Changes in anticoagulant prescription patterns over time for patients with atrial fibrillation around the world

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Abstract

Background: Prescribing patterns for stroke prevention in atrial fibrillation (AF) patients evolved with approval of non-Vitamin K antagonist oral anticoagulants (NOACs) over time.

Objectives: To assess changes in anticoagulant prescription patterns in various geographical regions upon first approval of a NOAC and to analyze the evolution of oral anticoagulants (OACs) use over time in relation to CHA2DS2-VASc and HAS-BLED risk profiles.

Methods: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phases II and III reported data on antithrombotic therapy for patients with newly diagnosed AF and ≥1 stroke risk factor. We focused on sites enrolling patients in both phases and reported treatment patterns for the first 4 years after initial NOAC approval.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, with both incidence and prevalence increasing with age. Nonvalvular AF is associated with a fivefold increase in risk of stroke. Therefore, stroke prevention is the cornerstone of the holistic approach to AF management. Currently, when oral anticoagulation (OAC) is indicated for stroke prevention in patients with AF, non-Vitamin K antagonist oral anticoagulants (NOACs) are recommended in preference to Vitamin K antagonists (VKAs).

In contrast, when NOACs were introduced and adopted into practice, clinical guidelines were still assessing results from pivotal trials. Since then, the rationale for using NOACs has changed. It is challenging to measure temporal trends of global prescription patterns, however, because the timing of NOAC approval varied across countries and prescription patterns can change rapidly as uptake of a new agent increases. Moreover, use of a particular OAC may reflect the manner in which physicians interpret stroke and bleeding risk scores, which have also been incorporated variably into clinical practice guidelines. Published descriptions of global NOAC uptake have not consistently accounted for these variables, overlooking distinctions based on the local availability of NOACs for clinical use. Therefore, results of such analyses are affected by the distribution of countries included in the evaluation.

The specific design of the large, prospective, global registry Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phases II and III provides an opportunity to assess temporal changes over time on a global scale. Enrolment for Phases II and III continued from 2011 to 2016 allowing for assessment of changes in practice patterns in a large number of patients over more than 4 years.

This report is based on baseline data, including antithrombotic prescriptions for stroke prevention in patients with newly diagnosed AF enrolled in Phases II and III of GLORIA-AF. We assessed temporal changes in antithrombotic prescription patterns within specific geographical regions, starting from initial NOAC approval. We also analyzed changes in types of OAC prescribed in relation to CHA₂DS₂-VASc (heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs or alcohol concomitantly) risk scores during each year of enrolment.

### Results

From GLORIA-AF Phases II and III, 27,432 patients were eligible for this analysis. When contrasting the first year with the fourth year of enrolment, the proportion of NOAC prescriptions increased in Asia from 29.2% to 60.8%, in Europe from 53.4% to 75.8%, in North America from 49.0% to 73.9% and in Latin America from 55.7% to 71.1%. The proportion of Vitamin K antagonists (VKAs) use decreased across all regions over time, in Asia from 26.0% to 9.8%, in Europe from 35.5% to 16.8%, in North America from 28.9% to 12.1%, and in Latin America from 32.4% to 17.8%. In the multivariable analysis, factors associated with NOAC prescription were as follows: enrolment year, type of site, region, stroke and bleeding risk scores, and type and categorization of AF.

### Conclusions

During 4 years after the approval of the first NOAC, NOAC use increased, while VKA use decreased, across all regions.

**Keywords**

atrial fibrillation, bleeding risk, GLORIA-AF, oral anticoagulants, stroke risk
VKA in Phase II showed substantial overlap, as measured by comparison of propensity score distributions. During Phase III, follow-up data were collected for up to 3 years regardless of prescribed antithrombotic therapy.

Adults with nonvalvular AF and ≥1 CHA$_2$DS$_2$-VASc risk factor score for stroke were included. Stroke and bleeding risks were assessed using the CHA$_2$DS$_2$-VASc and HAS-BLED risk scores. Patients were managed according to local practice. This report includes regions and sites enrolling patients during Phases II and III.

Standard electronic case reports forms (eCRFs) were used to collect patients' baseline characteristics and follow-up observation.
data. Baseline therapy was the treatment prescribed for long-term anticoagulation subsequent to the diagnosis of AF and recorded at the baseline visit.

Time zero in a participating country was set to the date of the baseline visit for the first patient in each country. The first year of enrolment for a participating country was the first year after time zero in that country. Most countries continued enrolment for up to 4 years. In this paper, we classify newly enrolled patients according to which prescribed treatment they received at their baseline visit, by year of enrolment.

2.1 | Statistical analysis

Treatment patterns are presented as a percentage of patients prescribed NOAC, VKA, or no OAC in each of the 4 years of enrolment, overall and by region. Categorical variables are reported as absolute frequencies and percentages, and continuous variables are summarized by median (Q1, Q3). Baseline characteristics were described by categorization of patients with AF according to stroke prevention treatment (NOAC, VKA, no OAC) and year of enrolment (first year versus last year, ie, Year 4), as well as by CHA₂DS₂-VASc and HAS-BLED risk scores. For each treatment, standardized differences were included to compare baseline characteristics between the last year and first year of enrolment.

Factors associated with OAC prescription patterns over time were evaluated using log-binomial regression models, providing estimates of relative probability for NOAC prescription (vs. VKA prescription). Both univariate and multivariable log-binomial regression analyses were fit to evaluate the crude as well as adjusted probability ratios together with 95% confidence intervals (CIs).

Missing data were imputed using multiple imputation. The imputation model was constructed with 56 baseline patient characteristic variables including those used in the multivariable analyses. The COPY method was used to obtain approximate maximum likelihood estimates when log-binomial models failed to converge. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

3 | RESULTS

There were 27,432 eligible patients who enrolled in GLORIA-AF during Phases II and III and who qualified to be included in this

![FIGURE 2](image-url) Temporal trends of antithrombotic therapy prescription globally. NOAC, non-Vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; VKA, Vitamin K antagonists
analysis. Of 8969 patients who enrolled in the first year, 46.6% were prescribed NOAC, 31.9% were prescribed VKA, and 21.5% were prescribed no OAC. Of 4388 patients enrolled in the fourth year, 71.6% received NOAC, 14.1% received VKA, and 14.3% received no OAC (Figure 2). A similar trend in treatment pattern over time, ie, increase in NOAC and decrease in VKA, was observed for Europe and North America. From the third to fourth year, an increase in NOAC prescriptions and a decrease in VKA or no OAC prescription was reported in Asia (Figure 3). The prevalence of non-OAC slightly decreased from Years 1-4, except Latin America (Figure 2).

Baseline characteristics of patients prescribed NOAC by region are summarized in Table 1. Paroxysmal AF was less prevalent in patients with NOAC during the first year of enrolment than in patients with NOAC during the last year of enrolment in Europe, North America, and Latin America. The standardized differences for stroke and bleeding risk scores (CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED) between the last and first year for NOAC patients were small in Europe, North America, and Latin America (less than 0.1).

Baseline characteristics of patients prescribed VKA by region are shown in Table 2. The standardized differences for CHA\textsubscript{2}DS\textsubscript{2}-VASc were small between the patients enrolled during the last and first year in North America, while they were more than 0.1 in Europe, Asia and Latin America. The standardized differences for HAS-BLED were more than 0.1 between last and first year in Asia, North America, and Latin America.

Prescription of oral antithrombotic treatment by region is presented in Table 3 and Figure 3. A decrease in no OAC use including acetylsalicylic acid (ASA) was reported in Asia between the third and fourth year of enrolment. An increase in NOAC use and decrease in VKA and no OAC use including ASA was present in Europe and North America. An increase in NOAC and a decrease in VKA were reported between second and fourth year in Latin America.

