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ABSTRACT

BACKGROUND GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) is a prospective, global registry program describing antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation at risk of stroke. Phase 2 began when dabigatran, the first non–vitamin K antagonist oral anticoagulant (NOAC), became available.

OBJECTIVES This study sought to describe phase 2 baseline data and compare these with the pre-NOAC era collected during phase 1.

METHODS During phase 2, 15,641 consenting patients were enrolled (November 2011 to December 2014); 15,092 were eligible. This pre-specified cross-sectional analysis describes eligible patients' baseline characteristics. Atrial fibrillation disease characteristics, medical outcomes, and concomitant diseases and medications were collected. Data were analyzed using descriptive statistics.

RESULTS Of the total patients, 45.5% were female; median age was 71 (interquartile range: 64, 78) years. Patients were from Europe (47.1%), North America (22.5%), Asia (20.3%), Latin America (6.0%), and the Middle East/Africa (4.0%). Most had high stroke risk (CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category] score ≥2; 86.1%); 13.9% had moderate risk (CHA_2DS_2-VASc = 1). Overall, 79.9% received oral anticoagulants, of whom 47.6% received NOAC and 32.3% vitamin K antagonists (VKA); 12.1% received antiplatelet agents; 7.8% received no antithrombotic treatment. For comparison, the proportion of phase 1 patients (of N = 1,063 all eligible) prescribed VKA was 32.8%, acetylsalicylic acid 41.7%, and no therapy 20.2%. In Europe in phase 2, treatment with NOAC was more common than VKA (52.3% and 37.8%, respectively); 6.0% of patients received antiplatelet treatment; and 3.8% received no antithrombotic treatment. In North America, 52.1%, 26.2%, and 14.0% of patients received NOAC, VKA, and antiplatelet drugs, respectively; 7.5% received no antithrombotic treatment. NOAC use was less common in Asia (27.7%), where 27.5% of patients received VKA, 25.0% antiplatelet drugs, and 19.8% no antithrombotic treatment.

CONCLUSIONS The baseline data from GLORIA-AF phase 2 demonstrate that in newly diagnosed nonvalvular atrial fibrillation patients, NOAC have been highly adopted into practice, becoming more frequently prescribed than VKA in Europe and North America. Worldwide, however, a large proportion of patients remain undertreated, particularly in Asia and North America. (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation [GLORIA-AF]; NCT01468701) (J Am Coll Cardiol 2017;69:777–85) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASA = acetylsalicylic acid

IQR = interquartile range

NOAC = non-vitamin K antagonist oral anticoagulant(s)

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulant(s)

VKA = vitamin K antagonist(s)

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. It increases the risk of stroke up to 5-fold (1,2). Oral anticoagulants (OAC), and vitamin K antagonists (VKA) in particular, have long been the cornerstone of treatment for patients with AF, providing a 64% reduction in risk of ischemic stroke and a 26% reduction in all-cause mortality compared with control or placebo when assessed in clinical trials according to intention-to-treat (3).

Until 6 years ago, the only OAC available were VKA (e.g., warfarin). Due to interpatient and intrapatient variability in their anticoagulant effect, many physicians were reluctant to prescribe VKA for fear of bleeding and due to misperception of the thrombotic risk for individual patients (2). Thus, up to 50% of AF patients did not receive OAC to prevent ischemic stroke (3). Non-vitamin K antagonist oral anticoagulants (NOAC) are equal to or more effective than VKA for stroke prevention in patients with nonvalvular AF (4–8). Whereas they have changed practice, the extent to which various anticoagulant drugs are prescribed is uncertain in some regions of the world, as is the manner in which physicians use indexes of risk, particularly the $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke), CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category), and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly [age >65 years], previous Drug, alcohol, or medication usage) scores, that have been incorporated into guidelines.

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Data to address these issues are available from the GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) registry program, a comprehensive worldwide registry program of AF patients developed to evaluate 3 phases of anticoagulant practice, as follows: phase 1: before the availability of NOAC; phase 2: following the availability of the direct thrombin inhibitor dabigatran, the first NOAC; and phase 3: when data from phase 2 indicate that characteristics of patients receiving dabigatran treatment overlap sufficiently with those given VKA treatment in a given region to support further statistical comparisons. In this paper, we report on patient characteristics and antithrombotic prescribing patterns

