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RESEARCH ARTICLE

Atrial fibrillation and comorbidities: Clinical characteristics and antithrombotic treatment in GLORIA-AF

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Abstract

Background

Patients with AF often have multimorbidity (the presence of ≥2 concomitant chronic conditions).

Objective

To describe baseline characteristics, patterns of antithrombotic therapy, and factors associated with oral anticoagulant (OAC) prescription in patients with AF and ≥2 concomitant, chronic, comorbid conditions.

Methods

Phase III of the GLORIA-AF Registry enrolled consecutive patients from January 2014 through December 2016 with recently diagnosed AF and CHA2DS2-VASc score ≥1 to assess the safety and effectiveness of antithrombotic treatment.

Results

Of 21,241 eligible patients, 15,119 (71.2%) had ≥2 concomitant, chronic, comorbid conditions. The proportions of patients with multimorbidity receiving non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKA) were 60.2% and 23.6%,
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**Competing interests:** The authors have read the journal’s policy and have the following competing interests: Dr. Teutsch, Sabrina Marler, and Venkatesh K. Gurusamy are paid employees of Boehringer Ingelheim. Dr. Lu was a paid employee of Boehringer Ingelheim at the time that the manuscript was written. Professor Halperin has engaged in consulting activities for Boehringer Ingelheim and advisory activities involving anticoagulants, and he is a member of the Executive Steering Committee of the GLORIA-AF Registry. Over the past 3 years, Professor Diener received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from: Abbott, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, Portola, Sanofi-Aventis, and WebMD Global. Financial support for research projects was provided by Boehringer Ingelheim. He received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation, and Heinz-Nixdorf Foundation. Professor Ma received honoraria from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer Ingelheim, Bayer, and AstraZeneca for giving lectures. Professor Huisman reports grants from ZonMW Dutch Healthcare Fund, grants and personal fees from Boehringer Ingelheim, Pfizer/Bristol-Myers Squibb, Bayer Health Care, Aspen, Daiichi Sankyo, outside the submitted work. Professor Lip has been a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Versehen, and Daiichi Sankyo. He has been a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo. No fees directly received personally. These competing interests do not alter our adherence to PLOS ONE policies on sharing data and materials. There are no patents, products in development or marketed products associated with this research to declare. Dr Kozieł and Professor Rothman declare no competing interests.

respectively. The proportion with paroxysmal AF was 57.0% in the NOAC group and 45.4% in the VKA group. Multivariable log-binomial regression analysis found the following factors were associated with no OAC prescription: pattern of AF (paroxysmal, persistent, or permanent), coronary artery disease, myocardial infarction, prior bleeding, smoking status, and region (Asia, North America, or Europe). Factors associated with OAC prescriptions were age, body mass index, renal function, hypertension, history of cerebral ischemic symptoms, and AF ablation.

**Conclusion**

Multimorbid AF patients prescribed NOACs have fewer comorbidities than those prescribed VKAs. Age, AF pattern, comorbidities, and renal function are associated with OAC prescription.

**Introduction**

Atrial fibrillation (AF) affects approximately 3% of adults and its prevalence and incidence are rising [1] with the aging of the population [2]. Older patients with AF often have other chronic conditions that affect their clinical course [3]. Multimorbidity (the presence of ≥2 concomitant chronic conditions) demands a holistic and integrated approach to patient care [4] since these patients face higher risks of stroke and bleeding than those without comorbidities [5, 6]. The interplay between comorbidity, AF, and optimal thromboprophylaxis has both medical and economic implications [7].

The aim of this analysis of the GLORIA-AF dataset is to describe baseline characteristics and antithrombotic therapy prescription patterns in patients with AF and multimorbidity and to identify factors associated with the selection of an oral anticoagulant (OAC) type for these complex patients.

**Materials and methods**

The design of the GLORIA-AF registry (https://clinicaltrials.gov/ct2/home; trial registration numbers NCT01468701, NCT01671007, NCT01937377) has been reported [8]. The study protocol is concordant with the ethical guidelines of the 1975 Declaration of Helsinki, and informed consent was obtained from each patient before enrollment.

