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Antithrombotic Usage, Including Three-Year Outcomes With Dabigatran and Vitamin K Antagonists for Atrial Fibrillation, in Eastern Europe: A Descriptive Analysis From Phase 3 of the GLORIA-AF Registry

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Background: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is a prospective registry of outcomes from patients with newly diagnosed AF at risk of stroke. In the propensity score (PS)-matched global population of phase 3 GLORIA-AF, at 3 years, dabigatran-treated patients experienced reduced risk for major bleeding, and similar risk for stroke and myocardial infarction, compared with vitamin K antagonist (VKA)-treated patients.

Study Question: Do patients in Eastern Europe benefit from treatment with dabigatran versus VKA?

Study Design: Descriptive analysis, without PS matching. To contextualize the Eastern Europe results of GLORIA-AF phase 3, we also descriptively analyzed the global population without PS matching. Consecutive patients with newly diagnosed AF and CHA2DS2-VASc-score ≥1 were enrolled until December 2016 in 38 countries (9 in Eastern Europe).

Measures and Outcomes: Three-year outcomes with dabigatran and VKA.

Results: In Eastern Europe, 1341 patients were eligible (6% of patients globally), and incidence rates (per 100 patient-years) for the following outcomes were numerically lower with dabigatran (N = 498) versus VKA (N = 466): major bleeding (0.26 vs. 0.90), all-cause death (2.04 vs. 3.50), and a composite of stroke, systemic embolism, myocardial infarction, life-threatening bleeding, and vascular death (1.37 vs. 1.92); stroke was comparable (0.51 vs. 0.50). All incidence rates were numerically lower in Eastern Europe versus the global population for both treatments. Chronic concomitant use of high bleeding risk medications (eg, nonsteroidal anti-inflammatories) was lower in Eastern Europe (dabigatran 3.8%, VKA 9.3%) than globally (dabigatran 14.8%, VKA 20.6%) and persistence with dabigatran was higher in Eastern Europe (76%) than globally (64%).

Conclusions: Dabigatran was associated with numerically reduced major bleeding, all-cause death, and cardiovascular (CV) composite, with comparable risk of stroke versus VKA, in Eastern Europe. Limitations of this descriptive analysis include few CV events (n = 11 for stroke, in the dabigatran and VKA groups combined) and a lack of statistical analysis and PS matching, which precludes definitive conclusions; however, the CV outcomes in Eastern Europe were consistent with the beneficial impact of dabigatran versus VKA in the statistically analyzed global population with PS matching.

Keywords: atrial fibrillation, dabigatran, vitamin K antagonist, stroke prevention, GLORIA-AF

INTRODUCTION

Atrial fibrillation (AF) affects up to 3% of adults,[1] with lifetime risk of approximately 25% for people more than 40 years of age,[2] and increasing prevalence in an aging population.[3] Patients with AF have a five-fold higher risk of stroke,[4] which is a particularly common cause of death[5] and major disability.[6]

Anticoagulation with vitamin K antagonists (VKA), such as warfarin, reduces the risk of stroke and mortality.[7] However, there are significant limitations to VKA therapy, including a narrow therapeutic margin, unpredictable dose–response, drug–drug, and drug–

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All authors contributed to the writing process by reviewing drafts of the manuscript for intellectual content and interpretation. All authors approved the final draft for publication.

GLORIA-AF was conducted in accordance with the principles of Good Clinical Practice, the Declaration of Helsinki, Good Epidemiological Practice and Good Pharmacoepidemiology Practices. The protocol was approved by the European Medicines Agency and institutional review boards at each participating site. For administrative purposes the study is divided into 2 protocol numbers: 1160.129 for all non-EU (European Union) and non-EEA (European Economic Area) countries, and 1160.136 for EU and EEA countries. The protocol dates are 8 June 2011 (revised 7 June 2013) and 23 March 2012 (revised 22 October 2014), respectively.

**Drs. M. V. Huisman and G. Y. H. Lip are co-Chairs of the GLORIA-AF registry and joint senior authors with Dr. D. Vinereanu.*

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/. Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can also be requested via the link https://trials.boehringer-ingelheim.com/. All requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use the https://trials.boehringer-ingelheim.com/ link to request access to study data.

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food interactions, and slow onset and offset of action, whereas antiplatelet treatment with clopidogrel or aspirin is ineffective and, therefore, not recommended for stroke prevention in AF by current guidelines.[8,9] In the past decade, these drawbacks have largely been circumvented by approval of the direct oral anticoagulants (DOACs) for stroke prevention in patients with AF in Europe and around the world.[8,10] These include the direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.[10] In 4 pivotal clinical trials, the efficacy of dabigatran and the factor Xa inhibitors was at least similar to that of VKA for the prevention of stroke or systemic embolism in patients with AF, with reduced risk of intracranial bleeding.[11–14]

Retrospective analyses of large medical databases support the effectiveness and safety of dabigatran in real-world clinical practice.[15–18] However, retrospective studies may be compromised by missing or inaccurate data (eg, relating to concomitant use of aspirin)[8] and, notably, are often limited to individual countries in North America and Western Europe.[15–18] Although clinical trial and real-world data hint at potential geographical differences in DOAC and VKA treatment outcomes,[11,19,20] there is a lack of data reported for regions such as Eastern Europe.

Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is a large, prospective, global registry program that, in its third phase, is providing outcome data for dabigatran versus VKA in routine clinical practice.[8] For the global population of GLORIA-AF, the recently reported final 3-year outcomes in phase 3 demonstrated that dabigatran-treated patients have reduced risk for major bleeding (hazard ratio [HR] 0.61; 95% CI [confidence interval], 0.42–0.88) and all-cause death (HR 0.78; 95% CI, 0.63–0.97), and similar risk for stroke (HR 0.89; 95% CI, 0.59–1.34) and myocardial infarction (HR 0.89; 95% CI, 0.53–1.48), compared with VKA-treated patients.[21] Notably, these outcomes were analyzed with a propensity score (PS)-matched population and multivariable Cox regression.[21]

Herein, we report a descriptive analysis of antithrombotic treatment usage (types and dosages), with the main objective of determining the final 3-year cardiovascular (CV) outcomes for dabigatran and VKA, in the subset of patients from Eastern Europe in phase 3 of GLORIA-AF. Because PS matching has the disadvantage of reducing the number of patients, the descriptive analysis of CV outcomes in the Eastern European subset was not PS matched. To contextualize the Eastern European results, we also descriptively analyze and report the 3-year CV outcomes and baseline characteristics of the global population without PS matching, and compare 3-year persistence with dabigatran in the Eastern European and global populations.

METHODS

Study design and patients

The design of the prospective GLORIA-AF registry program has been reported elsewhere (https://clinicaltrials.gov; trial registration numbers NCT01468701, NCT01671007, NCT01937377).

Briefly, data were collected for patients with newly diagnosed AF in routine clinical practice, to evaluate patient characteristics influencing treatment choice, and the effectiveness and safety of antithrombotic therapies.[8] Phase 1 was conducted using a cross-sectional approach, before approval of DOACs. Phase 2, which started when dabigatran was approved in participating countries, involved collection of baseline characteristics of patients receiving antithrombotic therapy, with effectiveness and safety outcomes reported for patients receiving dabigatran for 2 years.[22] Phase 3 used a cohort study design. Data were gathered for patients prescribed any antithrombotic treatment. To reduce confounding, phase 3 started when the baseline characteristics of patients in phase 2 were similar enough for comprehensive comparative analysis of effectiveness and safety outcomes with dabigatran versus VKA up to 3 years in the global population, based on PS methodology. Findings have recently been published for the PS-matched global population.[21] No PS matching was performed for comparisons of effectiveness and safety with dabigatran versus VKA in the analyses of the Eastern European and global populations reported here.

In phase 3 of GLORIA-AF, consecutive patients were enrolled between January 2014 and December 2016 in 38 countries in Asia, Europe, North America, and Latin America. Patients were to be recruited from several types of centers, such as general practices, specialist offices, community and university hospitals, outpatient care centers, and anticoagulant clinics. For the current analysis, the Eastern European population was comprised of patients from 9 countries (Bulgaria, Croatia, Czech Republic, Estonia, Latvia, Poland, Romania, Russia, and Slovenia). Detailed patient eligibility criteria have been reported previously.[8,21] Eligible patients were adults with newly diagnosed nonvalvular AF (<3 months before baseline visit; Latin America <4.5 months because of referral patterns) at risk of stroke (CHA2DS2-VASc score ≥1). GLORIA-AF was conducted in accordance with the Declaration of Helsinki, other relevant guidelines, and the study protocol. All patients provided written informed consent.

Objectives and outcomes

The main objective of this descriptive analysis was to determine the 3-year CV outcomes for dabigatran and VKA in the subset of patients from Eastern Europe, with comparisons to the global population. The outcomes were: stroke (hemorrhagic, ischemic, or uncertain classification); major bleeding, defined using International Society on Thrombosis and Haemostasis criteria[23]; all-cause death; and a CV composite of stroke, systemic embolism, myocardial infarction, life-threatening bleeding, and vascular death. To speculate on reasons for potential differences in CV outcomes between the Eastern European and global populations, we compared the baseline characteristics of patients in the 2 populations.

Given that patients were eligible for Phase 3 of GLORIA-AF regardless of antithrombotic therapy, we also reported treatment patterns for patients receiving any or no antithrombotic therapy.

Treatment persistence with dabigatran was also reported for the Eastern European and global populations, defined as remaining on therapy without interruption for longer than 30 days.

Statistical analysis

Baseline characteristics, demographics, treatment patterns (including dosage), and incidence rates of all key CV outcomes were summarized descriptively for all eligible patients in the Eastern European and global populations. Regarding the descriptive analysis of CV outcomes, incidence rates per 100 patient-years, with 95% CIs, were calculated in the dabigatran and VKA treatment groups, based on data from all eligible patients (excluding those not treated with prescribed antithrombotic therapy) in the Eastern European and global populations. The case report form was set up in such a way that investigators had to enter all outcome event information and changes in medication since the last study visit; therefore, complete information on outcome events was ensured even if intermittent visits were missed, using all available information from the completed study visits.

Treatment persistence with dabigatran at 6, 12, 24, and 36 months was estimated using the Kaplan–Meier method, based on data from all eligible patients (excluding those not treated with prescribed antithrombotic therapy) in the Eastern European and global populations.

Multivariable Cox regression analysis was prespecified only on the PS-matched global population[21]; no statistical testing was performed on the treatment outcomes for the current analyses. All analyses were performed using SAS® software version 9.4 or later (SAS Institute, Inc., Cary, NC).

RESULTS

Patient disposition and antithrombotic treatments

In Eastern Europe, 1341 patients were eligible for analysis, comprising 6% of 21,300 eligible patients enrolled between January 2014 and December 2016 in the global population. Eastern European patients were from Bulgaria (22%; N = 296), Romania (22%; N = 295), Poland (18%; N = 239), Russia (15%; N = 195), Croatia (10%; N = 139), Czech Republic (6%; N = 86), Slovenia (3%; N = 37), Latvia (2%; N = 29), and Estonia (2%; N = 25). In addition to Eastern Europe, the global population included patients from Western Europe (43%; N = 9158), North America (24%; N = 5120), Asia (19%; N = 4053), and Latin America (8%; N = 1628).