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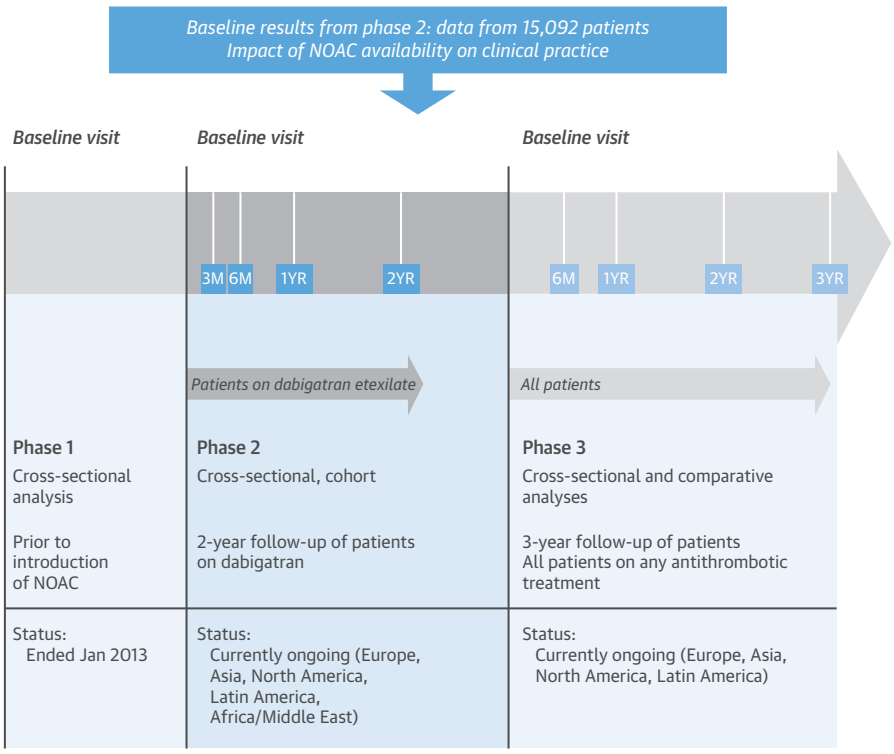
FIGURE 1 Gloria-AF Registry Phase 2 Baseline Data



Design of Gloria-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) registry. NOAC = non-vitamin K antagonist oral anticoagulant(s).

globally and regionally at baseline in phase 2, which was initiated when dabigatran became available, and compare the phase 2 data with the pre-NOAC era data (phase 1).