The registry collected routine clinical practice data regarding patients with newly diagnosed AF to evaluate patient characteristics influencing the selection, safety, and effectiveness of antithrombotic therapy. Phase I was conducted before non-vitamin K antagonist oral anticoagulants (NOACs) were available for stroke prevention in AF. Phase II began when dabigatran was approved in countries with participating clinical centers. Baseline characteristics were collected and those prescribed dabigatran were followed up for 2 years in Phase II. Phase III, which started when dabigatran had been more widely adopted, gathered data for up to 3 years, regardless of antithrombotic management [8].

Consecutive patients from 38 countries were enrolled between 2014 and 2016. Adult patients with recently diagnosed nonvalvular AF (<3 months before the baseline visit; Latin America <4.5 months) at risk of stroke (CHA2DS2-VASc score ≥1) achieved by any of the following: heart failure or left ventricular systolic dysfunction, hypertension, diabetes, prior stroke, transient ischemic attack (TIA) or systemic embolism, myocardial infarction (MI),
peripheral artery disease, age ≥65 years, or female sex, were enrolled [9]. The risks of stroke and bleeding were assessed using the CHA$_2$DS$_2$-VASc and HAS-BLED (1 point is achieved by any of the following: hypertension, abnormal renal or hepatic function, prior stroke, bleeding or predisposition, labile International Normalised Ratio, elderly (>65 years), or concomitant use of alcohol or anti-inflammatory medications) [10]. Antithrombotic therapy was prescribed by the treating physicians according to local standards. This report is focused on baseline data obtained from patients in Phase III, collected using electronic case report forms.

**Statistical analysis**

Baseline characteristics are summarized descriptively. Categorical variables are reported as absolute frequencies and percentages, and continuous variables are summarized by median (Quartile 1, Quartile 3). Baseline characteristics included stratification of patients with AF and multimorbidity according to stroke prevention strategies (OAC vs antiplatelet vs no antithrombotic therapy, NOAC vs vitamin K antagonists [VKAs], and NOACs once daily [QD] vs twice daily [BID]). Standardized differences were used to compare baseline characteristics across various stroke prevention strategies, focusing on variables with the highest standardized differences; differences ≤10% in absolute value were considered as balanced between groups [11].

Factors associated with antithrombotic treatment choice were analyzed by log-binomial, multivariable regression models, providing relative probability ratios for prescription (OAC vs no OAC use, NOAC vs VKA; and by region). Missing data were handled using multiple imputation, replacing missing data with multiple simulated values based on regression models to provide comparatively unbiased estimates under the missing-at-random assumption. The procedure introduces random error to compensate for the added, imputed information. The imputation regression models used 56 predictors to impute the missing data, and were repeated 20 times to give 20 datasets with imputed data [12].

Confidence intervals were calculated based on likelihood ratios and Rubin’s method to combine results across imputations. Both univariate and multivariable log-binomial regression analyses were performed to evaluate crude as well as the adjusted probability ratios together with 95% confidence intervals. The term “probability ratio” was used rather than “risk ratio”, as our measure describes treatment selections rather than adverse outcomes.

All data were calculated using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

**Results**

Of 21,241 eligible patients in this subanalysis, 15,119 (71.2%) had ≥2 concomitant, chronic conditions (Table 1).

**Baseline characteristics of AF multimorbid patients**

Baseline characteristics of patients are summarized based on antithrombotic therapy (Table 2). Among multimorbid AF patients, 83.8% were prescribed OACs, 11.0% were prescribed antiplatelet therapy, and 5.2% were prescribed no antithrombotic therapy. The median (66.0, 79.0) age was 73.0 years in the OAC group, 71.0 (63.0–79.0) years in the antiplatelet therapy group, and 72.0 (64.0–80.0) years in the no antithrombotic therapy group. The proportions of females in these groups were 44.5%, 41.7%, and 45.5%, respectively. The median CHA$_2$DS$_2$-VASc and HAS-BLED scores were similar across the 3 groups.

Baseline characteristics of patients prescribed NOACs or VKAs are shown in Table 3. The median age was 73.0 (66.0–79.0) years, and the proportion of females was 44% in both treatment groups. There were no differences in CHA$_2$DS$_2$-VASc and HAS-BLED scores between
these 2 groups. The prevalence of paroxysmal AF in patients with multimorbidity on NOACs and VKAs was 57.0% and 45.4%, respectively. Among patients on NOACs, 38.4% had a European Heart Rhythm Association symptom score of I, compared with 33.3% for patients on VKAs. A lower proportion (1.6%) of patients on NOACs had a glomerular filtration rate of 15–29 mL/min, compared with 4.4% of those on VKAs.