3.1 | Factors associated with NOAC prescription in phases II and III

Results from univariate analyses are presented in Table 4. In the multivariable log-binomial regression analysis, factors strongly associated with increased prescription of NOAC were as follows: enrolment year, type of site (higher probability outside of a university hospital, such as GP/primary care, specialist office, community hospital, and other), and region (higher prescription probability in North America compared with Europe) (Table 4).

Factors associated with decreased prescription of NOAC were the following: HAS-BLED score ≥3 (compared with HAS-BLED score <3), categorization of AF (lower probability of symptomatic AF compared with asymptomatic AF), CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≥2 (compared with CHA\textsubscript{2}DS\textsubscript{2}-VASc score <2), and type of AF (lower probability of persistent or permanent AF compared with paroxysmal AF) (Table 4).

3.2 | Prescription of antithrombotics over time by CHA\textsubscript{2}DS\textsubscript{2}-VASc score class

Regional patterns of prescription of antithrombotics over time by CHA\textsubscript{2}DS\textsubscript{2}-VASc score class are presented in Table S1.

In the first year after approval, 32.5% of those with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥2 received NOACs in Asia. Corresponding proportions for patients in Europe, North America, and Latin America were 53.5%, 49.6%, and 56.2%. In the fourth year after approval, 67.1% of patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥2 received NOACs in Asia. Corresponding proportions for patients in Europe, North America, and Latin America were 75.7%, 75.4%, and 70.4%.

Let interval change denote the change between Year 4 and Year 1 in prescription rate. The interval changes in those with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥2 who received NOACs in Asia were +34.6%. The
| Characteristic                        | Asia                                      | Europe                                      | North America                                    | Latin America                                    |
|--------------------------------------|-------------------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|                                      | Age, median, IQR, y                       | NOAC during first year (n = 666)            | NOAC during last year (n = 570)                  | NOAC during first year (n = 714)                  |
|                                      | 71.0                                      | (64.0-78.0)                                 | 72.0                                            | 72.0                                            |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.161                                    |                                            | 0.064                                          | −0.121                                          |
|                                      | Females, n (%)                            | 285 (42.8)                                 | 1191 (45.8)                                    | 305 (42.7)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.106                                     |                                            | 0.002                                          | 0.069                                          |
|                                      | Alcohol abuse, n (%)                      | 61 (9.2)                                   | 185 (7.1)                                      | 55 (7.7)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.310                                    |                                            | −0.094                                         | 0.013                                          |
|                                      | Unknown                                   | 24 (3.6)                                   | 277 (10.7)                                     | 36 (5.0)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.273                                     |                                            | −0.042                                         | 0.002                                          |
|                                      | BMI, median, IQR, kg/m²                    | 25.1 (22.2-28.4)                           | 27.7                                           | 29.6                                           |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.207                                    |                                            | 0.078                                          | 0.121                                          |
|                                      | Missed, n (%)                             | 26 (3.9)                                   | 21 (0.8)                                       | 0 (0.0)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.177                                     |                                            | 0.078                                          | 0.067                                          |
|                                      | Type of AF, n (%)                         | Paroxysmal                                 | 1212 (46.7)                                    | 422 (59.1)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.017                                     |                                            | 0.132                                          | 0.215                                          |
|                                      | Persistent                                | 196 (29.4)                                 | 1028 (39.6)                                    | 253 (35.4)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.151                                     |                                            | −0.053                                         | −0.169                                         |
|                                      | Permanent                                 | 77 (11.6)                                  | 358 (13.8)                                     | 39 (5.5)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.300                                    |                                            | −0.125                                         | −0.122                                         |
|                                      | Categorization of AF, n (%)               | Symptomatic                                 | 814 (31.3)                                     | 152 (21.3)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.117                                    |                                            | 0.189                                          | 0.072                                          |
|                                      | Minimally symptomatic                     | 256 (38.4)                                 | 1030 (39.6)                                    | 269 (37.7)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.021                                     |                                            | −0.184                                         | −0.089                                         |
|                                      | Asymptomatic                              | 192 (28.8)                                 | 754 (29.0)                                     | 293 (41.0)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.094                                     |                                            | −0.007                                         | 0.025                                          |
|                                      | Creatinine clearance (measured), median, | 65.4                                       | 74.4                                           | 80.1                                           |
|                                      | IQR, ml/min                               | (50.8-84.4)                                | (56.5-96.8)                                    | (59.7-107.4)                                    |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.062                                     |                                            | 0.079                                          | 0.075                                          |
|                                      | <15, n (%)                                | 0 (0.0)                                    | 1 (0.2)                                        | 0 (0.0)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.028                                     |                                            | 0.056                                          | 0.002                                          |
|                                      | 15-29, n (%)                              | 13 (2.0)                                   | 18 (0.7)                                       | 3 (0.4)                                        |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.043                                    |                                            | 0.053                                          | 0.002                                          |
|                                      | 30-49, n (%)                              | 117 (17.6)                                 | 319 (12.3)                                     | 72 (10.1)                                       |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.097                                    |                                            | 0.022                                          | 0.047                                          |
|                                      | 50-79, n (%)                              | 248 (37.2)                                 | 843 (32.4)                                     | 179 (25.1)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.052                                    |                                            | 0.047                                          | 0.032                                          |
|                                      | ≥80, n (%)                                | 169 (25.4)                                 | 898 (34.6)                                     | 265 (37.1)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.011                                    |                                            | 0.099                                          | 0.149                                          |
|                                      | Missing, n (%)                            | 119 (17.9)                                 | 505 (19.4)                                     | 186 (26.1)                                      |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | 0.168                                     |                                            | −0.175                                         | −0.169                                         |
|                                      | CHA2DS2-VASc score, median, IQR           | 3.0 (2.0-4.0)                              | 3.0 (2.0-4.0)                                  | 3.0 (2.0-4.0)                                   |
|                                      |                                           | Std diff                                   | Std diff                                        | Std diff                                        |
|                                      | −0.271                                    |                                            | −0.007                                         | −0.003                                         |