Of the 1341 eligible patients in Eastern Europe, 80.8% completed the planned 3-year observation period (range: 74.2% [VKA] to 85.7% [dabigatran]), compared with 80.5% in the global population (range: 77.6% [antiplatelets or no antithrombotic treatment] to 83.8% [dabigatran]) (see **Figure**, **Supplemental Digital Content 1**, http://links.lww.com/AJT/A142).

The distribution of prescribed antithrombotic treatments differed in Eastern Europe versus the global population (Figure 1). Dabigatran and VKA were the most prescribed antithrombotic treatments in the Eastern European population, more than in the global population (dabigatran 37.5% vs. 18.0%, VKA 35.2% vs. 22.7%). Factor Xa inhibitors were prescribed less often in the Eastern European population than in the global population (rivaroxaban 10.9% vs. 18.9%, apixaban 3.2% vs. 21.2%, edoxaban 0% vs. 1.6%). Antiplatelet agents (without concomitant dabigatran, VKA, or factor Xa inhibitors) were prescribed in 10.7% of the Eastern European population, similar to the global population (11.2%). Only 2.5% of the Eastern European population was prescribed no antithrombotic treatment, compared with 6.5% of the global population. As shown in **Supplemental Digital Content 1**, (see **Table**, http://links.lww.com/AJT/A142), there were large differences in prescriptions of antithrombotic treatments between countries; for instance, 54.0% of patients in Poland (n = 129/239) were prescribed dabigatran, compared with only 5.8% (n = 5/86) in the Czech Republic.

In Eastern Europe, 70% of patients were prescribed the standard dose (150 mg twice daily [BID]) and 29% were prescribed the lower dose of dabigatran (110/75 mg BID), compared with 52% and 46% in the global population, respectively (Figure 2). By contrast, the proportions of patients prescribed standard or lower

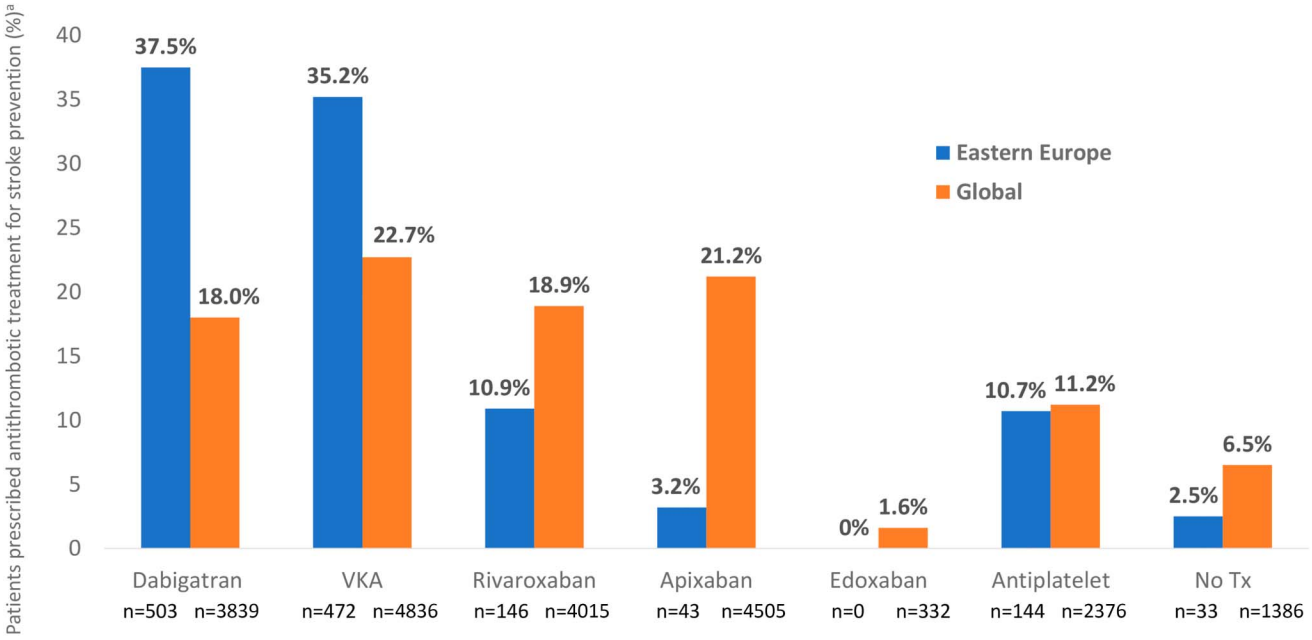

FIGURE 1. Baseline antithrombotic treatment prescriptions in the Eastern European and global populations. [a]The denominator for Eastern Europe is the total number of eligible patients in the Eastern European population (N = 1341). The denominator for the global population is the total number of eligible patients in the global population (N = 21,300). Tx, treatment; VKA, vitamin K antagonist.

doses of the factor Xa inhibitors were comparable in Eastern Europe versus the global population.

Patient characteristics

As shown in Table 1, Eastern European patients' demographics (mean age, 67.8 years [SD, 10.1]; body mass index [BMI], 29.1 [SD, 4.7]; 50.0% female; 99.0% White) and disease characteristics were generally well balanced across the treatment groups. A notable exception is that 78.0% of patients in the 'other' group experienced paroxysmal AF, relative to 40.0%–54.5% across the DOAC and VKA groups. Patients in the 'other' group received high bleeding risk medications such as antiplatelet agents (n = 144) or no antithrombotic treatment (n = 33). CHA2DS2-VASc scores were comparable, ranging from 3.0 to 3.4, across the treatment groups.