Cardioversion was performed in 19.9% of patients on NOACs vs 14.6% of those on VKAs. Treatment in specialist offices was more prevalent for patients on NOACs (33.5% vs 23.8% in the VKA group), while comorbidities such as heart failure (HF) and MI were less prevalent among patients given NOACs.

Patient demographics, cardiovascular risk factors, comorbid diseases, AF categorization, stroke and bleeding risks, and concomitant treatments of patients on NOACs QD vs BID are summarized in Table 4. There were generally small differences between patients taking NOACs QD vs BID. Previous TIA or stroke were present in 14.9% of the patients on NOACs QD vs 21.3% of the patients on NOACs BID (Table 4).

Factors associated with OAC non-prescription in multimorbid AF patients globally

Results from univariate analyses are presented in the S1 File. In the multivariable log-binomial regression analysis, factors associated with prescriptions for no OAC use in multimorbid AF patients were: type of AF (paroxysmal/persistent vs permanent), coronary artery disease (CAD), MI, history of bleeding, smoking status (current vs nonsmoker), and region (Asia, North America vs Europe). Factors associated with increased OAC use were: age 65–74 vs ≥75 years, body mass index (BMI) class (≥25 vs 18.5–24 kg/m²), creatinine clearance (30–59 vs ≥80 mL/min), hypertension, prior TIA or stroke, and AF ablation (Table 5).

Factors associated with OACs non-prescription in multimorbid AF patients in Asia, Europe, and North America

