 2.1. The proportion of GLORIA-AF patients with a history of stroke (10%) was lower than in the RE-LY study (20%). Moreover, the mean HAS-BLED score was relatively low in GLORIA-AF, which may partly explain the low major bleeding rates. Finally, in GLORIA-AF, the dose selection was determined by physician choice, while in the RE-LY[14] trial, dose selection was undertaken by randomization.

The fact that in GLORIA-AF the dabigatran dosages are prescribed by physician choice and stroke and bleeding rates of both examined dabigatran dosages were low is reassuring and underlines the safety of dabigatran in clinical practice.

Persistence

One important potential advantage of NOAC use is persistence on therapy. After 2 years of follow-up, approximately 70% of AF patients were still taking dabigatran, which compares favorably with reported persistence on warfarin, which in one study was only 45% at 1 year.[15] In the prospective study with once-daily rivaroxaban, the therapy persistence rate in clinical practice after 1 year was 80% (data after 2 years are not available), similar that observed in GLORIA-AF with the BID dabigatran regimen (77% after 1 year), indicating that once- or twice-daily dosing of a NOAC seems not to impact therapy persistence.[13]

Limitations and Strengths

Phase II of the GLORIA-AF registry program involved follow-up of dabigatran-treated patients. Consequently, no direct comparisons can be made with other anticoagulants. However, data can be put into perspective by using recent results from other non-interventional and interventional studies. In the ongoing phase III of GLORIA-AF, follow-up data will be collected from all patients, allowing safety and effectiveness analysis for other oral anticoagulants also in a global prospective cohort.[9] No direct comparisons can be made between the dabigatran 150 and 110 mg BID doses since the patient populations differ and, because of the sample size and low numbers of events, only crude incidence rates are provided here. In addition, the outcomes have not been adjudicated in this routine clinical practice analysis. Our cohort had a low HAS-BLED score, which may have led to low major bleeding rates. Moreover, this interim cohort predominantly contained patients from Europe (51%) and North America (28%), making it difficult to draw conclusions for other regions (Latin America, Africa and the Middle East, and Asia). Nonetheless, this study is the largest prospective global cohort of consecutive dabigatran-treated patients reported thus far.

Additional strengths include the regular bimonthly follow-up with physicians to ensure event capture, with regular on-site monitoring and quality reviewing, and the broad physician and site selection worldwide.

Conclusions

This large, global, prospective, observational analysis describing the use of dabigatran in a broad, non-valvular AF patient population with up to 2 years of follow-up showed a low incidence of ischemic stroke, major bleeding, and MI when used in routine clinical care. These data confirm the sustained safety and effectiveness of dabigatran in clinical practice over 2 years of follow-up, consistent with the results observed in clinical trials as well as in contemporary real-world analyses.

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Disclosures

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Figure Legends

Figure 1. Patients per region

A total of 15 092 patients from 44 countries were analyzed in GLORIA-AF phase II (November 2011 to December 2014); 2937 patients were prescribed dabigatran and completed 2-year follow-up before February 2016

Figure 2. Kaplan-Meier curves for stroke, major bleeding, and myocardial infarction in dabigatran-treated patients overall (N=2932 eligible patients)

Table 1. Patient Demographics and Baseline Characteristics by Dabigatran Dose Group*