(Continues)
| Characteristic                        | Asia | Europe | North America | Latin America |
|--------------------------------------|------|--------|--------------|---------------|
|                                      | NOAC during first year (n = 666) | NOAC during last year (n = 570) | Std diff      | Std diff      |
| HAS-BLED score, median, IQR          | 1.0  (1.0-2.0) | 1.0 (2598) | 1.0 (1330) | 1.0 (1.0-2.0) |
| Missing (HAS-BLED), n (%)            | 50 (7.5) | 354 (13.6) | 173 (13.0) | 64 (9.0) |
| Medical history, n (%)               |      |        |              |               |
| Congestive heart failure             | 189 (28.4) | 669 (25.8) | 265 (19.9) | 119 (16.7) |
| Unknown                              | 7 (1.1) | 23 (0.9) | 13 (1.0) | 6 (0.8) |
| Hypertension                         | 523 (78.5) | 1965 (75.6) | 1032 (77.6) | 580 (81.2) |
| Unknown                              | 5 (0.8) | 6 (0.2) | 4 (0.3) | 1 (0.1) |
| Diabetes mellitus                    | 159 (23.9) | 519 (20.0) | 272 (20.5) | 186 (26.1) |
| Previous stroke/TIA/systemic embolism | 103 (15.5) | 423 (16.3) | 196 (14.7) | 93 (13.0) |
| Myocardial infarction                | 38 (5.7) | 230 (8.9) | 117 (8.8) | 71 (9.9) |
| Unknown                              | 0 (0.0) | 2 (0.1) | 0 (0.0) | 1 (0.1) |
| Coronary artery disease              | 117 (17.6) | 419 (16.1) | 245 (18.4) | 199 (27.9) |
| Unknown                              | 15 (2.3) | 78 (3.0) | 48 (3.6) | 13 (1.8) |
| Vascular disease                     | 50 (7.5) | 313 (12.0) | 156 (11.7) | 94 (13.2) |
| Cancer                               | 62 (9.3) | 204 (7.9) | 131 (9.8) | 124 (17.4) |
| Unknown                              | 10 (1.5) | 33 (1.3) | 25 (1.9) | 2 (0.3) |
| Chronic gastrointestinal disease     | 146 (21.9) | 220 (8.5) | 95 (7.1) | 145 (20.3) |
| Unknown                              | 16 (2.4) | 41 (1.6) | 27 (2.0) | 3 (0.4) |
| Hepatic disease                      | 43 (6.5) | 29 (1.1) | 9 (0.7) | 10 (1.4) |
| Unknown                              | 11 (1.7) | 47 (1.8) | 32 (2.4) | 5 (0.7) |
| Chronic kidney disease               | 216 (32.4) | 623 (24.0) | 302 (22.7) | 135 (18.9) |
| Unknown                              | 119 (17.9) | 505 (19.4) | 173 (13.0) | 186 (26.1) |
| Prior bleeding                       | 40 (6.0) | 118 (4.5) | 53 (4.0) | 42 (5.9) |
| Characteristic                      | Asia                  | Europe                  | North America            | Latin America            |
|------------------------------------|-----------------------|-------------------------|--------------------------|--------------------------|
|                                    | NOAC during first year (n = 666) | NOAC during last year (n = 570) | Std diff                  | NOAC during first year (n = 714) | NOAC during last year (n = 930) | Std diff                  | NOAC during first year (n = 201) | NOAC during last year (n = 312) | Std diff                  |
| Unknown                            | 14 (2.1)              | 0 (0.0)                 | -0.195                   | 16 (2.2)                 | 10 (1.1)                 | -0.091                   | 2 (1.0)                    | 0 (0.0)                    | -0.110                   |

|                      | **NOAC**              | **during**              | ** Std**                  | **during**              | **last year**           | ** Std**                  | **during**              | **last year**           | ** Std**                  |
|                      | **first year**        | ** during first year ** | **(n = 2598)**            | ** during last year**   | **(n = 1330)**          | **(n = 714)**            | **(n = 930)**           | **(n = 201)**           | **(n = 312)**           |
| **Type of site, n (%)**      |                       |                         |                          |                          |                          |                          |                          |                          |                          |
| GP/primary care            | 48 (7.2)              | 0 (0.0)                 | -0.387                   | 68 (9.5)                 | 63 (6.8)                 | -0.100                   | 39 (19.4)                | 66 (21.2)                | 0.044                    |
| Specialist office          | 66 (9.9)              | 37 (6.5)                | -0.125                   | 557 (78.0)               | 677 (72.8)               | -0.121                   | 70 (34.8)                | 102 (32.7)               | -0.046                   |
| Community hospital         | 385 (57.8)            | 49 (8.6)                | -1.226                   | 48 (6.7)                 | 91 (9.8)                 | 0.112                    | 71 (35.3)                | 65 (20.8)                | -0.327                   |
| University hospital        | 154 (23.1)            | 484 (84.9)              | 1.580                    | 16 (2.2)                 | 10 (1.1)                 | -0.091                   | 2 (1.0)                  | 0 (0.0)                  | -0.110                   |
| Otherc                    | 13 (2.0)              | 0 (0.0)                 | -0.186                   | 9 (1.3)                  | 2 (0.2)                  | -0.122                   | 5 (2.5)                  | 30 (9.6)                 | 0.302                    |

|                      | **Physician specialty, n (%)** |                       |                          |                          |                          |                          |                          |                          |                          |
|                      | GP/PCP/geriatrician       | 13 (2.0)               | 1 (0.2)                  | -0.174                   | 50 (1.9)                 | 22 (1.7)                 | -0.020                   | 18 (2.5)                 | 33 (3.5)                 | 0.060                    |
| Cardiologist          | 649 (97.4)              | 554 (97.2)              | 0.016                    | 2279 (87.7)              | 1183 (88.9)              | 0.038                    | 622 (87.1)               | 801 (86.1)               | -0.029                   |
| Neurologist           | 0 (0.0)                 | 14 (2.5)                | 0.214                    | 118 (4.5)                | 95 (7.1)                 | 0.111                    | 22 (3.1)                 | 17 (1.8)                 | -0.081                   |
| Internist             | 4 (0.6)                 | 1 (0.2)                 | 0.068                    | 61 (2.3)                 | 16 (1.2)                 | -0.087                   | 49 (6.9)                 | 58 (6.2)                 | -0.025                   |
| Angiologist           | 0 (0.0)                 | 0 (0.0)                 | 0.000                    | 0 (0.0)                  | 0 (0.0)                  | 0.000                    | 0 (0.0)                  | 0 (0.0)                  | 0.000                    |
| Other                 | 0 (0.0)                 | 0 (0.0)                 | 0.000                    | 90 (3.5)                 | 14 (1.1)                 | -0.163                   | 3 (0.4)                  | 21 (2.3)                 | 0.160                    |

|                      | **Medical treatment reimbursed by, n (%)** |                       |                          |                          |                          |                          |                          |                          |                          |
|                      | Self-pay/no coverage    | 66 (9.9)               | 106 (18.6)               | 0.250                    | 105 (4.0)                | 21 (1.6)                 | -0.149                   | 13 (1.8)                 | 17 (1.8)                 | 0.001                    |
| Not self-payd        | 581 (87.2)             | 415 (72.8)             | -0.367                   | 2329 (89.6)             | 1263 (95.0)             | 0.201                    | 669 (93.7)             | 881 (94.7)             | 0.044                    |
| Unknown              | 19 (2.9)               | 49 (8.6)               | 0.249                    | 164 (6.3)               | 46 (3.5)                | -0.133                   | 32 (4.5)               | 32 (4.3)               | -0.053                   |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHA<sub>2</sub>-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/systemic embolism, vascular disease, age 65-74 years, sex category (female); GP, general practitioner; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs or alcohol concomitantly; IQR, interquartile range; NOAC, non-Vitamin K antagonist oral anticoagulant; PCP, primary care physician; TIA, transient ischemic attack.

*a* ≥ 8 units/wk.

*b* < 60 mL/min.

*Anticoagulation clinics, out-patient healthcare centers, and other healthcare settings.