Factors associated with prescriptions for no OAC use in multimorbid AF patients in Asia, Europe, and North America are presented in S1 Table in S2 File. Factors associated with increased OAC use are included in S1 Table in S2 File.
|                           | OAC (n = 12,677) | Antiplatelets (n = 1658) | No Antithrombotic Therapy (n = 784) |
|---------------------------|------------------|---------------------------|-----------------------------------|
| Age (y), median (Q1, Q3)  | 73.0 (66.0–79.0) | 71.0 (63.0–79.0)          | 72.0 (64.0–80.0)                  |
| Females, n (%)            | 5645 (44.5)      | 691 (41.7)                | 357 (45.5)                        |
| BMI (kg/m²), median (Q1, Q3)| 28.0 (24.8–32.0) | 26.1 (23.5–30.0)          | 26.1 (23.4–29.6)                  |
| Missing                   | 123 (1.0)        | 17 (1.0)                  | 8 (1.0)                           |
| Current smoker            | 1145 (9.0)       | 223 (13.4)                | 100 (12.8)                        |
| Alcohol abuse, ≥8 units/ week | 866 (6.8)      | 85 (5.1)                  | 54 (6.9)                          |
| Type of AF, n (%)         |                  |                           |                                   |
| Paroxysmal                | 6810 (53.7)      | 1166 (70.3)               | 496 (63.3)                        |
| Persistent                | 4478 (35.3)      | 401 (24.2)                | 242 (30.9)                        |
| Permanent                 | 1389 (11.0)      | 91 (5.5)                  | 46 (5.9)                          |
| Categorization of AF, n (%)|                  |                           |                                   |
| EHRA I                    | 4686 (37.0)      | 550 (33.2)                | 273 (34.8)                        |
| EHRA II                   | 4025 (31.8)      | 563 (34.0)                | 270 (34.4)                        |
| EHRA III                  | 3063 (24.2)      | 431 (26.0)                | 183 (23.3)                        |
| EHRA IV                   | 903 (7.1)        | 114 (6.9)                 | 58 (7.4)                          |
| Creatinine clearance (mL/min) (measured), median (Q1, Q3)| 70.6 (52.5–95.3) | 69.5 (50.9–92.4)          | 67.8 (49.7–90.3)                  |
| Creatinine clearance (mL/min), n (%)        |                  |                           |                                   |
| <15                       | 100 (0.8)        | 18 (1.1)                  | 10 (1.3)                          |
| 15–29                     | 305 (2.4)        | 62 (3.7)                  | 23 (2.9)                          |
| 30–49                     | 1848 (14.6)      | 252 (15.2)                | 136 (17.3)                        |
| 50–79                     | 4152 (32.8)      | 526 (31.7)                | 253 (32.3)                        |
| ≥80                       | 4080 (32.2)      | 520 (31.4)                | 243 (31.0)                        |
| Missing                   | 2192 (17.3)      | 280 (16.9)                | 119 (15.2)                        |
| CHA₂DS₂-VASc score, median (Q1, Q3) | 4.0 (3.0–5.0)  | 4.0 (2.0–5.0)             | 3.0 (2.0–4.0)                     |
| HAS-BLED score, median (Q1, Q3) | 1.0 (1.0–2.0)  | 2.0 (2.0–3.0)             | 1.0 (1.0–2.0)                     |
| Missing (HAS-BLED), n (%)  | 1234 (9.7)       | 134 (8.1)                 | 69 (8.8)                          |
| Medical history, n (%)    |                  |                           |                                   |
| Congestive heart failure  | 3509 (27.7)      | 487 (29.4)                | 215 (27.4)                        |
| Hypertension              | 10,989 (86.7)    | 1370 (82.6)               | 638 (81.4)                        |
| Diabetes mellitus         | 4021 (31.7)      | 510 (30.8)                | 226 (28.8)                        |
| Previous stroke or TIA    | 2347 (18.5)      | 336 (20.3)                | 159 (20.3)                        |
| Myocardial infarction     | 1580 (12.5)      | 384 (23.2)                | 58 (7.4)                          |
| Coronary artery disease   | 3017 (23.8)      | 745 (44.9)                | 149 (19.0)                        |
| Peripheral artery disease | 503 (4.0)        | 79 (4.8)                  | 21 (2.7)                          |
| Cancer                    | 1671 (13.2)      | 167 (10.1)                | 115 (14.7)                        |
| Dementia                  | 101 (0.8)        | 18 (1.1)                  | 1 (0.1)                           |
| Gastric ulcer             | 145 (1.1)        | 20 (1.2)                  | 13 (1.7)                          |
| Gastritis or duodenitis   | 455 (3.6)        | 70 (4.2)                  | 50 (6.4)                          |
| Chronic kidney disease    | 3881 (30.6)      | 526 (31.7)                | 271 (34.6)                        |
| COPD                      | 1045 (8.2)       | 120 (7.2)                 | 59 (7.5)                          |
| Bleeding (after diagnosis of AF), n (%) | 182 (1.4)     | 32 (1.9)                  | 33 (4.2)                          |
| Bleeding on OAC, n (%)     | 159 (87.4)       | 27 (84.4)                 | 18 (54.5)                         |
| Location of bleeding (after diagnosis of AF), n (%) |                  |                           |                                   |
| Intracranial hemorrhage   | 12 (6.6)         | 6 (18.8)                  | 8 (24.2)                          |
| Upper GI bleed            | 12 (6.6)         | 4 (12.5)                  | 3 (9.1)                           |
| Lower GI bleed            | 25 (13.7)        | 6 (18.8)                  | 5 (15.2)                          |
| GI bleed not further specified | 11 (6.0)      | 4 (12.5)                  | 4 (12.1)                          |

(Continued)
Factors associated with type of OAC use in multimorbid AF patients globally

Factors associated with prescriptions for VKA use globally in multimorbid AF patients were: age <75 vs ≥75 years, MI, congestive HF, diabetes mellitus, creatinine clearance (<60 vs ≥80 mL/min), S2 Table in S2 File.

Factors associated with decreased VKA use globally were: type of AF (paroxysmal/persistent vs permanent), previous TIA or stroke, medical treatment reimbursement (self-pay/no coverage vs not self-pay), S2 Table in S2 File.

Factors associated with OAC use in multimorbid AF patients in Asia, Europe, North America, and Latin America

Factors associated with prescriptions for VKA use in multimorbid AF patients in Asia, Europe, North America, and Latin America are presented in S3 Table in S2 File. Factors associated with decreased prescriptions for VKA use in multimorbid AF patients in Asia, Europe, North America, and Latin America are presented in S3 Table in S2 File.