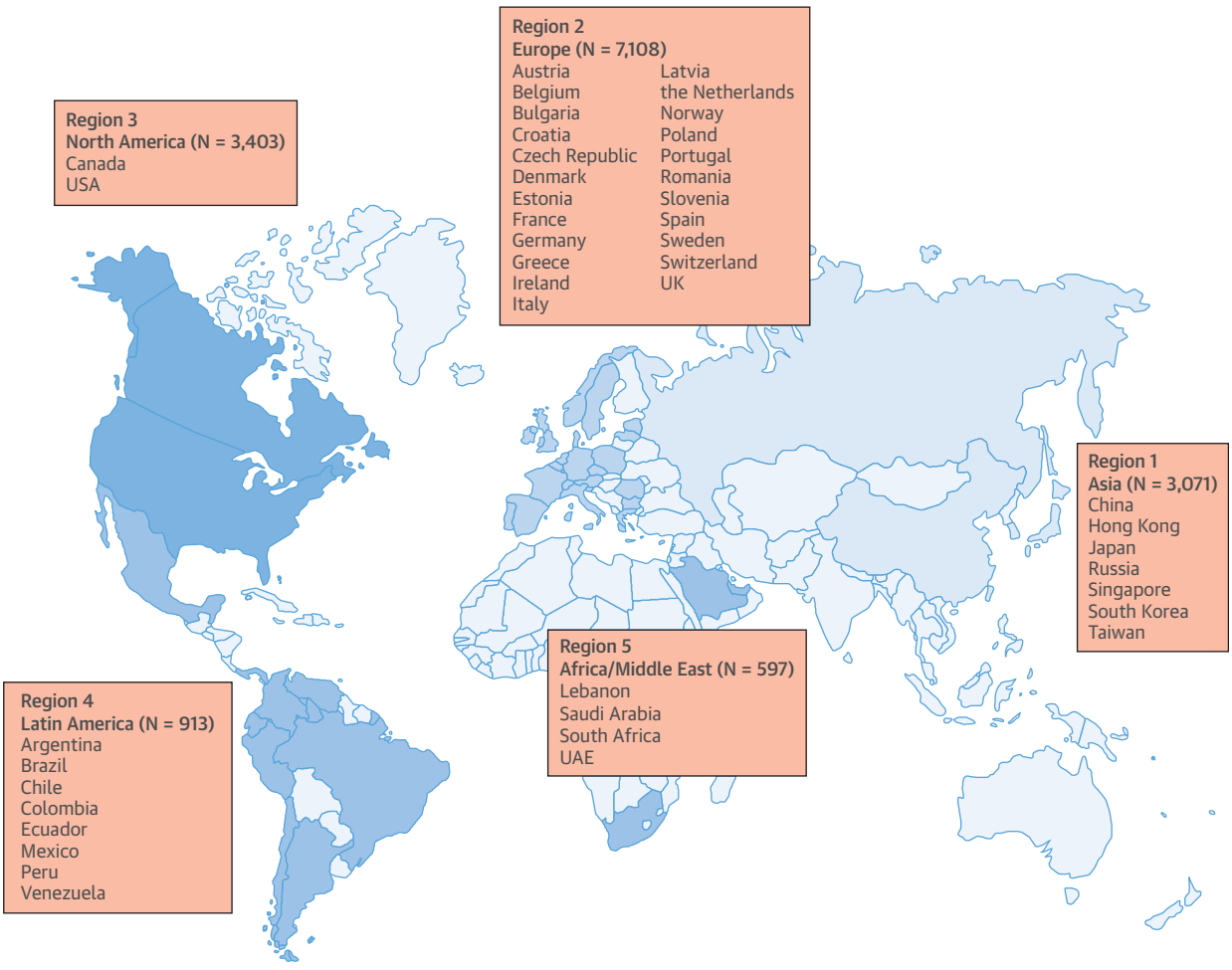
METHODS

DESIGN. This registry program entails ongoing data collection from patients with newly diagnosed nonvalvular AF during 3 separate phases (9) (**Figure 1**). The results of phase 1, conducted before approval of NOAC in each region, have been published (10). During phase 2, which began in each country when dabigatran was approved, cross-sectional data were collected at baseline for all enrolled patients with newly diagnosed AF. The data included AF disease characteristics, medical conditions including concomitant diseases, and medications. No additional procedures, apart from assessments performed as part of routine clinical practice, were required.

DATA COLLECTION AND QUALITY CONTROL. All clinical data were collected using a validated web-based system to ensure confidentiality and integrity. The study staff at each site entered data over a secure network. A complete electronic audit trail was maintained, with data quality being monitored on an ongoing basis, with a subset of sites audited onsite. Data quality and queries were addressed using bimonthly telephone calls to all sites and quarterly review meetings were held to assess aggregate data and address systematic issues. Data quality measures were implemented on an ongoing basis through automatic programmed data checks, manual data reviews conducted on a bimonthly basis, and quarterly medical quality reviews of aggregate data to address any systematic data issues identified (e.g., trends for missing data). A subset of sites was monitored with onsite source data verification and a different subset of sites was audited onsite by sponsor audit representatives.

PATIENTS. The registry program includes consecutive patients age ≥18 years with CHA_2DS_2-VASc scores ≥1 and nonvalvular AF diagnosed within 3 months before the first visit. Patients with mechanical heart valves, previous VKA therapy for >60 days, and AF due to a generally reversible cause were excluded. The term nonvalvular atrial fibrillation (NVAF) was

FIGURE 2 Regional Contribution



Countries involved in the GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) phase 2, and the distribution of patients per region.

used in this registry (and others) as this was used in the randomized trials and contemporary guidelines when GLORIA-AF was designed and ongoing. This excludes valvular AF, which refers to AF in association with prosthetic mechanical heart valves or hemodynamically significant native valvular heart disease where an intervention was to be performed (e.g., valve surgery) or there was an impact on the patient's likelihood of survival.

To be included, the patient's AF had to be documented by 12-lead electrocardiography, electrocardiographic rhythm strip, pacemaker/implantable cardioverter-defibrillator electrocardiogram, or Holter electrocardiography. Patients were recruited from a variety of 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. Patients were excluded for the following reasons: mechanical heart valves or valve disease expected to require valve replacement during the course of the registry; >60 days of VKA treatment for any indication in their lifetime; AF with a generally reversible cause, life expectancy <1 year; or an indication for OAC other than AF. Standard electronic case report forms were used to record baseline clinical and demographic characteristics, type of AF, and management approach. Patients without important protocol violations and who met data cleaning criteria for analysis were considered eligible for inclusion. Bleeding risk was assessed by the HAS-BLED score (11).