For comparison with the Eastern European population, patient characteristics for all eligible patients in the global population are also shown in Table 1. At baseline, chronic concomitant use of medications associated with a high risk of bleeding, including antiplatelets, was substantially lower in Eastern Europe (16.4%) than globally (28.3%). Consistent with this observation, mean HAS-BLED scores were lower in Eastern Europe (1.1 [SD, 0.8]) compared with the global population (1.4 [SD, 0.9]), and history of bleeding events was also less common in Eastern Europe (3.1%) than globally (5.3%). Although CHA2DS2-VASc scores did not differ, the proportion of patients with history of stroke was lower in Eastern Europe (7.3%) than globally (10.6%). Conversely, in Eastern Europe, congestive heart failure was more common (37.7%) than in the global population (21.7%). This was also the case for hypertension (Eastern Europe, controlled 72.9%, uncontrolled 13.7%; globally, controlled 62.9%, uncontrolled 10.2%).

At baseline, chronic concomitant use of medications associated with a high risk of bleeding was lower in the dabigatran group than VKA group in Eastern Europe (3.8% vs. 9.3%) and globally (14.8% vs. 20.6%). HAS-BLED and CHA2DS2-VASc scores, and history of bleeding and stroke were generally comparable in the dabigatran and VKA groups in Eastern Europe and globally (Table 2).

Effectiveness and safety of dabigatran versus VKA

In Eastern Europe, the incidence rates for major bleeding (0.26 vs. 0.90), all-cause death (2.04 vs. 3.50), and the CV composite outcome (1.37 vs. 1.92) were numerically lower with dabigatran versus VKA, and the incidence rates for stroke (0.51 vs. 0.50) were comparable for the 2 treatment groups (Figure 3). Although these incidence rates were consistent with the beneficial impact of dabigatran versus VKA in the global population, the rates of all 4 outcomes were lower in Eastern Europe versus the global population for both

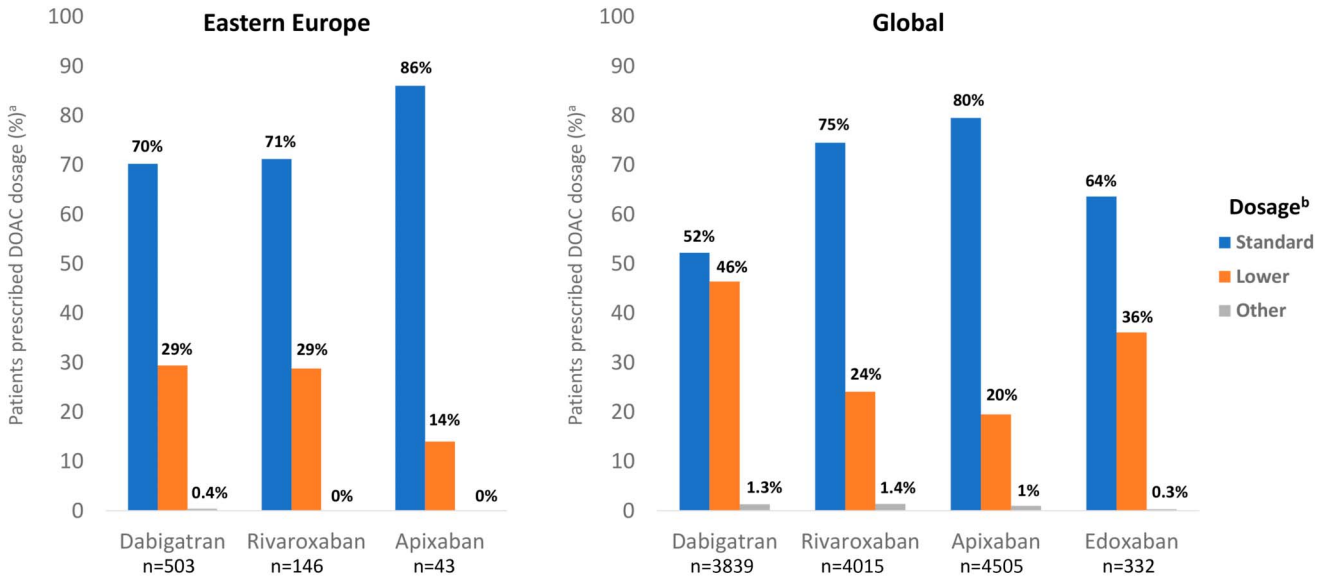

FIGURE 2. Baseline DOAC prescription dosage in the Eastern European and global populations. [a]The denominators are all eligible patients (ie, the ns shown per treatment group). No patients in Eastern Europe were prescribed or treated with edoxaban. [b]Dabigatran standard dose (150 mg BID), lower dose (110/75 mg BID); rivaroxaban standard dose (20 mg QD), lower dose (15/10 mg QD); apixaban standard dose (5 mg BID), lower dose (2.5 mg BID); edoxaban standard dose (60 mg QD), lower dose (30 mg QD); "other" doses were any dose that did not fit under the definitions of standard or lower doses per treatment. BID, twice daily; DOAC, direct oral anticoagulants; QD, once daily.

treatments (Figure 3). However, the numbers of patients (overall and with CV events) were substantially lower in Eastern Europe versus the global population.

Persistence with dabigatran treatment

Based on the Kaplan–Meier method, 36-month probabilities of dabigatran persistence (ie, without treatment interruptions longer than 30 days) were 76% and 64% in the Eastern European and global populations, respectively (Figure 4). Estimates of dabigatran treatment persistence were also higher in Eastern Europe versus the global population at all earlier time points: 89% versus 81% at 6 months, 84% versus 74% at 12 months, and 79% versus 68% at 24 months.

DISCUSSION

In this descriptive analysis of the GLORIA-AF registry, 3 years of treatment with dabigatran was associated with numerically reduced risks of major bleeding, all-cause death, and a composite CV outcome, and comparable risk of stroke, versus VKA in Eastern European patients with newly diagnosed AF. Definitive conclusions about the effectiveness and safety of dabigatran and VKA in this Eastern European population are prevented by the lack of statistical testing, small numbers of patients with CV events (eg, in the dabigatran and VKA groups combined, 11 patients vs. 158 patients in the global population experienced stroke, respectively), and no PS matching. Undetected factors could bias the findings, and causality cannot be attributed to the antithrombotic treatments. However, the findings in Eastern Europe are consistent with the beneficial impact of dabigatran versus VKA in the substantially larger global population, previously reported with PS matching and statistical testing[21] and reported herein without PS matching.