*d* Private and statutory/ federal insurance.
### TABLE 2 Baseline characteristics for VKA patients by first and last year of enrollment by region

| Characteristic                        | Asia                                      | Europe                                    | North America                             | Latin America                             |
|---------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
|                                      | VKA during first year (n = 594)           | VKA during first year (n = 1728)          | VKA during first year (n = 422)           | VKA during first year (n = 117)           |
|                                      | VKA during last year (n = 92)             | VKA during last year (n = 295)            | VKA during last year (n = 152)            | VKA during last year (n = 78)             |
|                                      | Std diff                                  | Std diff                                  | Std diff                                  | Std diff                                  |
| Age, median, IQR, y                  | 68.0 (60.0-75.0)                          | 74.0 (66.0-79.5)                          | 73.0 (65.0-81.0)                          | 70.0 (62.0-77.0)                          |
|                                      | (63.5 (56.0-71.5)                         | (75.0 (68.0-80.0)                         | (72.5 (63.5-79.0)                         | (69.0 (63.0-76.0)                         |
| Females, n (%)                       | 259 (43.6)                                | 819 (47.4)                                | 202 (47.9)                                | 46 (39.3)                                 |
|                                      | (32.4 (38.8)                             | (157 (53.2)                              | (68 (44.7)                                | (30 (38.5)                                |
| Alcohol abuse, n (%)                 | 46 (7.7)                                  | 156 (9.0)                                | 21 (5.0)                                  | 0 (0.0)                                   |
| Unknown                               | 68 (11.4)                                 | 112 (6.5)                                | 18 (4.3)                                  | 3 (2.6)                                   |
| BMI, median, IQR, kg/m²              | 24.7 (22.7-27.1)                          | 28.0 (25.0-31.6)                         | 30.0 (26.4-35.5)                          | 28.1 (25.6-31.6)                          |
|                                      | (24.8 (22.7-27.6)                         | (28.0 (25.0-32.4)                        | (31.2 (26.5-35.8)                         | (27.2 (24.4-31.9)                         |
| Missed, n (%)                        | 22 (3.7)                                  | 20 (1.2)                                  | 0 (0.0)                                   | 1 (0.9)                                   |
| Type of AF, n (%)                    |                                          |                                          |                                          |                                          |
| Paroxysmal                            | 294 (49.5)                                | 689 (39.9)                                | 245 (58.1)                                | 42 (35.9)                                 |
| Persistent                            | 275 (46.3)                                | 792 (45.8)                                | 150 (35.5)                                | 44 (37.6)                                 |
| Permanent                             | 25 (4.2)                                  | 247 (14.3)                                | 27 (6.4)                                  | 31 (26.5)                                 |
| Categorization of AF, n (%)          |                                          |                                          |                                          |                                          |
| Symptomatic                           | 135 (22.7)                                | 532 (30.8)                                | 97 (23.0)                                 | 31 (26.5)                                 |
| Minimally symptomatic                | 297 (50.0)                                | 661 (38.3)                                | 162 (38.4)                                | 44 (37.6)                                 |
| Asymptomatic                          | 162 (27.3)                                | 535 (31.0)                                | 163 (38.6)                                | 42 (35.9)                                 |
| Creatinine clearance (measured, median, IQR, ml/min) | 69.1 (52.1-86.3) | 72.0 (52.8-94.5) | 73.7 (50.4-109.7) | 74.1 (57.9-95.7) |
| <15, n (%)                            | 9 (1.5)                                   | 18 (1.0)                                  | 5 (1.2)                                   | 0 (0.0)                                   |
| 15-29, n (%)                          | 20 (3.4)                                  | 52 (3.0)                                  | 14 (3.3)                                  | 3 (2.6)                                   |
| 30-49, n (%)                          | 73 (12.3)                                 | 231 (13.4)                                | 61 (14.5)                                 | 10 (8.5)                                  |
| 50-79, n (%)                          | 215 (36.2)                                | 533 (30.8)                                | 61 (14.5)                                 | 4 (5.1)                                   |
| ≥80, n (%)                            | 148 (24.9)                                | 566 (32.8)                                | 10 (8.5)                                  | 0.000                                     |
| Missing, n (%)                        | 129 (21.7)                                | 328 (19.0)                                | 98 (19.7)                                 | 53 (45.3)                                 |
| CHA²DS²-VASc score, median, IQR      | 3.0 (2.0-4.0)                             | 3.0 (2.0-4.0)                             | 4.0 (2.0-4.0)                             | 3.0 (2.0-4.0)                             |
| HAS-BLED score, median, IQR          | 1.0 (1.0-2.0)                             | 1.0 (1.0-2.0)                             | 1.0 (1.0-2.0)                             | 1.0 (0.0-2.0)                             |

(Continues)
| Characteristic                        | Asia                          | Europe                       | North America                  | Latin America                  |
|-------------------------------------|-------------------------------|------------------------------|--------------------------------|--------------------------------|
|                                     | VKA during first year (n = 594) | VKA during last year (n = 92) | Std diff                      | VKA during first year (n = 422) | VKA during last year (n = 152) | Std diff |
| Missing (HAS-BLED), n (%)           | 95 (16.0)                     | 6 (6.5)                      | −0.303                        | 50 (11.8)                      | 10 (6.6)                      | −0.183  |
|                                     | VKA during first year (n = 1728) | VKA during last year (n = 295) | Std diff                      | VKA during first year (n = 117) | VKA during last year (n = 78)  | Std diff |
|                                     | 204 (11.8)                    | 38 (12.9)                    | 0.033                         | 50 (11.8)                      | 10 (6.6)                      | −0.183  |
|                                     | VKA during first year (n = 1172) | VKA during last year (n = 204) | Std diff                      | VKA during first year (n = 422) | VKA during last year (n = 152) | Std diff |
|                                     | 1728 (11.8)                   | 295 (12.9)                   | 0.033                         | 50 (11.8)                      | 10 (6.6)                      | −0.183  |
|                                     | Missing (HAS-BLED), n (%)            |                                |                               | VKA during first year (n = 117) | VKA during last year (n = 78)  | Std diff |
|                                     | 95 (16.0)                     | 6 (6.5)                      | −0.303                        | 50 (11.8)                      | 10 (6.6)                      | −0.183  |
|                                     | Medical history, n (%)          |                                |                               | VKA during first year (n = 117) | VKA during last year (n = 78)  | Std diff |
|                                     | Congestive heart failure       |                                |                               | 60 (11.8)                      | 10 (6.6)                      | −0.183  |
|                                     | Unknown                        |                                |                               | 5 (0.8)                        | 0 (0.0)                       | −0.036  |
|                                     | Hypertension                   |                                |                               | 402 (67.7)                     | 52 (65.6)                     | −0.232  |
|                                     | Unknown                        |                                |                               | 1 (0.2)                        | 0 (0.0)                       | 0.063   |
|                                     | Diabetes mellitus              |                                |                               | 135 (22.7)                     | 17 (18.5)                     | −0.105  |
|                                     | Unknown                        |                                |                               | 0 (0.0)                        | 0 (0.0)                       | 0.000   |
|                                     | Previous stroke/ TIA/systemic  |                                |                               | 91 (15.3)                      | 8 (8.7)                       | −0.205  |
|                                     | Unknown                        |                                |                               | 0 (0.0)                        | 0 (0.0)                       | 0.000   |
|                                     | Congestive heart failure       |                                |                               | 117 (19.7)                     | 30 (32.6)                     | 0.297   |
|                                     | Unknown                        |                                |                               | 5 (0.8)                        | 0 (0.0)                       | −0.036  |
|                                     | Hypertension                   |                                |                               | 402 (67.7)                     | 52 (65.6)                     | −0.232  |
|                                     | Unknown                        |                                |                               | 1 (0.2)                        | 0 (0.0)                       | 0.063   |
|                                     | Diabetes mellitus              |                                |                               | 135 (22.7)                     | 17 (18.5)                     | −0.105  |
|                                     | Unknown                        |                                |                               | 0 (0.0)                        | 0 (0.0)                       | 0.000   |
|                                     | Previous stroke/ TIA/systemic  |                                |                               | 91 (15.3)                      | 8 (8.7)                       | −0.205  |
|                                     | Unknown                        |                                |                               | 0 (0.0)                        | 0 (0.0)                       | 0.000   |
TABLE 2  (Continued)