	Dabigatran 150 mg BID (N=1748)	**Dabigatran 110 mg BID (N=1106)**	**Dabigatran 75 mg BID (N=73)**	**Dabigatran overall (N=2937)**
Age, mean (SD), years	67.2 (9.6)	74.6 (9.3)	78.7 (8.7)	70.3 (10.2)
Age class 1, n (%)				
<80 y	1597 (91.4)	734 (66.4)	34 (46.6)	2372 (80.8)
≥80 y	151 (8.6)	372 (33.6)	39 (53.4)	565 (19.2)
Age class 2, n (%)				
<65 y	628 (35.9)	155 (14.0)	5 (6.8)	790 (26.9)
65–<75 y	737 (42.2)	316 (28.6)	13 (17.8)	1070 (36.4)
≥75 y	383 (21.9)	635 (57.4)	55 (75.3)	1077 (36.7)
BMI, mean (SD), kg/m^2	30.3 (6.4)	27.5 (5.0)	28.4 (8.7)	29.2 (6.1)
Sex, male, n (%)	1049 (60.0)	544 (49.2)	27 (37.0)	1623 (55.3)
Type of AF, n (%)				
Paroxysmal	917 (52.5)	523 (47.3)	37 (50.7)	1486 (50.6)
Persistent	660 (37.8)	369 (33.4)	34 (46.6)	1063 (36.2)
Permanent	171 (9.8)	214 (19.3)	2 (2.7)	388 (13.2)
Categorization of AF, n (%)				
Symptomatic	480 (27.5)	277 (25.0)	19 (26.0)	779 (26.5)
Minimally symptomatic	784 (44.9)	537 (48.6)	37 (50.7)	1365 (46.5)
Asymptomatic	484 (27.7)	292 (26.4)	17 (23.3)	793 (27.0)
Medical history, n (%)				
Previous stroke	149 (8.5)	140 (12.7)	5 (6.8)	296 (10.1)
MI	120 (6.9)	118 (10.7)	10 (13.7)	248 (8.4)

Coronary artery disease	316 (18.1)	247 (22.3)	28 (38.4)	592 (20.2)
Congestive heart failure	398 (22.8)	312 (28.2)	19 (26.0)	732 (24.9)
History of hypertension	1394 (79.7)	846 (76.5)	69 (94.5)	2317 (78.9)
Diabetes mellitus	416 (23.8)	220 (19.9)	26 (35.6)	666 (22.7)
Hyperlipidemia	823 (47.1)	433 (39.2)	45 (61.6)	1307 (44.5)
Prior bleeding	80 (4.6)	63 (5.7)	4 (5.5)	147 (5.0)
Renal impairment†, n (%)	4 (0.2)	3 (0.3)	5 (6.8)	12 (0.4)
Creatinine clearance, mean, mL/min	93.9 (37.3)	68.4 (26.6)	57.6 (34.0)	83.2 (35.9)
CHA_2DS_2-VASc score, mean (SD)	2.9 (1.3)	3.7 (1.4)	4.4 (1.4)	3.2 (1.4)
CHA_2DS_2-VASc score, n (%)				
Score=1	274 (15.7)–	70 (6.3)–	1 (1.4)–	346 (11.8)
Score ≥2	1474 (84.3)–	1036 (93.7)–	72 (98.6)–	2591 (88.2)
$CHADS_2$ score, mean (SD)	1.7 (1.0)	2.2 (1.1)	2.6 (1.1)	1.9 (1.1)
$CHADS_2$ score category, n (%)				
Low, score=0	124 (7.1)	51 (4.6)	0 (0.0)–	175 (6.0)
Moderate, score=1	719 (41.1)–	284 (25.7)–	11 (15.1)–	1019 (34.7)
High, score ≥2	904 (51.7)–	771 (69.7)–	62 (84.9)–	1742 (59.3)
Missing	1 (0.1)–	0 (0.0)–	0 (0.0)–	1 (0.0)
HAS-BLED score, mean (SD)	1.1 (0.9)	1.4 (0.8)	1.6 (0.9)	1.2 (0.8)
HAS-BLED score category, n (%)				

Low, score <3	1448 (82.8)–	939 (84.9)–	57 (78.1)–	2452 (83.5)
High, score ≥3	101 (5.8)–	70 (6.3)–	11 (15.1)–	184 (6.3)
Missing	199 (11.4)–	97 (8.8)–	5 (6.8)–	301 (10.2)

AF, atrial fibrillation; BID, twice daily; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex category (female); $CHADS_2$, congestive heart failure, hypertension, age (>65 years =1 point, >75 years =2 points), diabetes, and stroke/transient ischemic attack (=2 points); HAS-BLED, hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (65 years), drugs and/or alcohol concomitantly; MI, myocardial infarction; SD, standard deviation.

*10 patients with other dosages of dabigatran are included in "Dabigatran overall" but not in the other columns in this table.