Regardless of treatment (dabigatran or VKA), the incidence rates of all 4 outcomes at 3 years were numerically lower in Eastern Europe than globally. Three-year dabigatran treatment persistence was higher (76% and 64%, respectively) and use of chronic concomitant high bleeding risk therapies at baseline was lower in Eastern Europe than globally, possibly contributing to the good outcomes in the Eastern European population. There could also be an element of chance, owing to the small number of patients experiencing these CV events in the Eastern European versus global population.

In the Eastern European population, which was enrolled up to December 2016, a higher proportion (78.0%) of patients in the "other" group (receiving high bleeding risk therapies without concomitant DOACs or VKA, or no antithrombotic treatment) experienced paroxysmal AF than across the DOAC and VKA groups

Table 1. Baseline characteristics of eligible patients in the Eastern European and global populations.

	Eastern Europe					Global
	Dabigatran (N = 503)	VKA (N = 472)	Factor Xa inhibitor* (N = 189)	Other† (N = 177)	Total (N = 1341)	Total (N = 21,300)
Age (yr), mean (SD)	67.0 (10.1)	69.2 (9.2)	68.2 (10.4)	66.1 (11.6)	67.8 (10.1)	70.5 (10.6)
65–74, n (%)	193 (38.4)	184 (39.0)	66 (34.9)	58 (32.8)	501 (37.4)	7712 (36.2)
≥75, n (%)	128 (25.4)	146 (30.9)	57 (30.2)	45 (25.4)	376 (28.0)	8166 (38.3)
Female, n (%)	250 (49.7)	234 (49.6)	95 (50.3)	92 (52.0)	671 (50.0)	9568 (44.9)
Race, n (%)‡						
Asian	0	0	0	0	0	4132 (19.4)
Black/African American	2 (0.4)	4 (0.8)	0	1 (0.6)	7 (0.5)	398 (1.9)
White	498 (99.0)	466 (98.7)	188 (99.5)	176 (99.4)	1328 (99.0)	14,823 (69.6)
BMI (kg/m^2), mean (SD)	29.1 (4.8)	29.2 (4.7)	28.9 (4.8)	28.6 (4.6)	29.1 (4.7)	28.6 (6.4)
CrCl (mL/min), mean (SD)	86.6 (32.0)	80.1 (30.6)	81.3 (32.9)	85.9 (37.9)	83.5 (32.6)	81.4 (60.5)
HAS-BLED score, mean (SD)	0.9 (0.7)	1.0 (0.8)	1.0 (0.8)	1.7 (0.9)	1.1 (0.8)	1.4 (0.9)
CHA_2DS_2-VASc score, mean (SD)	3.1 (1.4)	3.3 (1.4)	3.4 (1.6)	3.0 (1.4)	3.2 (1.4)	3.2 (1.5)
Type of AF, n (%)						
Paroxysmal	225 (44.7)	189 (40.0)	103 (54.5)	138 (78.0)	655 (48.8)	12,001 (56.3)
Persistent	216 (42.9)	220 (46.6)	68 (36.0)	32 (18.1)	536 (40.0)	7277 (34.2)
Permanent	62 (12.3)	63 (13.3)	18 (9.5)	7 (4.0)	150 (11.2)	2022 (9.5)
Chronic concomitant medications, n (%)						
Antiplatelet	13 (2.6)	32 (6.8)	9 (4.8)	22 (12.4)	76 (5.7)	5558 (26.1)
High bleeding risk medications§	19 (3.8)	44 (9.3)	17 (9.0)	140 (79.1)	220 (16.4)	6034 (28.3)
Medical history, n (%)						
Controlled hypertension	363 (72.2)	344 (72.9)	146 (77.2)	124 (70.1)	977 (72.9)	13,404 (62.9)
Uncontrolled hypertension	76 (15.1)	63 (13.3)	18 (9.5)	27 (15.3)	184 (13.7)	2162 (10.2)
Stroke	37 (7.4)	30 (6.4)	17 (9.0)	14 (7.9)	98 (7.3)	2260 (10.6)
Transient ischemic attack	17 (3.4)	12 (2.5)	8 (4.2)	3 (1.7)	40 (3.0)	952 (4.5)
Deep vein thrombosis	6 (1.2)	2 (0.4)	0	0	8 (0.6)	248 (1.2)
Coronary artery disease	76 (15.1)	91 (19.3)	45 (23.8)	45 (25.4)	257 (19.2)	4000 (18.8)
Angina pectoris	65 (12.9)	79 (16.7)	28 (14.8)	33 (18.6)	205 (15.3)	1964 (9.2)
Myocardial infarction	28 (5.6)	48 (10.2)	21 (11.1)	14 (7.9)	111 (8.3)	2062 (9.7)
Congestive heart failure	192 (38.2)	198 (41.9)	66 (34.9)	50 (28.2)	506 (37.7)	4632 (21.7)
Rheumatic heart disease	1 (0.2)	4 (0.8)	1 (0.5)	0	6 (0.4)	92 (0.4)
Peripheral artery disease	5 (1.0)	14 (3.0)	6 (3.2)	7 (4.0)	32 (2.4)	623 (2.9)
Bleeding	12 (2.4)	9 (1.9)	15 (7.9)	6 (3.4)	42 (3.1)	1130 (5.3)
Pulmonary embolism	2 (0.4)	1 (0.2)	2 (1.1)	0	5 (0.4)	125 (0.6)
Non-CNS arterial embolism	3 (0.6)	1 (0.2)	0	0	4 (0.3)	77 (0.4)
Complex aortic plaque	8 (1.6)	8 (1.7)	6 (3.2)	4 (2.3)	26 (1.9)	205 (1.0)
Diabetes	102 (20.3)	98 (20.8)	55 (29.1)	39 (22.0)	294 (21.9)	4960 (23.3)
Hyperlipidaemia	198 (39.4)	201 (42.6)	74 (39.2)	82 (46.3)	555 (41.4)	8340 (39.2)
Hepatic disease	9 (1.8)	10 (2.1)	2 (1.1)	4 (2.3)	25 (1.9)	310 (1.5)
Abnormal kidney function	1 (0.2)	7 (1.5)	1 (0.5)	2 (1.1)	11 (0.8)	392 (1.8)