| Characteristic       | Asia (n = 594) | Europe (n = 1728) | North America (n = 422) | Latin America (n = 117) |
|----------------------|---------------|-------------------|-------------------------|-------------------------|
|                      | VKA during first year | VKA during last year | Std diff | VKA during first year | VKA during last year | Std diff | VKA during first year | VKA during last year | Std diff |
| Prior bleeding       | 28 (4.7)      | 3 (3.3)           | -0.074     | 90 (5.2)             | 12 (4.1)            | -0.054     | 34 (8.1)             | 17 (11.2)             | 0.106     |
| Unknown              | 10 (1.7)      | 0 (0.0)           | -0.109     | 23 (1.3)             | 10 (3.4)            | 0.136      | 16 (3.8)             | 1 (0.7)                | -0.214    |
| Type of site, n (%)  |               |                   |            |                       |                     |            |                       |                       |          |
| GP/primary care      | 5 (0.8)       | 0 (0.0)           | -0.036     | 62 (3.6)             | 1 (0.3)             | -0.236     | 55 (13.0)            | 12 (7.9)             | -0.169    |
| Specialist office    | 83 (14.0)     | 15 (16.3)         | 0.065      | 193 (11.2)           | 75 (25.4)           | 0.375      | 295 (69.9)           | 93 (61.2)            | -0.184    |
| Community hospital   | 43 (7.2)      | 9 (9.8)           | 0.091      | 695 (40.2)           | 120 (40.7)          | 0.009      | 35 (8.3)             | 14 (9.2)             | 0.032     |
| University hospital  | 460 (77.4)    | 69 (73.9)         | -0.082     | 714 (41.3)           | 99 (33.6)           | -0.161     | 27 (6.4)             | 28 (18.4)            | 0.371     |
| Other                | 3 (0.5)       | 0 (0.0)           | 0.005      | 64 (3.7)             | 0 (0.0)             | -0.259     | 10 (2.4)             | 5 (3.3)                | 0.056     |
| Physician specialty, n (%) |            |                   |            |                       |                     |            |                       |                       |          |
| GP/PCP/geriatrician  | 1 (0.2)       | 0 (0.0)           | 0.063      | 68 (3.9)             | 2 (0.7)             | -0.218     | 21 (5.0)             | 10 (6.6)              | 0.069     |
| Cardiologist         | 592 (99.7)    | 92 (100.0)        | -0.031     | 1385 (80.2)          | 281 (95.3)          | 0.473      | 360 (85.3)           | 122 (80.3)            | -0.134    |
| Neurologist          | 1 (0.2)       | 0 (0.0)           | 0.063      | 32 (1.9)             | 9 (3.1)             | 0.078      | 5 (1.2)              | 6 (3.9)               | 0.175     |
| Internist            | 0 (0.0)       | 0 (0.0)           | 0.000      | 57 (3.3)             | 3 (1.0)             | -0.158     | 35 (8.3)             | 12 (7.9)              | -0.015    |
| Angiologist          | 0 (0.0)       | 0 (0.0)           | 0.000      | 0 (0.0)              | 0 (0.0)             | 0.000      | 0 (0.0)              | 0 (0.0)               | 0.000     |
| Other                | 0 (0.0)       | 0 (0.0)           | 0.000      | 166 (10.8)           | 0 (0.0)             | -0.479     | 1 (0.2)              | 2 (1.3)               | 0.123     |
| Medical treatment reimbursed by, n (%) |          |                   |            |                       |                     |            |                       |                       |          |
| Self-pay/no coverage | 69 (11.6)     | 5 (5.4)           | -0.223     | 108 (6.3)            | 7 (2.4)             | -0.192     | 14 (3.3)             | 8 (5.3)               | 0.096     |
| Not self-pay<sup>d</sup> | 510 (85.9)   | 76 (82.6)         | -0.089     | 1437 (83.2)          | 284 (96.3)          | 0.442      | 376 (89.1)           | 136 (89.5)            | 0.012     |
| Unknown              | 15 (2.5)      | 11 (12.0)         | 0.370      | 183 (10.6)           | 4 (1.4)             | -0.397     | 32 (7.6)             | 8 (5.3)               | -0.095    |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/systemic embolism, vascular disease, age 65-74 years, sex category (female); GP, general practitioner; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs or alcohol concomitantly; IQR, interquartile range; PCP, primary care physician; TIA, transient ischemic attack; VKA, Vitamin K antagonists.

<sup>a</sup> ≥ 8 units/wk.
<sup>b</sup> < 60 mL/min.
<sup>c</sup> Anticoagulation clinics, out-patient healthcare centers, and other healthcare settings.
<sup>d</sup> Private and statutory/ federal insurance.
## TABLE 3  Prescription of oral antithrombotic treatment over time by region

| Region: Asia | Year 1 | Year 2 | Year 3 | Year 4 | Total |
|-------------|--------|--------|--------|--------|-------|
| Number of patients | 2284 (100.0) | 1336 (100.0) | 1396 (100.0) | 937 (100.0) | 5953 (100.0) |
| NOAC (N, %) | 666 (29.2) | 619 (46.3) | 527 (37.8) | 570 (60.8) | 2382 (40.0) |
| On NOACs standard dose (N, %) | | | | | |
| Yes | 214 (9.4) | 239 (17.9) | 204 (14.6) | 224 (23.9) | 881 (14.8) |
| No | 452 (19.8) | 380 (28.4) | 323 (23.1) | 346 (36.9) | 1501 (25.2) |
| On NOACs reduced dose (N, %) | | | | | |
| Yes | 452 (19.8) | 380 (28.4) | 323 (23.1) | 346 (36.9) | 1501 (25.2) |
| No | 214 (9.4) | 239 (17.9) | 204 (14.6) | 224 (23.9) | 881 (14.8) |
| VKA (N, %) | 594 (26.0) | 266 (19.9) | 330 (23.6) | 92 (9.8) | 1282 (21.5) |
| No OAC (N, %) | 1024 (44.8) | 451 (33.8) | 539 (38.6) | 275 (29.3) | 2289 (38.5) |
| ASA (N, %) | 522 (22.9) | 251 (18.8) | 313 (22.4) | 150 (16.0) | 1236 (20.8) |
| Antiplt other than ASA (N, %) | 34 (1.5) | 22 (1.6) | 35 (2.5) | 16 (1.7) | 107 (1.8) |
| None (N, %) | 468 (20.5) | 178 (13.3) | 191 (13.7) | 109 (11.6) | 946 (15.9) |

| Region: Europe | Year 1 | Year 2 | Year 3 | Year 4 | Total |
|-------------|--------|--------|--------|--------|-------|
| Number of patients | 4866 (100.0) | 4090 (100.0) | 2911 (100.0) | 1754 (100.0) | 13 621 (100.0) |
| NOAC (N, %) | 2598 (53.4) | 2308 (56.4) | 1899 (65.2) | 1300 (75.8) | 8135 (59.7) |
| On NOACs standard dose (N, %) | | | | | |
| Yes | 1523 (31.3) | 1514 (37.0) | 1373 (47.2) | 1016 (57.9) | 5426 (39.8) |
| No | 1075 (22.1) | 794 (19.4) | 526 (18.1) | 314 (17.9) | 2709 (19.9) |
| On NOACs reduced dose (N, %) | | | | | |
| Yes | 1075 (22.1) | 794 (19.4) | 526 (18.1) | 314 (17.9) | 2709 (19.9) |
| No | 1523 (31.3) | 1514 (37.0) | 1373 (47.2) | 1016 (57.9) | 5426 (39.8) |
| VKA (N, %) | 1728 (35.5) | 1367 (33.4) | 741 (25.5) | 295 (16.8) | 4131 (30.3) |
| No OAC (N, %) | 540 (11.1) | 415 (10.1) | 271 (9.3) | 129 (7.4) | 1335 (9.9) |
| ASA (N, %) | 280 (5.8) | 228 (5.6) | 115 (4.0) | 66 (3.8) | 689 (5.1) |
| Antiplt other than ASA (N, %) | 43 (0.9) | 36 (0.9) | 22 (0.8) | 4 (0.2) | 105 (0.8) |
| None (N, %) | 217 (4.5) | 151 (3.7) | 134 (4.6) | 59 (3.4) | 561 (4.1) |