†Defined as chronic dialysis, renal transplantation, serum creatinine >200 μmol/L (2.26 mg/dL) in case report forms.

Table 2. Incidence of Events in Dabigatran-Treated Patients Overall

	Patients With Event,* n	Person-Years	Incidence Rate Per 100 Person-Years	95% CI
Stroke (ischemic or hemorrhagic)	27	4261	0.63	0.42–0.92
Systemic embolism	2	4274	0.05	0.01–0.17
Major bleeding	48	4267	1.12	0.83–1.49
Life-threatening bleeding	23	4275	0.54	0.34–0.81
Myocardial infarction	20	4270	0.47	0.29–0.72
Vascular death	39	4277	0.91	0.65–1.25
All-cause death†	115	4277	2.69	2.22–3.23
Composite end point‡	95	4249	2.24	1.81–2.73

CI, confidence interval; MI, myocardial infarction.

*In the case of a recurrent event, the first event was considered.

†Including cause of death unknown, n=36 (31.3%).

‡Stroke, systemic embolism, MI, life-threatening bleeding, vascular death. N=2932 eligible patients.

Table 3. Incidence of Events by Type or Location in Dabigatran-Treated Patients Overall

	Incidence Rate Per 100 Person-Years	95% CI
Stroke	0.63	0.42–0.92
Hemorrhagic stroke	0.07	0.01–0.20
Ischemic stroke	0.45	0.27–0.70
Secondary hemorrhagic transformation	0.05	0.01–0.17
Unknown type/uncertain classification	0.12	0.04–0.27
Major bleeding	1.12	0.83–1.49
Life-threatening bleed	0.54	0.34–0.81
Led to transfusion of ≥2 units of blood/red cells	0.68	0.45–0.98
Fall in hemoglobin level of 2 g/dL	0.63	0.42–0.92
Fatal bleeds	0.12	0.04–0.27
Trauma involved	0.07	0.01–0.20
Location of bleed		
Intracranial	0.19	0.08–0.37
Gastrointestinal	0.73	0.49–1.03
Other	0.16	0.07–0.34
Unknown	0.05	0.01–0.17
All-cause death	2.69	2.22–3.23
Vascular death	0.91	0.65–1.25
Non-vascular death	0.94	0.67–1.27
Unknown	0.84	0.59–1.17

CI, confidence interval.

N=2932 eligible patients.

Table 4. Incidence of Events by Dabigatran Dose Group

	Patients With Event*, n	Patient-Years	Incidence Rate Per 100 Person-years	95% CI
Dabigatran 150 mg BID (n=1747)				
Stroke (ischemic or hemorrhagic)	14	2521	0.56	0.30–0.94
Major bleeding	25	2526	1.00	0.64–1.47
MI	12	2528	0.48	0.25–0.83
All-cause death	52	2532	2.07	1.55–2.72
Dabigatran 110 mg BID (n=1105)				
Stroke (ischemic or hemorrhagic)	11	1654	0.67	0.33–1.20
Major bleeding	19	1656	1.16	0.70–1.80
MI	7	1656	0.43	0.17–0.88
All-cause death	52	1659	3.16	2.36–4.15

BID, twice daily; CI, confidence interval; MI, myocardial infarction.

*In the case of a recurrent event, the first event was considered.

Figure 1.

