Safety and effectiveness of dabigatran at 2 years: Final outcomes from Phase II of the GLORIA-AF registry program

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GLORIA-AF is a large, ongoing, prospective, global registry program run in 3 phases, assessing long-term safety and effectiveness of dabigatran etexilate (dabigatran) in patients with newly diagnosed atrial fibrillation (AF) in clinical practice. This report provides the final analysis of 2-year clinical outcomes of the full cohort of 4873 patients prescribed dabigatran and followed for a mean of 18.0 +/− 9.4 months out of the 15,308 eligible patients enrolled in Phase II (2011-2014). The overall incidence rates per 100 person-years were: stroke 0.65 (95% CI 0.48-0.87), major bleeding 0.97 (0.76-1.23) and myocardial infarction (MI) 0.50 (0.35-0.69), with observed event rates broadly consistent in all study regions, which confirms the sustained safety and effectiveness of dabigatran over 2 years of observation in clinical practice. (Am Heart J 2019;218:123-27.)

The oral direct thrombin inhibitor, dabigatran etexilate (dabigatran), the first nonvitamin K antagonist oral anticoagulant (NOAC) in widespread use, was studied in patients with nonvalvular atrial fibrillation (AF) in the pivotal RE-LY trial.[1] In that study, dabigatran 150 mg twice daily (DE150) was superior to warfarin for preventing all stroke/systemic embolism and ischemic stroke, with rates of major bleeding similar to warfarin. The dabigatran 110 mg twice-daily (DE110) dose was noninferior to warfarin for preventing stroke/systemic embolism, with considerably less major bleeding. Both doses of dabigatran resulted in less intracranial hemorrhage (ICH) compared with warfarin.

Practice-based evidence provides important information to clinicians to assess the extent to which outcomes from routine clinical practice settings are consistent with randomized clinical trial results.[2,3] GLORIA-AF is an ongoing, global registry program of patients newly diagnosed with nonvalvular AF at risk of stroke run in 3 phases. We report the final results of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phase II (conducted between 2011 and 2016), in which dabigatran patients were followed for up to 2 years.

Methods

The design of GLORIA-AF has been previously reported.[4] In brief, this registry is run in a phased design to reduce bias and allow assessment of NOAC use. Phase II commenced when dabigatran became available in a participating country.

Consecutive patients with new-onset, nonvalvular AF at risk of stroke (CHA_2DS_2-VASc score ≥ 1) were enrolled in 5 regions between 2011 and 2014. Stroke and bleeding risks were described using CHA_2DS_2-VASc[5] and HAS-BLED[6] scores. Extensive measures were undertaken to ensure accurate and complete reporting of outcomes, as well as overall data integrity. The study protocol was endorsed by the European Medicines Agency (EMA) as a post-authorization safety study and part of the dabigatran post-approval plan.

Major outcomes were stroke, major bleeding (International Society on Thrombosis and Haemostasis definition),

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life-threatening bleeding, fatal bleeding, myocardial infarction (MI), vascular death, and all-cause death. Subgroup analyses included geographic region and dabigatran dose (DE150 and DE110).

Statistical analysis

Categorical variables were reported as absolute frequencies and percentages, and continuous variables as mean and standard deviation (SD). To compare clinical demography of patients by region and dabigatran dose, we reported standardized differences[7] between groups. We considered standardized differences <10% to indicate an unimportant difference between the compared groups. Crude incidence rates per 100 person-years and 2-sided 95% confidence intervals (CIs) were reported for dabigatran patients. To control for CHA_2DS_2-VASc and HAS-BLED scores, incidence rates for Europe, North America, and Asia were standardized for these indices. To facilitate interpretation of the incidence rates, we compared them with the results observed in a post-hoc analysis of the RE-LY trial, including a quantitative bias analysis to adjust for confounding differences between the 2 study populations[8,9] (supplemental material). All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Treatment patterns and baseline characteristics from GLORIA-AF Phase II have been previously published.[4] In this analysis, 15,308 patients were enrolled during Phase II (2011-2014) at 982 centers in 44 countries. Dabigatran was prescribed to 4873 patients and 4859 took at least 1 dose. For the analysis of clinical outcomes, 14 patients who were prescribed but never took dabigatran were excluded. Of the 4873 eligible dabigatran patients, 212/4873 (4.4%) were lost to follow-up without information available on vital status (Supplemental Figure 1). The regional distribution of dabigatran patients is shown in Supplemental Figure 2. The majority (55%) were in Europe, 17.3% in North America, 13.4% in Asia, 7.8% in Latin America, and 6.4% in Africa/Middle East. Mean therapy duration in the initial treatment period was 18.0 months (SD = 9.4). The probability of patients remaining on dabigatran for at least 1 year was 77.2% (Kaplan-Meier method), and for at least 2 years was 70.5%.