| Region: North America | Year 1 | Year 2 | Year 3 | Year 4 | Total |
|-------------|--------|--------|--------|--------|-------|
| Number of patients | 1458 (100.0) | 2045 (100.0) | 1593 (100.0) | 1258 (100.0) | 6354 (100.0) |
| NOAC (N, %) | 714 (49.0) | 1215 (59.4) | 1093 (68.6) | 930 (73.9) | 3952 (62.2) |
| On NOACs standard dose (N, %) | | | | | |
| Yes | 599 (41.1) | 1033 (50.5) | 943 (59.2) | 772 (61.4) | 3347 (52.7) |
| No | 115 (7.9) | 182 (8.9) | 150 (9.4) | 158 (12.6) | 605 (9.5) |
| On NOACs reduced dose (N, %) | | | | | |
| Yes | 115 (7.9) | 182 (8.9) | 150 (9.4) | 158 (12.6) | 605 (9.5) |
| No | 599 (41.1) | 1033 (50.5) | 943 (59.2) | 772 (61.4) | 3347 (52.7) |
| VKA (N, %) | 422 (28.9) | 442 (21.6) | 216 (13.6) | 152 (12.1) | 1232 (19.4) |
| No OAC (N, %) | 322 (22.1) | 388 (19.0) | 284 (17.8) | 176 (14.0) | 1170 (18.4) |
| ASA (N, %) | 200 (13.7) | 262 (12.8) | 200 (12.6) | 134 (10.7) | 796 (12.5) |
| Antiplt other than ASA (N, %) | 4 (0.3) | 21 (1.0) | 5 (0.3) | 4 (0.3) | 34 (0.5) |
| None (N, %) | 118 (8.1) | 105 (5.1) | 79 (5.0) | 38 (3.0) | 340 (5.4) |

| Region: Latin America | Year 1 | Year 2 | Year 3 | Year 4 | Total |
|-------------|--------|--------|--------|--------|-------|
| Number of patients | 361 (100.0) | 420 (100.0) | 284 (100.0) | 439 (100.0) | 1504 (100.0) |
| NOAC (N, %) | 201 (55.7) | 219 (52.1) | 164 (57.7) | 312 (71.1) | 896 (59.6) |

(Continues)
corresponding interval changes for Europe, North America, and Latin America were +22.2%, +25.8%, and +14.2%. The interval changes in those with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥2 who received VKAs in Asia were −17.5%. The corresponding interval changes for Europe, North America, and Latin America were −18.5%, −17.2%, and −15.3% (Table S2).

### 3.3 Prescription of antithrombotics over time by HAS-BLED score class

Regional patterns of prescription of antithrombotic drugs over time by HAS-BLED score class are presented in Table S3. The interval changes in those with HAS-BLED scores ≥3 who received NOACs in Asia were +4.1%. The corresponding interval changes for Europe, North America and Latin America were +20.7, +20.3, and +22.5%. The interval changes in those with HAS-BLED scores ≥3 who received VKAs in Asia were −9.7%. The corresponding interval changes for Europe, North America, and Latin America were −18.5%, −17.2%, and −21.3% (Table S4).

### 4 DISCUSSION

We found that use of NOAC increased and VKA decreased over time in patients with newly diagnosed AF. In consecutive years after their introduction, the proportions of patients prescribed NOAC increased and exceeded that of VKA or no OAC in all geographical regions, just as prescriptions for VKA decreased in all regions. North America was associated with NOAC prescription in the univariate analysis of NOAC vs. VKA prescription. The interval changes between fourth and first year after NOAC approval regarding NOAC prescription in patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥2 were the highest in Asia and North America. The interval changes between fourth and first year after NOAC approval regarding NOAC prescription in patients with HAS-BLED score ≥3 were the highest in Latin America, Europe, and North America but remained little changed in Latin America.

The use of NOAC appears to have increased over time in Europe. This finding is consistent with other reports.\textsuperscript{7-9} After the release of NOAC, the prevalence of NOAC use rose steadily in Japan.\textsuperscript{10} Similar patterns of NOAC and VKA prescription were shown in Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF).\textsuperscript{11}

Smaller proportions of patients from Latin America were prescribed NOAC or VKA at baseline in the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) than in our registry.\textsuperscript{12} Patients prescribed VKA during the last year of enrolment were more likely to have concomitant diseases, such as CHF, diabetes or vascular disease, than those who use NOAC during their last year of enrolment in Europe. In other studies, patients prescribed VKAs also had more comorbidities than those prescribed NOACs.\textsuperscript{13-14} Similar to our study, patients prescribed VKA were more likely to have permanent AF than those prescribed NOAC in each region.\textsuperscript{13-14} Interestingly, in Korean patients those who used VKAs were less likely to have prior stroke/TIA/systemic embolism than those who used NOACs.\textsuperscript{15}

In our study, the proportion of patients who were prescribed a reduced dose of NOAC is highest in Asia, a finding that could be related to smaller body size in Asian patients. The risk of major bleeding seems to be higher in Asian patients medicated with VKAs than in non-Asian patients.\textsuperscript{16} In one study, lower NOAC doses were frequently used in Asian patients in routine daily practice. However, unjustified underdosing of apixaban was associated with a less apparent clinical benefit over warfarin in patients.\textsuperscript{17}

The data from baseline Phase II of GLORIA-AF showed that considerable numbers of patients were not treated with OAC, especially in Asia and North America.\textsuperscript{18} Our observations are concordant with other studies in the United States, Denmark, Australia, and Korea.\textsuperscript{15,19-21} However, data from the United States (from

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**Note:** Standard dose: Dabigatran 150-mg BID, Rivaroxaban 20-mg QD, Apixaban 5-mg BID, Edoxaban 60-mg QD. The other doses are reduced.

**Abbreviations:** ASA, acetylsalicylic acid, NOAC, non-vitamin K antagonist oral anticoagulants, VKA, Vitamin K antagonists.
**TABLE 4** Multivariable log-binomial analysis for factors associated with prescription of oral antithrombotic therapy (NOAC versus VKA)