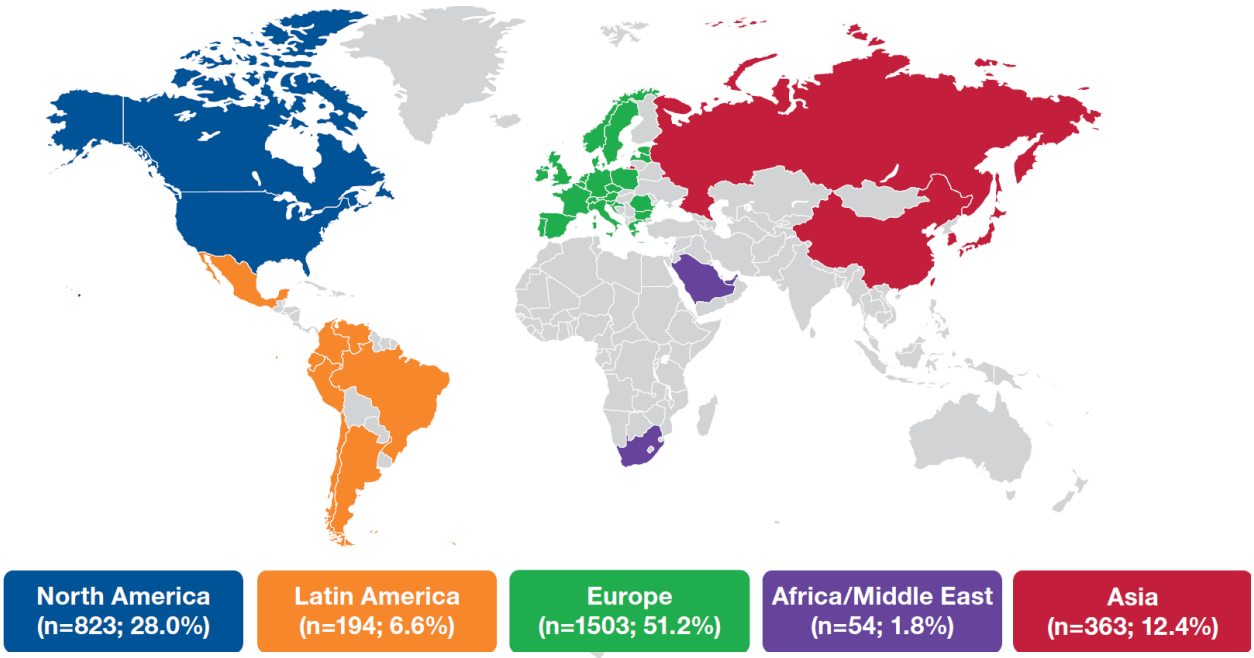
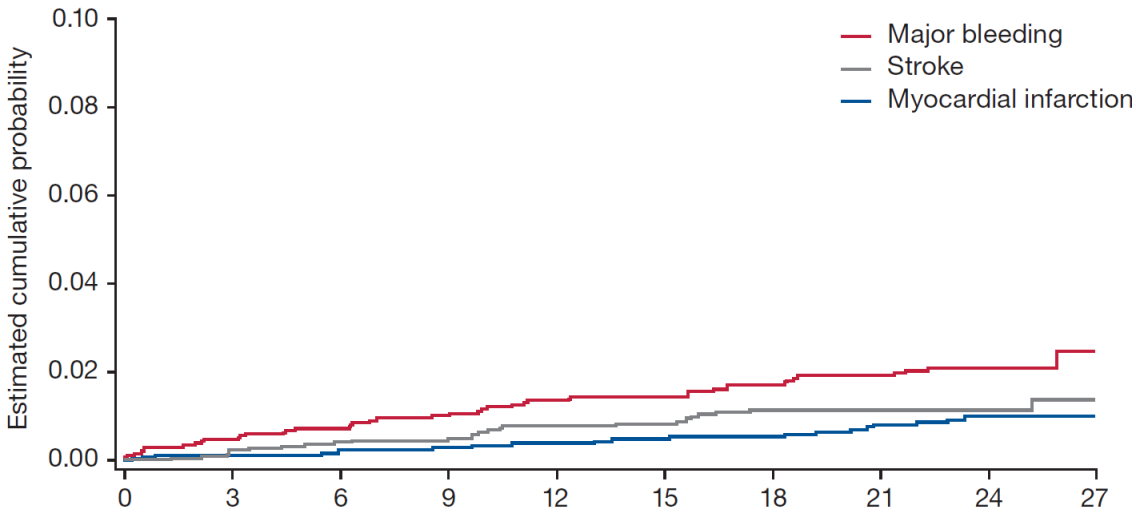


Figure 2.



Patients at risk:										
Major bleeding	2932	2570	2332	2169	2044	1926	1858	1772	1306	88
Stroke	2932	2567	2326	2167	2039	1920	1852	1769	1308	88
Myocardial infarction	2932	2571	2332	2171	2046	1926	1859	1771	1308	87