Discussion

There are still knowledge gaps in how OACs are used in clinical practice in patients with AF and multiple comorbidities and which factors influence OAC prescription in such patients. Our study shows that, despite a median CHA\textsubscript{2}DS\textsubscript{2}-VASc score >3, approximately 16% of patients with multimorbidity and AF are not anticoagulated. The baseline characteristics in

Table 2. (Continued)

| Factor                          | OAC (n = 12,677) | Antiplatelets (n = 1658) | No Antithrombotic Therapy (n = 784) |
|--------------------------------|-----------------|-------------------------|-------------------------------------|
| Urogenital hemorrhage          | 31 (17.0)       | 3 (9.4)                 | 3 (9.1)                             |
| Bleeding at other location     | 81 (44.5)       | 7 (21.9)                | 8 (24.2)                            |
| Bleeding with unknown location | 10 (5.5)        | 2 (6.3)                 | 2 (6.1)                             |
| Region, n (%)                  |                 |                         |                                     |
| Asia                           | 1739 (13.7)     | 719 (43.4)              | 325 (41.5)                          |
| Europe                         | 6514 (51.4)     | 443 (26.7)              | 266 (33.9)                          |
| North America                  | 3429 (27.0)     | 415 (25.0)              | 144 (18.4)                          |
| Latin America                  | 995 (7.8)       | 81 (4.9)                | 49 (6.3)                            |
| Type of site, n (%)            |                 |                         |                                     |
| GP/primary care                | 686 (5.4)       | 171 (10.3)              | 77 (9.8)                            |
| Specialist office              | 3902 (30.8)     | 512 (30.9)              | 191 (24.4)                          |
| Community hospital             | 3757 (29.6)     | 350 (21.1)              | 175 (22.3)                          |
| University hospital            | 3878 (30.6)     | 543 (32.8)              | 326 (41.6)                          |
| Outpatient health care centre  | 222 (1.8)       | 51 (3.1)                | 6 (0.8)                             |
| Anticoagulation clinics        | 82 (0.6)        | 6 (0.4)                 | 4 (0.5)                             |
| Other                          | 150 (1.2)       | 25 (1.5)                | 5 (0.6)                             |

*AF = atrial fibrillation; BMI = body mass index; CHA\textsubscript{2}DS\textsubscript{2}-VASc = congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/systemic embolism, vascular disease, age 65–74 years, sex category (female); COPD = chronic obstructive pulmonary disease; EHRA = European Heart Rhythm Association; GI = gastrointestinal; GP = general practitioner; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (>65 years), drugs or alcohol concomitantly; OAC = oral anticoagulant; Q = quartile; TIA = transient ischemic attack; y = years.

*Proportion calculated out of Bleeding (after diagnosis of AF).

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Table 3. Baseline characteristics of AF multimorbid patients prescribed NOACs or VKAs.