| Variable                        | Total N (100%) | NOAC n (%) | VKA n (%) | Univariate analysis relative proportion (95% CI) for NOAC prescription | Multivariate analysis relative proportion (95% CI) for NOAC prescription |
|--------------------------------|----------------|------------|-----------|---------------------------------------------------------------------|---------------------------------------------------------------------|
| **Time (categorical, Years 1-4)** |                |            |           |                                                                     |                                                                     |
| Year 1                          | 7040           | 4179 (59.4)| 2861 (40.6)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| Year 2                          | 6573           | 4361 (66.3)| 2212 (33.7)| 1.118 (1.09-1.15)                                                   | 1.10 (1.07-1.12)                                                   |
| Year 3                          | 5043           | 3683 (73.0)| 1360 (27.0)| 1.23 (1.20-1.26)                                                    | 1.20 (1.17-1.23)                                                    |
| Year 4                          | 3759           | 3142 (83.6)| 617 (16.4) | 1.41 (1.38-1.44)                                                    | 1.34 (1.31-1.37)                                                    |
| **Region**                      |                |            |           |                                                                     |                                                                     |
| Asia                            | 3664           | 2382 (65.0)| 1282 (35.0)| 0.98 (0.95-1.01)                                                    | 1.03 (0.99-1.05)                                                    |
| Europe                          | 12 266         | 8135 (66.3)| 4131 (33.7)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| North America                   | 5184           | 3952 (76.2)| 1232 (23.8)| 1.15 (1.13-1.17)                                                    | 1.05 (1.03-1.08)                                                    |
| Latin America                   | 1301           | 896 (68.9) | 405 (31.1) | 1.04 (0.99-1.08)                                                    | 0.99 (0.96-1.04)                                                    |
| **BMI class**                   |                |            |           |                                                                     |                                                                     |
| <18.5                           | 297            | 201 (67.7) | 96 (32.3) | 0.99 (0.92-1.09)                                                    | 0.98 (0.91-1.05)                                                    |
| 18.5-24                         | 5856           | 3970 (67.8)| 1887 (32.2)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| 25-29                           | 8623           | 5884 (68.2)| 2738 (31.8)| 1.01 (0.98-1.03)                                                    | 1.00 (0.98-1.02)                                                    |
| ≥35                             | 4582           | 3165 (69.1)| 1417 (30.9)| 1.02 (0.99-1.05)                                                    | 0.99 (0.97-1.01)                                                    |
| **Categorization of AF**        |                |            |           |                                                                     |                                                                     |
| Symptomatic                     | 6996           | 4740 (67.8)| 2256 (32.2)| 0.96 (0.94-0.98)                                                    | 0.98 (0.96-0.99)                                                    |
| Minimally symptomatic           | 7915           | 5332 (67.4)| 2583 (32.6)| 0.96 (0.94-0.98)                                                    | 0.99 (0.97-1.00)                                                    |
| Asymptomatic                    | 7504           | 5293 (70.5)| 2211 (29.5)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| **HAS-BLED score**              |                |            |           |                                                                     |                                                                     |
| <3                              | 20 619         | 14 176 (68.8)| 6443 (31.2)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| ≥3                              | 1796           | 1189 (66.2)| 607 (33.8) | 0.96 (0.93-0.99)                                                    | 0.96 (0.93-0.99)                                                    |
| **CHA2DS2-VASc score**          |                |            |           |                                                                     |                                                                     |
| =1                              | 2741           | 1902 (69.4)| 839 (30.6) | 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| ≥2                              | 19 674         | 13 463 (68.4)| 6211 (31.6)| 0.99 (0.96-1.01)                                                    | 0.97 (0.95-0.99)                                                    |
| **Chronic gastrointestinal disease** |            |            |           |                                                                     |                                                                     |
| Yes                             | 2968           | 2101 (70.8)| 867 (29.2) | 1.04 (1.01-1.06)                                                    | 1.01 (0.99-1.03)                                                    |
| No                              | 19 447         | 13 264 (68.2)| 6183 (31.8)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| **Type of AF**                  |                |            |           |                                                                     |                                                                     |
| Paroxysmal                      | 11 828         | 8536 (72.2)| 3292 (27.8)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| Persistent                      | 8239           | 5304 (64.4)| 2935 (35.6)| 0.89 (0.88-0.91)                                                    | 0.93 (0.92-0.95)                                                    |
| Permanent                       | 2348           | 1525 (64.9)| 823 (35.1) | 0.90 (0.87-0.93)                                                    | 0.93 (0.90-0.96)                                                    |
| **Type of site**                |                |            |           |                                                                     |                                                                     |
| GP/primary care                 | 1123           | 830 (73.9)| 293 (26.1) | 1.282 (1.230-1.334)                                                  | 1.24 (1.19-1.29)                                                    |
| Specialist office               | 6945           | 5199 (74.9)| 1746 (25.1)| 1.29 (1.27-1.33)                                                    | 1.22 (1.19-1.25)                                                    |
| Community hospital              | 7205           | 5171 (71.8)| 2034 (28.2)| 1.25 (1.21-1.28)                                                    | 1.23 (1.20-1.27)                                                    |
| University hospital             | 6540           | 3769 (57.6)| 2771 (42.4)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |
| Other                           | 602            | 396 (65.8) | 206 (34.2) | 1.14 (1.07-1.21)                                                    | 1.15 (1.09-1.22)                                                    |
| **Cancer**                      |                |            |           |                                                                     |                                                                     |
| Yes                             | 2261           | 1586 (70.1)| 675 (29.9) | 1.026 (0.99-1.06)                                                   | 0.99 (0.97-1.02)                                                    |
| No                              | 20 154         | 13 779 (68.4)| 6375 (31.6)| 1.0 (ref)                                                           | 1.0 (ref)                                                           |

(Continues)
The proportion of patients on OAC increased with CHA²DS₂-VASc score, as described in other datasets.\(^{24}\)

### Table 4 (Continued)

| Variable | Total N (100%) | NOAC n (%) | VKA n (%) | Univariate analysis relative proportion (95% CI) for NOAC prescription | Multivariate analysis relative proportion (95% CI) for NOAC prescription |
|----------|----------------|------------|-----------|---------------------------------------------------------------|---------------------------------------------------------------|
| Self-pay/no overage | 1362 | 894 (65.6) | 467 (34.3) | 0.956 (0.92-0.99) | 0.99 (0.96-1.03) |
| Not self-pay | 21 053 | 14 471 (68.7) | 6583 (31.3) | 1.0 (ref) | 1.0 (ref) |

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHA²DS₂-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/systemic embolism, vascular disease, age 65-74 years, sex category (female); CI, confidence interval; GP, general practitioner; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs or alcohol concomitantly; NOAC, nonvitamin K antagonist oral anticoagulants; ref, reference; VKA, Vitamin K antagonist.

2008 to 2014) indicate no increase in OAC prescriptions overall due to an increase in NOAC uptake being offset by a decrease in VKA use.\(^{22}\)

In our analysis, the prescription of NOAC for stroke prevention has been increasingly associated with individual patient stroke risk as recommended by the European Society of Cardiology guidelines.\(^{23}\)

The proportion of patients on OAC increased with CHA²DS₂-VASc score, as described in other datasets.\(^{24}\)

Increased prescription of NOAC over the 4 years of enrollment in GLORIA-AF is consistent with other reports.\(^{15,20,25}\) The proportion of patients with moderate-to-high risk of stroke who are not prescribed OAC has declined continuously. Increased awareness of physicians and patients, improved implementation of guidelines, and educational programs might have resulted in greater NOAC prescription.\(^{26}\)

Indeed, noticeable differences in patients’ baseline characteristics between consecutive years of enrollment are evident. The use of NOAC has also been increasing among patients with higher bleeding risk.

This study has important practical implications and may help in identifying the “action points” needed to improve stroke prevention in AF patients in “routine” clinical practice. Our observations also reflect the evolution of international guidelines on the management of AF in clinical practice.\(^{27}\)

Numerous registries have reported data on prescription patterns of antithrombotics for stroke prevention in AF, but comparison across registries appears to be challenging for a variety of reasons. The GLORIA-AF registry’s specific design facilitated a description of how the OAC prescription patterns changed across participating countries after NOAC approval. In contrast, in the EURObservational Research Programme (EORP) and the GARFIELD-AF registries, temporal OAC prescription patterns were presented by calendar year, which led to an aggregation of countries with and without NOAC approval particularly in the first years of NOAC availability; ie, while the first NOAC, dabigatran, was approved in the United States in 2011, the first approval in Italy only occurred in 2013; therefore, country composition as well as the amount patients by country had an impact on the observed treatment patterns. aggregated\(^{7,25}\)

In our study, that only started with NOACs availability, the proportion of patients prescribed NOAC increased within a period of between 1 and 4 years, while the proportions of VKA and non-OAC prescriptions decreased. A pattern similar to that in our study has also been seen in other studies,\(^{25}\) with a decline in the use of VKA as well as antiplatelets, and a rise in the use of NOAC. In the EORP-AF registry\(^{7}\), most of patients who were medicated with VKA or NOAC at the baseline and at 1-year follow-up were still anticoagulated with the same OAC at 2-year follow-up.