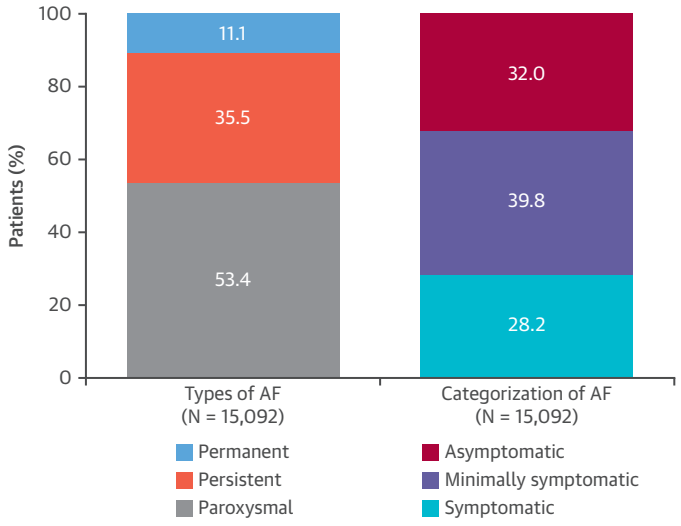
TABLE 1 Patient Demographics and Medical History (N = 15,092)

Demographics	
Age, yrs	71.0 (64.0-78.0)
Female	6,872 (45.5)
BMI, kg/m^2	27.5 (24.5-31.4)
Geographical region	
Asia	3,071 (20.3)
Europe	7,108 (47.1)
North America	3,403 (22.5)
Latin America	913 (6.0)
Africa/Middle East	597 (4.0)
Medical history	
History of hypertension*	11,255 (74.6)
Hyperlipidemia†	6,026 (39.9)
Congestive heart failure‡	3,647 (24.2)
Diabetes mellitus	3,487 (23.1)
Left ventricular hypertrophy§	3,061 (20.3)
Coronary artery disease‖	3,068 (20.3)
Cardioversion¶	2,431 (16.1)
Chronic GI disease#	1,976 (13.1)
Myocardial infarction**	1,600 (10.6)
Previous stroke††	1,582 (10.5)
Cardioablation‡‡	161 (1.1)
Creatinine clearance class,§§ ml/min	
<15	113 (0.7)
15 to <30	315 (2.1)
30 to <50	1,779 (11.8)
50 to <80	4,638 (30.7)
≥80	5,023 (33.3)
Previous bleed‖‖	842 (5.6)

Values are median (interquartile range) or n (%). *Information is unknown for 36 patients. †Information is unknown for 440 patients. ‡Information for 149 patients is missing. §Information is unknown for 667 patients. ‖Information is unknown for 411 patients. ¶Information is unknown for 220 patients. #Information is unknown in 173 patients. **Information is unknown for 9 patients. ††Information is unknown for 10 patients. ‡‡Information is unknown in 145 patients. §§Information is missing for 3,224 patients. ‖‖Information is unknown in 276 patients.

BMI = body mass index; GI = gastrointestinal.

FIGURE 3 Distribution of AF Types and Symptom Categories of AF



AF = atrial fibrillation.

STATISTICAL ANALYSIS. Data are summarized by median (interquartile range [IQR]) for continuous variables and by frequencies and percentages for categorical variables. Statistical analysis was performed using SAS software version 9.4, (SAS Institute Inc., Cary, North Carolina). This is a descriptive study—no inferential statistical analyses were made. No statistical hypothesis tests were performed.

RESULTS

PATIENTS. From November 2011 to December 2014, a total of 15,641 patients at 984 centers in 44 countries were enrolled in phase 2. Of these, 15,092 were eligible for analysis (did not have important protocol violations and met data cleaning criteria for analysis), with the following distribution across regions: Europe 7,108 (47.1%); North America 3,403 (22.5%); Asia 3,071 (20.3%); Latin America 913 (6.0%); and Africa/Middle East 597 (4.0%). In phase 1, 1,063 patients were included as eligible for the analysis, from some centers that were not the same as phase 2 (10). The participating countries in phase 2 per region, as well as the regional contributions, are summarized in **Figure 2**.

DEMOGRAPHICS AND COMORBIDITIES. The majority of participating sites were university hospitals (33.7%), followed by specialist offices (30.3%), community hospitals (26.3%), primary care (6.4%), outpatient clinics or anticoagulation clinics (2.5%), and "other" site types not specified (0.8%). The median age at enrollment was 71 years (IQR: 64, 78), similar to phase 1 (70 years) (10). Patient demographics and comorbidities are shown in **Table 1**. The most prevalent comorbidities at baseline were history of hypertension (74.6%), hyperlipidemia (39.9%), heart failure (24.2%), diabetes mellitus (23.1%), left ventricular hypertrophy (20.3%), and coronary artery disease (20.3%). In phase 1, the most common comorbidities were hypertension (74.8%), coronary artery disease (24.1%), congestive heart failure (24.1%), and diabetes mellitus (22.6%) (10).

Paroxysmal AF was present in 53.4% of patients, 35.5% had persistent AF, and 11.1% had permanent AF, compared with 62.6%, 33.8%, and 3.7%, respectively, in phase 1 (10) (**Figure 3**). AF was symptomatic in 28.2% of patients and minimally symptomatic or asymptomatic in 71.8%; in phase 1, AF was symptomatic in 62.2% (10) (**Figure 3**).