| Characteristic                                      | NOAC (n = 9105) | VKA (n = 3572) | Standardized Difference |
|-----------------------------------------------------|-----------------|----------------|-------------------------|
| Age (y), median (Q1, Q3)                            | 73.0 (66.0–79.0) | 73.0 (66.0–79.0) | 0.005                   |
| Females, n (%)                                      | 4072 (44.7)     | 1573 (44.0)    | −0.014                  |
| BMI (kg/m²), median (Q1, Q3)                        | 28.0 (24.8–32.2)| 27.8 (24.6–31.6)| −0.066                  |
| Missing                                             | 37 (1.2)        | 60 (1.0)       | 0.020                   |
| Current smoker                                      | 812 (8.9)       | 333 (9.3)      | 0.014                   |
| Alcohol abuse, ≥8 units/week                       | 651 (7.1)       | 215 (6.0)      | −0.046                  |
| Type of AF, n (%)                                   |                 |                |                         |
| Paroxysmal                                          | 5187 (57.0)     | 1623 (45.4)    | −0.232                  |
| Persistent                                          | 3052 (33.5)     | 1426 (39.9)    | 0.133                   |
| Permanent                                           | 866 (9.5)       | 523 (14.6)     | 0.158                   |
| Categorization of AF, n (%)                         |                 |                |                         |
| EHRA I                                              | 3496 (38.4)     | 1190 (33.3)    | −0.106                  |
| EHRA II                                             | 2886 (31.7)     | 1139 (31.9)    | 0.004                   |
| EHRA III                                            | 2131 (23.4)     | 932 (26.1)     | 0.062                   |
| EHRA IV                                             | 592 (6.5)       | 311 (8.7)      | 0.083                   |
| Creatinine clearance (mL/min) (measured), median (Q1, Q3) | 72.1 (53.7–97.0) | 66.8 (48.9–91.0) | −0.078                  |
| Creatinine clearance (mL/min) n (%)                 |                 |                |                         |
| <15                                                 | 50 (0.5)        | 50 (1.4)       | 0.087                   |
| 15–29                                               | 148 (1.6)       | 157 (4.4)      | 0.163                   |
| 30–49                                               | 1280 (14.1)     | 568 (15.9)     | 0.052                   |
| 50–79                                               | 3046 (33.5)     | 1106 (31.0)    | −0.053                  |
| ≥80                                                 | 3053 (33.5)     | 1027 (28.8)    | −0.103                  |
| Missing                                             | 1528 (16.8)     | 664 (18.6)     | 0.047                   |
| CHA₂DS₂-VASc score, median (Q1, Q3)                 | 4.0 (3.0–5.0)   | 4.0 (3.0–5.0)  | 0.080                   |
| HAS-BLED score, median (Q1, Q3)                     | 1.0 (1.0–2.0)   | 1.0 (1.0–2.0)  | 0.016                   |
| Missing (HAS-BLED), n (%)                           | 858 (9.4)       | 376 (10.5)     | 0.037                   |
| Medical history, n (%)                              |                 |                |                         |
| Congestive heart failure                            | 2232 (24.5)     | 1277 (35.8)    | 0.247                   |
| Hypertension                                        | 7907 (86.8)     | 3082 (86.3)    | −0.016                  |
| Diabetes mellitus                                   | 2839 (31.2)     | 1182 (33.1)    | 0.041                   |
| Previous stroke or TIA                              | 1741 (19.1)     | 606 (17.0)     | −0.056                  |
| Myocardial infarction                               | 1039 (11.4)     | 541 (15.1)     | 0.110                   |
| Coronary artery disease                             | 2104 (23.1)     | 913 (25.6)     | 0.057                   |
| Peripheral artery disease                          | 355 (3.9)       | 148 (4.1)      | 0.012                   |
| Cancer                                              | 1223 (13.4)     | 448 (12.5)     | −0.027                  |
| Dementia                                            | 76 (0.8)        | 25 (0.7)       | −0.016                  |
| Gastric ulcer                                       | 111 (1.2)       | 34 (1.0)       | −0.026                  |
| Gastritis or duodenitis                             | 317 (3.5)       | 138 (3.9)      | 0.020                   |
| Chronic kidney disease                              | 2663 (29.2)     | 1218 (34.1)    | 0.104                   |
| COPD                                                | 743 (8.2)       | 302 (8.5)      | 0.011                   |
| Bleeding (after diagnosis of AF), n (%)             | 130 (1.4)       | 52 (1.5)       | 0.002                   |
| Bleeding on OAC, n (%)                              | 112 (86.2)      | 47 (90.4)      | 0.132                   |
| Location of bleeding (after diagnosis of AF), n (%) |                 |                |                         |
| Intracranial hemorrhage                             | 11 (8.5)        | 1 (1.9)        | −0.298                  |
| Upper GI bleed                                      | 8 (6.2)         | 4 (7.7)        | 0.061                   |
| Lower GI bleed                                      | 20 (15.4)       | 5 (9.6)        | −0.175                  |
| GI bleed not further specified                      | 9 (6.9)         | 2 (3.8)        | −0.137                  |

(Continued)
these complex patients differ in relation to antithrombotic therapy selection, suggesting that comorbidities may influence antithrombotic therapy prescription patterns for patients with AF. For example, prescription of OACs globally in patients with AF and multimorbidity was associated with age, BMI, cardiovascular risk factors (smoking status), AF pattern, concomitant diseases (ie, hypertension, CAD, MI, previous TIA or stroke), history of bleeding, renal function, rhythm control strategy (AF ablation and AF cardioversion), and region (Asia and North America). Prescriptions patterns were also subject to regional differences in clinical practice.

**Patient characteristics according to antithrombotic therapy use**

The results suggest that patients with AF and multimorbidity prescribed NOACs are more likely to have paroxysmal AF, and have fewer comorbidities than those prescribed VKAs, consistent with other reports [13–15]. Declining renal function may influence the choice of VKA in those with chronic kidney disease. Healthcare system-related factors (such as center type) also influence treatment strategies. Patients with AF and multimorbidity treated in specialist offices and community hospitals are more often prescribed NOACs than VKAs.