*Rivaroxaban or apixaban.
†Aspirin, antiplatelets other than aspirin, or no antithrombotic treatment.
‡In the Eastern European and global populations, patients also identified as Native American/Alaskan/Hawaiian/Other Pacific Islander (0.5%, 0.6%), other (0.1%, 3.0%), or a racial designation was not available (0.3%, 5.5%), respectively.
§Risk based on the HAS-BLED score (antiplatelet agent, Cox-2 inhibitor, or other nonsteroidal anti-inflammatory drug).
AF, atrial fibrillation; BMI, body mass index; CNS, central nervous system; CrCL, creatinine clearance SD, standard deviation; VKA, vitamin K antagonist.

Table 2. Selected* baseline characteristics of eligible patients in the dabigatran and VKA groups in the Eastern European and global populations.

	Eastern Europe		Global	
	Dabigatran (N = 503)	VKA (N = 472)	Dabigatran (N = 3839)	VKA (N = 4836)
Age (yr), mean (SD)	67.0 (10.1)	69.2 (9.2)	70.1 (10.2)	71.2 (10.3)
Female, n (%)	250 (49.7)	234 (49.6)	1718 (44.8)	2152 (44.5)
Race, n (%)†				
Asian	0	0	841 (21.9)	760 (15.7)
Black/African American	2 (0.4)	4 (0.8)	47 (1.2)	85 (1.7)
White	498 (99.0)	466 (98.7)	2484 (64.7)	3611 (74.7)
CrCl (mL/min), mean (SD)	86.6 (32.0)	80.1 (30.6)	83.5 (117.4)	76.8 (35.4)
HAS-BLED score, mean (SD)	0.9 (0.7)	1.0 (0.8)	1.2 (0.8)	1.3 (0.9)
CHA_2DS_2-VASc score, mean (SD)	3.1 (1.4)	3.3 (1.4)	3.1 (1.4)	3.3 (1.5)
Type of AF, n (%)				
Paroxysmal	225 (44.7)	189 (40.0)	2082 (54.2)	2174 (45.0)
Persistent	216 (42.9)	220 (46.6)	1309 (34.1)	1977 (40.9)
Permanent	62 (12.3)	63 (13.3)	448 (11.7)	685 (14.2)
Chronic concomitant medications, n (%)				
Antiplatelet	13 (2.6)	32 (6.8)	508 (13.2)	913 (18.9)
High bleeding risk medications‡	19 (3.8)	44 (9.3)	569 (14.8)	998 (20.6)
Medical history, n (%)				
Controlled hypertension	363 (72.2)	344 (72.9)	2416 (62.9)	3104 (64.2)
Uncontrolled hypertension	76 (15.1)	63 (13.3)	421 (11.0)	467 (9.7)
Congestive heart failure	192 (38.2)	198 (41.9)	749 (19.5)	1374 (28.4)
Diabetes	102 (20.3)	98 (20.8)	828 (21.6)	1233 (25.5)
Stroke	37 (7.4)	30 (6.4)	441 (11.5)	462 (9.6)
Coronary artery disease	76 (15.1)	91 (19.3)	511 (13.3)	916 (18.9)
Bleeding	12 (2.4)	9 (1.9)	138 (3.6)	251 (5.2)

*Selected from the characteristics in Table 1.

†In the Eastern European population (dabigatran vs. VKA), patients also identified as Native American/Alaskan (0.2% vs. 0%) or a racial designation was not available (0.4% vs. 0.4%), respectively. In the global population (dabigatran vs. VKA), patients also identified as Native American/Alaskan (0.7% vs. 0.7%), other (4.7% vs. 3.0%), or a racial designation was not available (6.7% vs. 4.2%), respectively.

‡Risk based on the HAS-BLED score (antiplatelet agent, Cox-2 inhibitor, or other nonsteroidal anti-inflammatory drug).

AF, atrial fibrillation; CNS, central nervous system; CrCL, creatinine clearance; SD, standard deviation; VKA, vitamin K antagonist.

(40.0%–54.5%), despite comparable CHA2DS2-VASc scores (3.0–3.4). Although the 2020 ESC guidelines state that AF type "should not condition the indication to thromboprophylaxis,"[9] choice of treatment may have been influenced by the short-term nature of paroxysmal AF.