Stroke and bleeding-risk scores are shown in **Table 2**. The median CHA_2DS_2-VASc score was 3

TABLE 2 Stroke and Bleeding Risk Scores (N = 15,092)

$CHADS_2$ score categories	
Low, score = 0	1,221 (8.1)
Moderate, score = 1	5,150 (34.1)
High, score ≥2	8,719 (57.8)
Missing	2 (0.0)
CHA_2DS_2-VASc score categories*	
Low/moderate, score = 1†	2,093 (13.9)
High, score ≥2	12,999 (86.1)
HAS-BLED risk score categories	
Low-intermediate, score <3	11,927 (79.0)
High, score ≥3	1,376 (9.1)
Missing	1,789 (11.9)

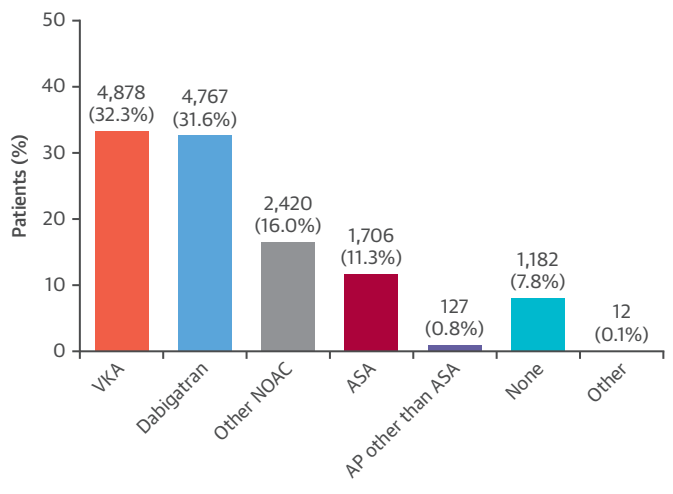
Values are n (%). *According to eligibility criteria, patients had to have a CHA_2DS_2-VASc score ≥1 to be eligible for the study. †Including 332 female patients.

$CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category; HAS-BLED = Hypertension, Abnormal renal/liver function; Stroke, Bleeding, Labile international normalized ratio, Elderly (age > 65 years), previous drug, alcohol, or medication usage.

(IQR: 2 to 4). The median $CHADS_2$ score was 2 (IQR: 1 to 3) and more than one-half of the patients (57.8%) had $CHADS_2$ scores of ≥2. The median HAS-BLED score was 1 (IQR: 1 to 2), with scores <3 in most patients (n = 11,927; 79.0%). These median scores were all similar to those observed in phase 1 (10).

ANTITHROMBOTIC THERAPY. Overall, OAC was prescribed in 79.9% of patients. Nearly one-half (47.6%) received a NOAC, while 32.3% received a VKA, and 12.1% either received acetylsalicylic acid (ASA) or another antiplatelet agent alone or in combination with ASA. A total of 7.8% of patients received no antithrombotic agent (Figure 4). Among patients with CHA_2DS_2-VASc scores of 1, 19.3% received ASA and 14.1% received no antithrombotic treatment, whereas 10.0% of those with CHA_2DS_2-VASc scores ≥2 received ASA and 6.8% received no treatment (Figure 5). These figures contrast with phase 1 results, in which ASA was most commonly prescribed (41.7%), followed by VKA (32.8%), and other antiplatelet agents (3.4%); 20.2% did not receive antithrombotic therapy (10).

FIGURE 4 Antithrombotic Treatment at Baseline



Distribution of patients per antithrombotic treatment at baseline. n = 15,092. Other NOAC includes rivaroxaban, apixaban, and edoxaban. AP = antiplatelet; ASA = acetylsalicylic acid; NOAC = non-vitamin K antagonist oral anticoagulant(s); VKA = vitamin K antagonist(s).

REGIONAL DEMOGRAPHIC PATTERNS. In the European cohort, the median age was 73.0 (IQR: 66.0 to 79.0) years and the median CHA_2DS_2-VASc score was 3 (IQR: 2 to 4). The most prevalent comorbidities were diabetes (21.2%), left ventricular hypertrophy (22.0%), heart failure (23.4%), hyperlipidemia (36.5%), and hypertension (73.4%). In North America, the median age was 71.0 (IQR: 64.0 to 79.0) years and the median CHA_2DS_2-VASc score was 3 (IQR: 2 to 4). The most prevalent comorbidities were chronic gastrointestinal disease (22.0%), coronary artery disease (27.0%), diabetes (27.1%), hyperlipidemia (61.3%), and hypertension (80.5%). In Asia, the median age was 68.0 (IQR: 60.0 to 76.0), the median CHA_2DS_2-VASc score was 3 (IQR: 2 to 4), and the most prevalent comorbidities were diabetes (20.2%), hyperlipidemia (26.7%), heart failure (27.3%), and hypertension (69.4%).