The patients in this cohort prescribed antiplatelet agents had a higher risk of bleeding according to HAS-BLED score than those who were prescribed OACs. They also more often had paroxysmal AF compared to those prescribed OACs. Patients with AF and CAD were more often prescribed antiplatelets than OACs despite the fact that antiplatelet therapy does not prevent stroke or reduce mortality, elevates the risk of bleeding, and is not recommended

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**Table 3. (Continued)**

|                          | NOAC (n = 9105) | VKA (n = 3572) | Standardized Difference |
|--------------------------|----------------|---------------|-------------------------|
| Urogenital hemorrhage    | 20 (15.4)      | 11 (21.2)     | 0.150                   |
| Bleeding at other location | 56 (43.1)    | 25 (48.1)     | 0.101                   |
| Bleeding with unknown location | 6 (4.6)        | 4 (7.7)       | 0.128                   |
| AF cardioversion         | 1814 (19.9)    | 521 (14.6)    | −0.142                  |

**Region, n (%)**

|              | NOAC (n = 9105) | VKA (n = 3572) | Standardized Difference |
|--------------|----------------|---------------|-------------------------|
| Asia         | 1222 (13.4)    | 517 (14.5)    | 0.030                   |
| Europe       | 4498 (49.4)    | 2016 (56.4)   | 0.141                   |
| North America| 2808 (30.8)    | 621 (17.4)    | −0.319                  |
| Latin America| 577 (6.3)      | 418 (11.7)    | 0.188                   |

**Type of site, n (%)**

|                        | NOAC (n = 9105) | VKA (n = 3572) | Standardized Difference |
|------------------------|----------------|---------------|-------------------------|
| GP/primary care        | 502 (5.5)      | 184 (5.2)     | −0.016                  |
| Specialist office      | 3053 (33.5)    | 849 (23.8)    | −0.217                  |
| Community hospital     | 2880 (31.6)    | 877 (24.6)    | −0.158                  |
| University hospital    | 2454 (27.0)    | 1424 (39.9)   | 0.276                   |
| Outpatient health care centre | 72 (0.8) | 150 (4.2) | 0.220 |
| Anticoagulation clinics| 37 (0.4)       | 45 (1.3)      | 0.094                   |
| Other                  | 107 (1.2)      | 43 (1.2)      | 0.003                   |

*AF = atrial fibrillation; BMI = body mass index; CHA₂DS₂-VASc = congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack/systemic embolism, vascular disease, age 65–74 years, sex category (female); COPD = chronic obstructive pulmonary disease; EHRA = European Heart Rhythm Association; GI = gastrointestinal; GP = general practitioner; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly (>65 years), drugs or alcohol concomitantly; NOAC = nonvitamin K antagonist oral anticoagulants; OAC = oral anticoagulant; Q = quartile; TIA = transient ischemic attack; VKA = vitamin K antagonists; y = years.