In this study, patients with a high HAS-BLED score had a generally increasing proportion of OAC prescriptions between the first and fourth year of enrollment. The percentage of patients with no OAC among patients with HAS-BLED score ≥3 was relatively stable (approximately one third of the patients) over the same period. A high percentage of patients with HAS-BLED score ≥3 had no OAC prescription, possibly reflecting the lack of concordance between empirical bleeding scores and physician assessment of bleeding risk in AF.\(^{28}\) Importantly, there appears to be a need to emphasize that AF patients with a high risk of bleeding should continue taking OAC with close monitoring and frequent visits and individual reassessment of thromboembolic and bleeding risks.\(^{23,29-30}\) In the mobile atrial fibrillation application (mAFA-II) randomized trial, proactive use of HAS-BLED for dynamic bleeding risk assessment was associated with lower bleeding rates and an increase in OAC use.\(^{31}\)

Furthermore, year of enrollment, type of site, region, type and categorization of AF, and stroke and bleeding risks are associated with NOAC prescription in the combined Phase II and III data in our analysis. A similar pattern was found in another report where persistent or permanent AF was inversely associated with NOAC prescription.\(^{13}\)

Also, the year of enrollment was associated with NOAC prescription.\(^{13}\)

### 4.1 Limitations

These findings may not generalize to the entire global nonvalvular AF patient population or even to the patient population of the participating countries, because the study is restricted to patients with a CHA²DS₂-VASc score ≥1. Furthermore, this analysis represents only a snapshot of the prescribing practice in the course of treatment and does not take into account treatment continuation, switching or adherence. These issues were addressed in other reports from GLORIA-AF. Data on the reasons for OAC non-prescription were not collected.
5 | CONCLUSIONS

In this global registry of prospectively enrolled AF patients, NOACs have been more commonly prescribed than VKA. During 4 years after approval of the first NOAC for stroke prevention in AF, NOAC use increased over time, while VKA use decreased across all regions.

ACKNOWLEDGEMENTS

The study was funded by Boehringer Ingelheim. The authors thank the patients who participated in this trial, their families, the investigators, study co-ordinators, and study teams.

CONFLICT OF INTEREST

Dr Kozieł and Professor Rothman declare they have no conflict of interest. Dr Bayer, Gurusamy, and Dr Teutsch are employees of Boehringer Ingelheim. Dr Lu was employee of Boehringer Ingelheim at time of manuscript writing. Dr Diener has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Bayer Vital, Bristol-Myers Squibb (BMS), Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Pfizer, Portola, Sanofi-Aventis, and WebMD Global. Financial support for research projects was provided by Boehringer Ingelheim. Dr Diener chairs the Treatment Guidelines Committee of the German Society of Neurology and contributed to the EHRA and ESC guidelines for the treatment of AF. Professor Halperin has engaged in consulting activities with Boehringer Ingelheim, for advisory activities involving anticoagulants, and he is a member of the Executive Steering Committee of the GLORIA-AF Registry. Professor Ma has received honoraria for lectures from AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, BMS, Johnson & Johnson, and Pfizer. Professor Huisman reports grants from ZonMW Dutch Healthcare Fund, grants and personal fees from Boehringer Ingelheim, Pfizer-BMS, Bayer HealthCare, Aspen, Daiichi-Sankyo, outside the submitted work. Professor Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

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REFERENCES

1. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154:1121–201.
2. Huisman MV, Lip GYH, Diener HC, Dubner SJ, Halperin JL, Ma CS, 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.
3. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest. 2010;137:263–72.
4. 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.
5. Rothman KJ. Disengaging from statistical significance. Eur J Epidemiol. 2016;31:443–4.
6. Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. Occup Environ Med. 2008;65(8):501–486.
7. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GYH. Real-world’ atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. Europace. 2017;19(5):722–33.
8. Catev T, Ten Cate H, Verheugt FWA. The global anticoagulant registry in the FIELD-atrial fibrillation (GARFIELD-AF): exploring the changes in anticoagulant practice in patients with non-valvular atrial fibrillation in the Netherlands. Neth Heart J. 2016;24(10):574–80.
9. Apenteng P, Gao H, Hobbs R, Fitzmaurice D. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ Open. 2018;8(1):e018905.
10. Yamashita Y, Uozumi R, Hamatani Y, Esato M, Chun YH, Tsuji H, et al. Current status and outcomes of direct oral anticoagulant use in real-world atrial fibrillation patients - Fushimi AF Registry. Circ J. 2017;81(9):1278–85.
11. Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF’, ORBIT-AF I’, and ORBIT-AF II registries. Am Heart J. 2017;194:132–40.
12. Jerjes-Sanchez C, Corbalan R, Barretto ACP, Luciardi HL, Allu J, Illingworth L, et al. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: insights from the GARFIELD-AF registry. Clin Cardiol. 2019;42(5):553–60.
13. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Contemporary stroke prevention strategies in 11,096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace. 2018;20(5):747–57.
14. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Factors associated with non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). Am Heart J. 2017;189:40–7.
15. Lee S-R, Choi E-K, Han K-D, Cha M-J, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One. 2017;12(12):e0189495.
16. Wang KL, Lip GYH, Lin S-J, Chiang C-E. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. Stroke. 2015;46(9):2555–61.
17. Cho MS, Yun JE, Park JJ, Kim YJ, Lee J, Kim H, et al. Outcomes after use of standard- and low-dose non-vitamin K oral anticoagulants in Asian patients with atrial fibrillation. Stroke. 2018;STROKEAHA118023093.
18. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. J Am Coll Cardiol. 2017;69:777–85.
19. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Goeckl KL, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol. 2017;69:2475–84.
20. Gadsbøll K, Staerk L, Fosbøl EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J. 2017;38:899–906.
21. Admassie E, Chalmers L, Bereznicki LR. Changes in oral anticoagu-
lant prescribing for stroke prevention in patients with atrial fibril-
lation. Am J Cardiol. 2017;120:1133–8.
22. Alalwan AA, Voils SA, Hartzema AG. Trends in utilization of warfa-
rin and direct oral anticoagulants in older adult patients with atrial fibrillation. Am J Health Syst Pharm. 2017;74:1237–44.
23. Kirchhof P, Benussi S, Kotecha D, Aalsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation de-
veloped in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.
24. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. JAMA Cardiol. 2016;1:55–62.
25. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand J-P, Berge E, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart. 2017;103:307.
26. Clarkesmith DE, Pattison HM, Lip GYH, Lane DA. Educational in-
tervention improves anticoagulation control in atrial fibrillation pa-
ients: the TREAT randomised trial. PLoS One. 2013;8:e74037.
27. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. comparing the guidelines and practical decision-making. Thromb Haemost. 2017;117:1230–9.
28. Steinberg BA, Kim S, Thomas L, Fonarow GC, Hylek E, Ansell J, et al. Lack of concordance between empirical scores and

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kozieł M, Teutsch C, Bayer V, Lu S, Gurusamy VK, Halperin JL, et al; the GLORIA-AF Investigators. Changes in anticoagulant prescription patterns over time for patients with atrial fibrillation around the world. J Arrhythmia. 2021:37:990–1006. https://doi.org/10.1002/joa3.12588