REGIONAL PATTERNS OF ANITHROMBOTIC THERAPY. Antithrombotic treatment choices at baseline in the 5 participating regions are summarized in the Central Illustration. Regions with the greatest number of patients were Europe, North America, and Asia, which together provided 90.0% of all patients in the registry program. In European centers, more patients were treated with NOAC (52.3%) than with VKA (37.8%). ASA or other antiplatelet treatments were given to 6.0% of patients, whereas 3.8% received no antithrombotic treatment. Similarly, in North American centers, more than one-half of the patients were treated with a NOAC (52.1%), VKA was prescribed in 26.2%, 14.0% received antiplatelet treatment, and 7.5% received no antithrombotic treatment. In Asia, 27.5% of patients received VKA and 27.7% NOAC. Antiplatelet treatment was given to 25.0%, whereas 19.8% received no antithrombotic treatment.

DISCUSSION

In the first few years after approval of dabigatran, and later following other NOAC, the overall uptake of NOAC was observed to be more frequent than that of

VKA in all regions except Asia. In addition, particularly in Europe, Latin America, and Africa/Middle East, the majority of patients received OAC. Whereas OAC therapy was also commonly prescribed in North America, antiplatelet therapy use was higher than in Europe, Latin America, or Africa/Middle East. In Asia, the use of OAC therapy, either with NOAC or VKA, was increasing; however, 1 in 5 patients of this high-risk population (CHA_2DS_2-VASc ≥2) still received no adequate therapy for stroke prevention.

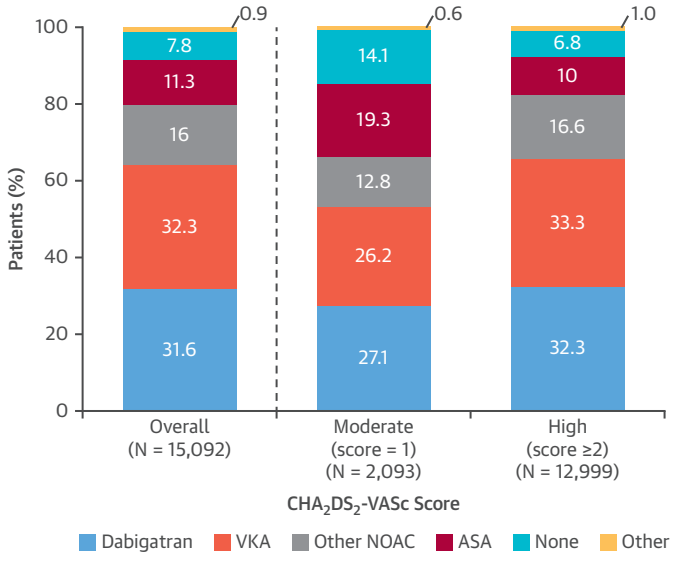
Nearly 80.0% of patients received an OAC, compared with 64.0% during phase 1, when no NOAC were available (10). In phase 2, nearly one-half of patients (47.6%) received a NOAC, whereas 32.3% received a VKA, and 12.1% ASA or another antiplatelet drug, but 7.8% received no treatment. For comparison, the proportion of phase 1 patients prescribed VKA was 32.8%, ASA 41.7%, and no therapy 20.2%. In Europe in phase 1, OAC (essentially VKA) were prescribed in 63.9%, ASA in 25.4%, and no therapy in 8.6%. In Europe, the use of antiplatelet treatment decreased from 27.1% in phase 1 to 6.0% in phase 2. Similarly, the percentage of European patients receiving no antithrombotic therapy decreased from 8.6% in phase 1 to 3.8% in phase 2.

These observations offer important insights into how clinical practice has been changed by the advent of NOAC, as well as the different evolution in international guidelines on the management of AF (12–15). In North America, nearly 80.0% of patients received OAC, more than 50.0% received NOAC but 14.0% received antiplatelet therapy. This pattern may reflect the U.S. guidelines, which advised antiplatelet therapy or no antithrombotic therapy as an alternative to OAC in patients with CHA_2DS_2-VASc scores of 1 (16,17).