Consistent with the higher three-year persistence with dabigatran treatment in Eastern Europe than globally, previous GLORIA-AF papers have suggested regional differences in persistence with DOACs, including dabigatran, up to 2 years of treatment.[19,20,24,25] Factors that predicted discontinuation of DOACs during 1-year and 2-year follow-ups of GLORIA-AF included geographical region (Asia and North America vs. Europe) and, perhaps counterintuitively, private versus federal insurance.[24,25]

In the first 2 years of therapy, several investigations have reported high persistence rates for DOACs, including dabigatran versus VKA.[24,26–29] The current study extends these findings, demonstrating high persistence with 3 years of dabigatran treatment. Reasons for high levels of compliance with DOACs likely include ease of use, including no requirement to monitor DOAC levels except for special cases such as in patients with particularly high or low body weight.[30–

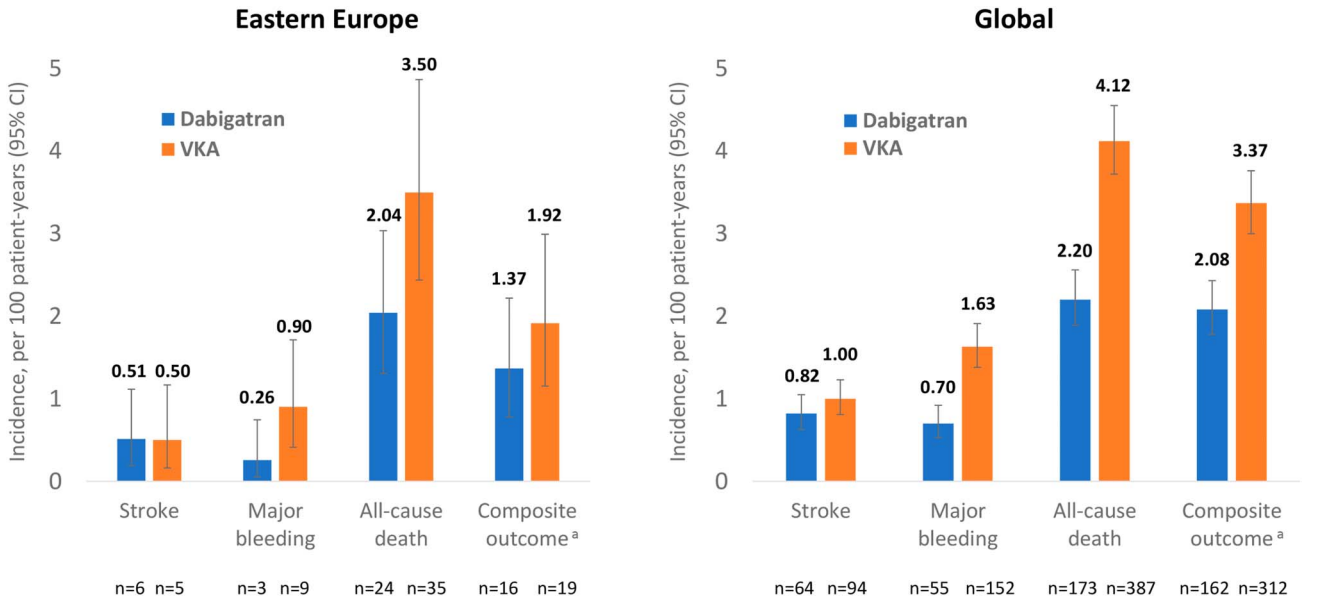

FIGURE 3. Incidence rates of important clinical outcomes during 3 years of treatment with dabigatran versus VKA in Eastern Europe versus the global population. Each n denotes the number of patients with events. Results are shown for all eligible patients treated with dabigatran and VKA in Eastern Europe (N = 498 and N = 466, respectively) and globally (N = 3807 and N = 4788, respectively), that is, excluding a few patients with a prescription but not treated. [a]Stroke, systemic embolism, myocardial infarction, life-threatening bleed, vascular death CI, confidence interval; VKA, vitamin K antagonist.

[33] The advantage of lack of necessity to monitor anticoagulation with DOACs may improve patients' access to treatment (eg, for those in remote rural areas). DOAC plasma levels also decrease quickly,[33] allowing more straightforward surgical interventions.

In the current study, the beneficial impact of dabigatran versus VKA on the incidence of CV outcomes was observed with different proportions of patients receiving the standard dabigatran dose (70%, 150 mg BID) and lower dose of dabigatran (29%, 110/75 mg BID) in Eastern Europe than in the global population (52% and 46%, respectively). This is notable, given that some differences in CV outcomes between and within studies may be explained by dabigatran dosing. In the RE-LY phase 3 trial (N = 18,113), dabigatran 150 mg BID was more beneficial than warfarin for stroke prevention (relative risk [RR] 0.64; 95% CI, 0.51–0.81), whereas 110 mg BID was comparable to warfarin (RR, 0.92; 95% CI, 0.74–1.13). Conversely, dabigatran 110 mg BID was more beneficial than warfarin for major bleeding (RR 0.80; 95% CI, 0.69–0.93), whereas 150 mg BID was comparable to warfarin (RR 0.93; 95% CI, 0.81–1.07).[11] In 2 large US claims database studies, dabigatran was associated with lower incidence of stroke and fewer intracranial bleeding events than with warfarin,[15,17] particularly with the 150-mg dose of dabigatran, whereas the 75-mg dose was associated with no difference in stroke prevention and reduced intracranial hemorrhage versus warfarin.[17]

Although our descriptive analysis suggests that antithrombotic treatment patterns differ in Eastern Europe relative to the global population, these patterns will have changed since the last patients were enrolled into GLORIA-AF phase 3 in December 2016. A survey in the Balkan region (N = 2663) demonstrated greater use of VKA than in our study (60.9% vs. 35.2%), and increasing use of dabigatran and factor Xa inhibitors during a 14-week period between December 2014 and February 2015.[34,35] Although changes in clinical practice will have been influenced by research published in the intervening years, OAC use in the Balkan region was largely guided by factors other than evidence-based medicine, such as drug availability and reimbursement policy.[35] Clinical practices have benefitted in recent years from greater awareness and education, including greater communication between cardiology subspecialities, neurology, and general practice. Even though the situation has improved with the introduction of DOACs in the last decade, there is still an issue with drug–drug interactions and patients taking too many medicines at full dosage, such as nonsteroidal anti-inflammatory drugs, antiplatelets, and OACs, in combination regimens. The issue of drug–drug interactions is less common with DOACs than VKA.[30] However, it is still important to optimize DOACs and other treatment regimens for efficacy and safety (eg, for kidney function, leading to potential adaptation of dosage), which, in