Baseline characteristics of patients on dabigatran, overall and stratified by geographic region, are presented in Supplemental Table I and II. Clinical outcomes are summarized in Table I.

Incidence rates were 0.65 (95% CI 0.48-0.87) per 100 person-years for stroke, 0.97 (95% CI 0.76-1.23) for major bleeding, 0.62 (95% CI 0.46-0.84) for life-threatening bleeding, and 0.10 (95% CI 0.04-0.20) for fatal bleeding. Incidence rates for MI, vascular death, and all-cause death were 0.50 (95% CI 0.35-0.69), 0.85 (95% CI 0.65-1.09), and 2.48 (95% CI 2.13-2.87), respectively. Overall, 70% of strokes were ischemic, 12.8% were primary hemorrhagic and 4.3% secondary hemorrhagic transformations. Major bleeding was rarely fatal. The most common site of major bleeding was the gastrointestinal tract, with intracranial bleeds less commonly reported. The results of quantitative bias analysis (comparing outcomes of GLORIA-AF and the RE-LY European Union [EU]–label analysis[8]) are presented in the Supplemental Results and Supplemental Figure 3.

Table II shows crude and standardized 2-year incidence rates per 100 patient-years for stroke and bleeding

Table I. Crude incidence rates of 2-year clinical outcomes for patients treated with dabigatran (n = 4859)

Outcome	Patients with event	Patient-years	Crude IR per 100 PY (95% CI)
Stroke	47	7192	0.65 (0.48-0.87)
Ischemic	31	7197	0.43 (0.29-0.61)
Secondary hemorrhagic transformation	2	7213	0.03 (0.00-0.10)
Hemorrhagic	6	7213	0.08 (0.03-0.18)
Unknown type/uncertain classification	10	7212	0.14 (0.07-0.26)
Systemic embolism	3	7212	0.04 (0.01-0.12)
Major bleeding	70	7199	0.97 (0.76-1.23)
Life-threatening	33	7209	0.46 (0.32-0.64)
Fatal	5	7215	0.07 (0.02-0.16)
Location of bleed			
ICH	12	7213	0.17 (0.09-0.29)
Gastrointestinal	43	7206	0.60 (0.43-0.80)
Other	13	7210	0.18 (0.10-0.31)
Unknown	2	7215	0.03 (0.00-0.10)
MI	36	7204	0.50 (0.35-0.69)
All-cause death	179	7215	2.48 (2.13-2.87)
Vascular	61	7215	0.85 (0.65-1.09)
Nonvascular	70	7215	0.97 (0.76-1.23)
Unknown	48	7215	0.67 (0.49-0.88)

CI, confidence interval; *ICH*, intracranial hemorrhage; *IR*, incidence rate; *MI*, myocardial infarction; *PY*, patient years.

Table II. Crude and standardized incidence rates of 2-year clinical outcomes by region (Europe, North America, and Asia)

Outcome	Europe (n = 2675)			North America (n = 839)			Asia (n = 654)		
	Patients with event	Crude IR per 100 PY (95% CI)	Standardized IR per 100 PY* (95% CI)	Patients with event	Crude IR per 100 PY (95% CI)	Standardized IR per 100 PY* (95% CI)	Patients with event	Crude IR per 100 PY (95% CI)	Standardized IR per 100 PY* (95% CI)
Stroke	28	0.70 (0.46-1.01)	0.70 (0.45-0.98)	6	0.55 (0.20-1.19)	0.54 (0.14-1.03)	8	0.90 (0.39-1.77)	0.91 (0.34-1.63)
MI	20	0.50 (0.30-0.77)	0.50 (0.29-0.74)	6	0.55 (0.20-1.19)	0.57 (0.17-1.09)	2	0.22 (0.03-0.81)	0.20 (0.00-0.53)
Major bleeding	35	0.87 (0.60-1.21)	0.87 (0.60-1.17)	23	2.10 (1.33-3.15)	1.97 (1.19-2.91)	8	0.90 (0.39-1.77)	0.96 (0.35-1.77)
All-cause death	100	2.48 (2.01-3.01)	2.49 (2.02-2.98)	36	3.27 (2.29-4.53)	3.43 (2.38-4.70)	10	1.12 (0.54-2.06)	1.31 (0.57-2.27)
Vascular death	37	0.92 (0.64-1.26)	0.92 (0.64-1.23)	13	1.18 (0.63-2.02)	1.36 (0.66-2.15)	1	0.11 (0.00-0.62)	0.11 (0.00-0.38)