Phase 2 of GLORIA-AF provides data shortly after the launch of NOAC in a given region. Other registries have reported data describing treatment patterns in AF patients, but comparisons across registries can be challenging for a variety of reasons. Differences in inclusion/exclusion criteria, participating physician specialties, and practice settings (e.g., academic vs. community hospitals) can result in substantially different patient populations or treatment preferences. Also, different time frames for enrollment compared with approval dates of available treatments (i.e., uptake of new treatments in the context of marketing approvals and availabilities) can result in different treatment patterns in a given region. Antithrombotic therapy differs considerably by region; hence the number of patients contributed by different regions affects the overall treatment pattern.

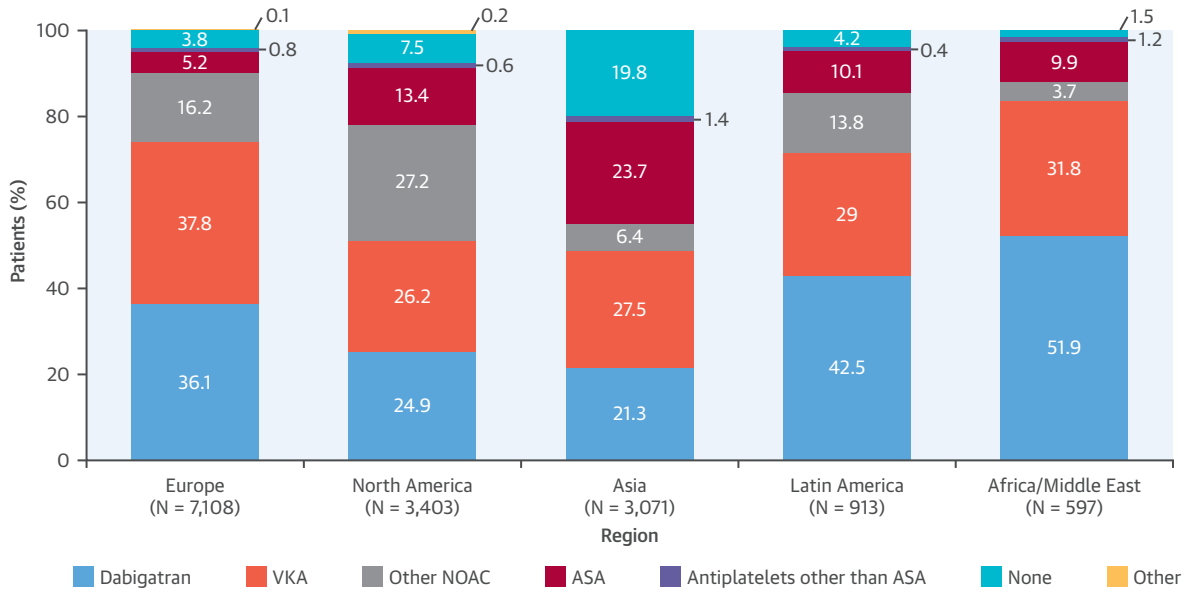
One registry has been collecting data during a time frame that overlapped GLORIA-AF. In the EORP-AF (EurObservational Research Programme on Atrial Fibrillation) registry, more than 3,000 patients were enrolled from February 2012 to March 2013 independent of NOAC approval status in the respective country (18). In this registry, patients had electrocardiogram-documented AF in the year before enrollment, unlike GLORIA-AF, which enrolled only incident AF cases with a new diagnosis of AF within the past 3 months. OAC therapy was prescribed in 80.0% of patients, most often VKA (71.6%), with NOAC used in 8.4%. Of note, the first NOAC became registered in most European countries in 2012, with subsequent approvals for additional NOAC in 2013 and later. Therefore, more than one-third of patients enrolled in EORP-AF came from countries where NOAC were not yet approved during the enrollment time, which explains the low use of NOAC in EORP-AF compared with GLORIA-AF. In addition, in GLORIA-AF, patients were enrolled from a broad range of practice settings and physician specialties until December 2014, potentially also contributing to the lower use of NOAC in the EORP-AF registry, which enrolled patients from cardiology practices only. In the EORP-AF study, antiplatelet therapy was used in one-third of patients. The mean CHA_2DS_2-VASc score in EORP-AF was 3.2, with 3.2 also the mean score in GLORIA-AF.

FIGURE 5 Antithrombotic Therapy by CHA_2DS_2-VASc Score



Patient distribution by antithrombotic therapy for the overall population (n = 15,092), CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category) score = 1 (n = 2,093), and CHA_2DS_2-VASc score ≥2 (n = 12,999). Factor Xa inhibitors includes rivaroxaban, apixaban, and edoxaban. Abbreviations as in Figure 4.

CENTRAL ILLUSTRATION **Stroke Prevention in AF: Antithrombotic Treatment per Region**



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Patient distribution by antithrombotic therapy and region (N = 15,092). Other NOAC includes rivaroxaban, apixaban, and edoxaban. ASA = acetylsalicylic acid; NOAC = non-vitamin K antagonist oral anticoagulant(s); VKA = vitamin K antagonist(s).