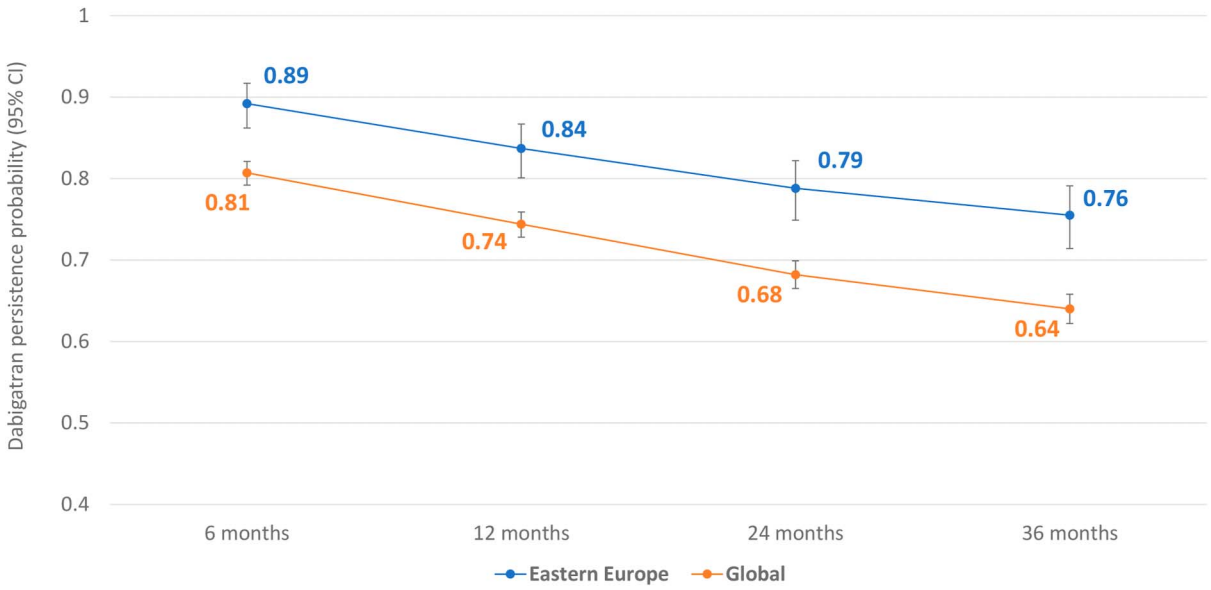

FIGURE 4. Probability of persistence with dabigatran during 3 years of treatment in Eastern Europe versus the global population. Results are shown for all eligible patients treated with dabigatran and VKA in Eastern Europe (N = 498 and N = 466, respectively) and globally (N = 3807 and N = 4788, respectively), that is, excluding a few patients with a prescription but not treated. CI, confidence interval; VKA, vitamin K antagonist.

our experience, may be achieved via multifaceted and multilevel educational intervention.[36]

Strengths and limitations

Our study has several important strengths and limitations. Although dabigatran was associated with treatment outcomes that were comparable or superior to those with VKA, the study was not designed to prove causality and, notably, no PS matching or statistical tests were applied. However, our findings are compatible with those previously reported for the PS-matched global population, analyzed by multivariable Cox regression.[21] PS matching has the disadvantage of reducing the number of patients in the analyzed population and, notably, our Eastern European population had a small number of patients with CV events (eg, in the dabigatran and VKA groups combined, 11 patients vs. 158 patients in the global population experienced stroke). Similarly, for the Eastern European population, the small number of patients treated with factor Xa inhibitors (N = 188) precluded comparisons of their effectiveness and safety with dabigatran (N = 498) and VKA (N = 466). For the global population, post hoc analyses suggest that patients treated with dabigatran may benefit from a reduced (by 41%) or similar risk of major bleeding versus rivaroxaban and apixaban, respectively, and that all 3 treatments had similar risk of stroke, myocardial infarction, and death.[37] Another potential drawback is that treatment persistence may be enhanced by frequent clinical follow-up. Conversely, regular follow-up with physicians, and the associated procedures to gather and review data (eg, 10% on-site monitoring) have resulted in data that are of particularly high quality for a real-world study. The 3-year follow-up period is also notable, given that there is a high risk of discontinuing antithrombotic therapy before 1 year,[24,25,38] and limited information for the effectiveness, persistence, and safety beyond 2 years of treatment with DOACs in real-world settings.

Summary

In summary, in this 3-year descriptive analysis of the prospective GLORIA-AF registry, dabigatran was associated with numerically reduced risk of major bleeding, all-cause death, and a composite CV outcome, whereas the risk of stroke was comparable, relative to VKA, in the Eastern European and global populations. The Eastern European population, compared with the global population, was associated with substantially less use of chronic concomitant high bleeding risk therapies at baseline and substantially higher persistence with dabigatran treatment. The incidence of CV outcomes with dabigatran, compared with VKA, in the current descriptive analysis are compatible with those in other comparative analyses including the pivotal RE-LY trial, retrospective studies, and analyses performed in regions other than Eastern Europe.[11,15,17]

Our 3-year descriptive analysis of CV outcomes from GLORIA-AF phase 3 is limited by the lack of statistical testing or PS-matching and the small numbers of patients with CV events (eg, in the dabigatran and VKA groups combined, 11 patients experienced stroke), preventing definitive conclusions about the effectiveness and safety of antithrombotic treatments in the Eastern European population. However, comparison with the CV outcomes in the substantially larger global population (previously reported with PS matching and statistical testing[21] and reported herein without PS matching) suggests that dabigatran versus VKA has a favorable benefit–risk profile in routine clinical practice in Eastern European patients with newly diagnosed AF.

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