* Incidence rates standardized by stroke and bleeding risk (as per CHA_2DS_2-VASc and HAS-BLED scores). *CI*, confidence interval; *IR*, incidence rate; *MI*, myocardial infarction; *PY*, patient-years.

in Europe, North America, and Asia—the most represented regions. Results for Latin America and Africa/Middle East are presented in Supplemental Table III. Standardized stroke and MI rates were similar in the 3 main regions (<1.0/100 patient-years). Some differences were observed for major bleeding (1.97 [1.19, 2.91] in North America versus 0.87 [0.60, 1.17] in Europe) and mortality (3.43 [2.38, 4.70] in North America versus 1.3 [0.57, 2.27] in Asia).

DE150 was prescribed to 54.6% of patients (n = 2659), DE110, the risk-adapted dose (according to local label), to 42.9% (n = 2092), and DE75 (approved in the United States for AF patients with creatinine clearance 15-30 mL/min) to 2.5% (n = 122). Patients prescribed DE110 compared with DE150 were older (mean 74.1 vs 66.8 years), had higher risk of stroke (mean CHA_2DS_2-VASc score of 3.7 [SD 1.5] vs 2.8 [1.4]) and bleeding (mean HAS-BLED score of 1.4 [0.8] vs 1.1 [0.9]), more often had coronary artery disease, heart failure, prior MI or stroke, and had lower creatinine clearance (Supplemental Table IV). Of those patients aged ≥75 and ≥80 years, respectively, 65.3% and 74.2% were prescribed DE110.

Supplemental Table V shows 2-year outcomes stratified by dabigatran dose. Crude incidence rates per 100 person-years for stroke were 0.69 (0.45-1.00) for patients on DE150 and 0.58 (0.34-0.91) for DE110. The corresponding event rates for major bleeding were 0.79 (0.53-1.12) and 1.22 (0.86-1.67), respectively. All-cause death was 1.64 (1.27-2.09) for DE150 and 3.19 (2.59-3.88) for DE110 while MI rates were similar.

Discussion

In this large, prospectively collected data-set of dabigatran outcomes in clinical practice, overall rates of stroke (<1.0/100 patient-years) and major bleeding (<1.0/100 patient-years) were low, confirming the sustained safety and effectiveness of dabigatran over 2 years of follow-up.

In RE-LY, incidence rates per 100 patient-years for DE150 and DE110 were, respectively: stroke (1.02, 1.44), major bleeding (3.40, 2.92), and all-cause death (3.64, 3.75).[1,10] The observed incidence rates for DE150 and DE110, respectively, in GLORIA-AF were: stroke (0.69, 0.58), major bleeding (0.76, 1.12), and all-cause death (1.64, 3.19). Direct comparisons of incidence rates for dabigatran in GLORIA-AF and RE-LY can be misleading due to differences in study design (eg, randomization in RE-LY) or patient characteristics. Registered labels determine dabigatran use in clinical practice; therefore, GLORIA-AF results were set in context to a RE-LY EU–label analysis, which simulated based on the global RE-LY dataset the comparison of dabigatran, used according to the EU label, with well-controlled warfarin.[8] Figure 1 contrasts incidence rates from this analysis with the overall incidence rates from GLORIA-AF. The rates of outcome events were lower in GLORIA-AF than in the RE-LY EU–label analysis; however, the pattern of stroke and bleeding rates remained consistent.

In a quantitative bias analysis, after correcting for potential uncontrolled confounding due to differences between GLORIA-AF and RE-LY, incidence rates of stroke and major bleeding in the GLORIA-AF study population were slightly increased but remained lower than those of RE-LY. Stroke rates were <1.0/100 patient-years and comparable in all regions. Major bleeding was higher in North America (approximately 2.0/100 patient-years) and lower in Europe and Asia (approximately 0.9/100 patient-years). All-cause mortality in North America was higher than in Asia, with Europe in the middle. Notably, important differences in clinical characteristics among patients in regions were observed, eg, coronary disease,