STUDY STRENGTHS AND LIMITATIONS. As a consequence of the design, there are considerable limitations for generalizability of these data, when considering all patients with NVAF. The GLORIA-AF study includes only patients at participating sites, and the overall majority of patients came from cardiology practices. Consequently, treatment patterns could be influenced by site selection. Moreover, patients had to give informed consent, which is another selection factor. However, patients enrolled were consecutive at each center. It is possible that obtaining informed consent resulted in a higher percentage of participating patients receiving oral anticoagulant treatment than the proportion seen among all patients. Sixty percent of study centers were either university hospitals or community hospitals, which may have increased the prevalence of patients treated with either dabigatran or other NOAC. Nonetheless our results may not be representative of the overall general AF population but are as representative as other registries of the newly diagnosed NVAF patient population as defined in the inclusion/exclusion criteria.

We tried to reduce selection factors within sites by asking participating sites to include consecutive patients, a point that is emphasized in the study protocol. Although training was provided to investigators and site personnel on this point, we could not verify adherence to this protocol for each site in phase 2, as screening logs were not implemented. As a result of recruitment of newly diagnosed AF, a relatively high percentage of patients had paroxysmal AF. This would therefore differ from registries that enroll pre-existing NVAF patients and in addition do not consider NOAC availability in a country, for example, patients from countries are included where no NOAC was available at that time.

Our broad reach of many centers and countries in this global registry, as well as the inclusion of recently diagnosed patients (<3 months), are strengths, as is the timing of data collection in phase 2, which was initiated immediately after the launch of the first NOAC in a given country. As a result, it is difficult to disentangle change among enrolled patients over time from changes in the site makeup over time.

CONCLUSIONS

The baseline phase 2 data from GLORIA-AF demonstrate that in newly diagnosed NVAF patients there is

a high adoption of NOAC seen in the first years after their availability, especially in Europe and North America, where NOAC were prescribed more often than VKA were. At the same time, considerable numbers of patients remained untreated, or were treated with ASA, especially in Asia and North America.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Non-vitamin K antagonist oral anticoagulants (NOAC) were widely adopted in clinical practice for patients with recently identified NVAF in the first years after their introduction, becoming more frequently prescribed than VKA in Europe and North America, but less so in Asia. Despite these trends, antiplatelet drugs or no antithrombotic therapy were still relatively common even for patients with CHA_2DS_2-VASc scores ≥1.

TRANSLATIONAL OUTLOOK: The next phase of this global registry program will address the comparative follow-up of patients in the later phase of market maturation, once those selected for therapy with dabigatran are demographically comparable to those given VKA.

REFERENCES

1. Peters NS, Schilling RJ, Kanagaratnam P, Markides V. Atrial fibrillation: strategies to control, combat, and cure. Lancet 2002;359:593–603.

2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.

3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.

4. Connolly SJ, Ezekowitz MD, Yusuf S, et al., for the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

5. Giugliano RP, Ruff CT, Braunwald E, et al., for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

6. Granger CB, Alexander JH, McMurray JJ, et al., for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

7. Nieuwlaat R, Capucci A, Lip GY, et al., for the Euro Heart Survey Investigators. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2006;27:3018–26.

8. Tulner LR, Van Campen JP, Kuper IM, et al. Reasons for undertreatment with oral anticoagulants in frail geriatric outpatients with atrial fibrillation: a prospective, descriptive study. Drugs Aging 2010;27:39–50.

9. Huisman MV, Lip GY, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. Am Heart J 2014;167:329–34.

10. Huisman MV, Ma SM, Diener HC, et al. Antithrombotic therapy use in patients with atrial fibrillation before the era of non-vitamin K antagonist oral anticoagulants: the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) phase I cohort. Europace 2016;18:1308–18.

11. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–100.

12. Camm AJ, Kirchhof P, Lip GY, et al., for the European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–429.

13. Camm AJ, Lip GY, De Caterina R, et al., for the ESC Committee for Practice Guidelines. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation: developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719–47.

14. National Institute for Health and Care Excellence. Atrial fibrillation: management. NICE guidelines CG180. NICE Website. Available at: https://www.nice.org.uk/guidance/cg180. Accessed May, 2016.

15. Verma A, Cairns JA, Mitchell LB, et al., for the CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30:1114–30.

16. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

17. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 Suppl 2:e531S–75S.

18. Lip GY, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace 2014;16:308–19.

KEY WORDS atrial fibrillation, oral anticoagulation, registry

APPENDIX For the list of GLORIA-AF phase 2 principal investigators, please see the online version of this paper.