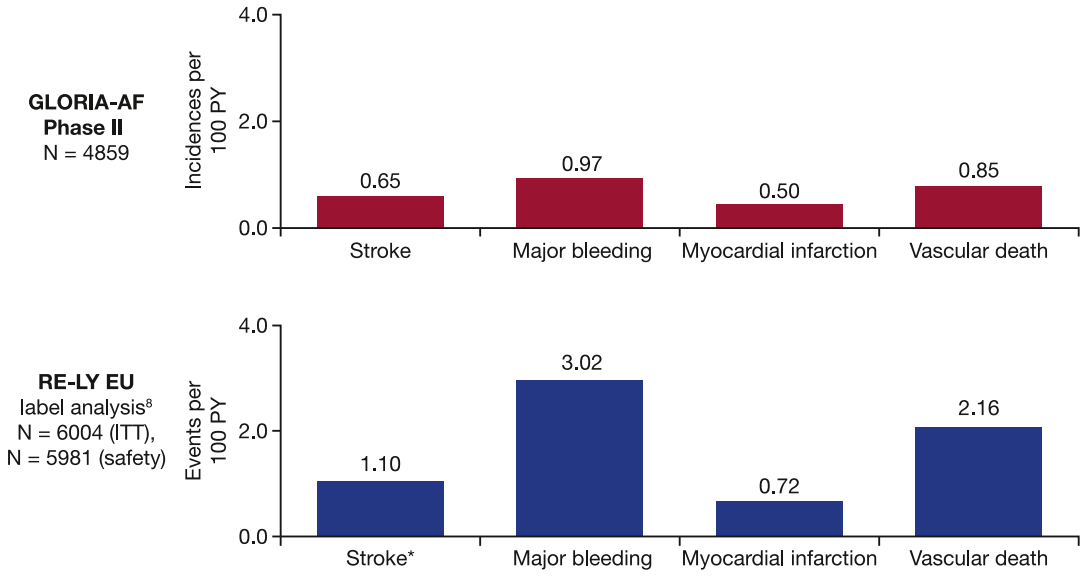

Figure 1

Clinical outcomes of dabigatran in GLORIA-AF and RE-LY EU-label analysis.[8] No direct comparison is intended as populations may differ. *Ischemic stroke only in RE-LY analysis; ischemic plus hemorrhagic stroke in GLORIA-AF analysis. *ITT*, intention-to-treat; *PY*, patient-years.

diabetes, hypertension, and previous bleeding were all more prevalent in North America than Europe (stroke and bleeding risks were standardized by CHA_2DS_2-VASc and HAS-BLED scores to reduce bias).

We assessed patient characteristics and outcomes for DE150 and the risk-adapted dose of DE110. Except for the United States (where only DE150 and DE75 are available), DE110 was given to ~50% of all patients prescribed dabigatran worldwide. As expected, patients prescribed DE110 were older with considerably more cardiovascular comorbidities. However, stroke and bleeding rates were low with both doses prescribed. Importantly, in patients receiving DE110, there was no excess of thromboembolic or bleeding events during treatment, despite usage in patients at a higher risk of stroke and bleeding. Indeed, patients receiving DE110 had low stroke, MI, major bleeding, and intracranial bleeding rates (0.58, 0.67, 1.12, and 0.19, respectively) consistent with nationwide cohort studies.[11,12]

In summary, in this large prospective cohort of AF patients treated with dabigatran, we observed low rates of stroke, major bleeding, and MI, confirming the sustained safety and effectiveness of dabigatran over 2 years of follow-up in clinical practice.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.08.012.

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Conflicts of interest

Dr Mazurek declared no conflict of interest.

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Dr Dubner has received consultancy fees for serving as a steering committee member for Boehringer Ingelheim.

He also holds research grants from Abbott (St Jude Medical).

Professor Halperin is currently conducting research sponsored by Boehringer Ingelheim as a member of the Executive Steering Committee for the GLORIA-AF Registry; he has received consulting fees from Bayer HealthCare, Janssen-Ortho-McNeil, and Pfizer for advisory activities involving the development of anticoagulant drugs.

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Dr Rothman is an employee of RTI Health Solutions, an independent, nonprofit research organization that does work for government agencies and pharmaceutical companies.

Professor Bartels, Dr Teutsch, Miney Paquette, Dr Zint, and Dr Shihai Lu are employees of Boehringer Ingelheim.

Dr Riou França was an employee of Boehringer Ingelheim at the time of manuscript writing and is now an employee of Sanofi-Aventis.

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