*Proportion calculated out of Bleeding (after diagnosis of AF).
| Characteristic                                           | NOAC QD (n = 3071) | NOAC BID (n = 6034) | Standardized Difference |
|---------------------------------------------------------|--------------------|--------------------|------------------------|
| Age (y), median (Q1, Q3)                               | 72.0 (65.0–79.0)   | 73.0 (66.0–79.0)   | -0.098                 |
| Females, n (%)                                          | 1306 (42.5)        | 2766 (45.8)        | -0.067                 |
| BMI (kg/m²), median (Q1, Q3)                           | 28.3 (25.0–32.8)   | 27.9 (24.8–32.0)   | 0.089                  |
| Current smoker                                          | 250 (8.1)          | 562 (9.3)          | -0.042                 |
| Alcohol abuse, ≥8 units/week                           | 242 (7.9)          | 409 (6.8)          | 0.042                  |
| Type of AF, n (%)                                       |                    |                    |                        |
| Paroxysmal                                              | 1767 (57.5)        | 3420 (56.7)        | 0.017                  |
| Persistent                                              | 1045 (34.0)        | 2007 (33.3)        | 0.016                  |
| Permanent                                               | 259 (8.4)          | 607 (10.1)         | -0.056                 |
| Categorization of AF, n (%)                             |                    |                    |                        |
| EHRA I                                                  | 1138 (37.1)        | 2358 (39.1)        | -0.042                 |
| EHRA II                                                 | 983 (32.0)         | 1903 (31.5)        | 0.010                  |
| EHRA III                                                | 775 (25.2)         | 1356 (22.5)        | 0.065                  |
| EHRA IV                                                 | 175 (5.7)          | 417 (6.9)          | -0.050                 |
| Creatinine clearance (mL/min), median (Q1, Q3)          | 74.4 (55.3–101.8)  | 70.5 (53.1–94.3)   | 0.041                  |
| Creatinine clearance, n (%)                             |                    |                    |                        |
| <15                                                     | 18 (0.6)           | 32 (0.5)           | 0.008                  |
| 15–29                                                   | 40 (1.3)           | 108 (1.8)          | -0.040                 |
| 30–49                                                   | 401 (13.1)         | 879 (14.6)         | -0.044                 |
| 50–79                                                   | 1018 (33.1)        | 2028 (33.6)        | -0.010                 |
| ≥80                                                     | 1125 (36.6)        | 1928 (32.0)        | 0.099                  |
| Missing                                                 | 469 (15.3)         | 1059 (17.6)        | -0.062                 |
| CHA₂DS₂-VASc score, median (Q1, Q3)                    | 3.0 (2.0–4.0)      | 4.0 (3.0–5.0)      | -0.127                 |
| HAS-BLED score, median (Q1, Q3)                         | 1.0 (1.0–2.0)      | 1.0 (1.0–2.0)      | -0.066                 |
| Missing (HAS-BLED), n (%)                               | 302 (9.8)          | 556 (9.2)          | 0.021                  |
| Medical history, n (%)                                  |                    |                    |                        |
| Congestive heart failure                                | 772 (25.1)         | 1460 (24.2)        | 0.022                  |
| Hypertension                                            | 2672 (87.0)        | 5235 (86.8)        | 0.007                  |
| Diabetes mellitus                                       | 1021 (33.2)        | 1818 (30.1)        | 0.067                  |
| Previous stroke or TIA                                  | 457 (14.9)         | 1284 (21.3)        | -0.167                 |
| Myocardial infarction                                   | 366 (11.9)         | 673 (11.2)         | 0.024                  |
| Coronary artery disease                                 | 746 (24.3)         | 1358 (22.5)        | 0.042                  |
| Peripheral artery disease                               | 119 (3.9)          | 236 (3.9)          | -0.002                 |
| Cancer                                                  | 407 (13.3)         | 816 (13.5)         | -0.008                 |
| Dementia                                                | 24 (0.8)           | 52 (0.9)           | -0.009                 |
| Gastric ulcer                                           | 40 (1.3)           | 71 (1.2)           | 0.011                  |
| Gastritis or duodenitis                                 | 116 (3.8)          | 201 (3.3)          | 0.024                  |
| Chronic kidney disease                                 | 839 (27.3)         | 1824 (30.2)        | -0.064                 |
| COPD                                                    | 258 (8.4)          | 485 (8.0)          | 0.013                  |
| Bleeding (after diagnosis of AF), n (%)                 | 57 (1.9)           | 73 (1.2)           | 0.053                  |
| Bleeding on OAC, n (%)                                  | 52 (9.1)           | 60 (8.2)           | 0.269                  |
| Location of bleeding (after diagnosis of AF), n (%)     |                    |                    |                        |
| Intracranial hemorrhage                                 | 2 (3.5)            | 9 (12.3)           | -0.331                 |
| Upper GI bleed                                          | 4 (7.0)            | 4 (5.5)            | 0.064                  |
| Lower GI bleed                                          | 10 (17.5)          | 10 (13.7)          | 0.106                  |
| GI bleed not further specified                          | 5 (8.8)            | 4 (5.5)            | 0.128                  |
| Urogenital hemorrhage                                   | 6 (10.5)           | 14 (19.2)          | -0.245                 |

(Continued)
for prevention of AF-related thromboembolism [16]. Unfortunately, antiplatelet monotherapy is still a frequent choice of prescribing physicians based on several European reports [17, 18].

Factors associated with OAC prescription in multimorbid AF patients globally

The majority of multimorbid AF patients had a high risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2) and oral anticoagulation therapy is recommended for these patients [19]. Hypertension and HF were the most prevalent risk factors for thromboembolic complications [20] and these factors and previous stroke or TIA are associated with a greater frequency of OAC prescription. Prescription of OACs was inversely associated with comorbidities that are strongly associated with elevated thromboembolic risk (eg, MI, CAD), just as conditions associated with an increased risk of bleeding (eg, previous hemorrhagic events) were associated with less frequent prescription of OACs. This is also consistent with prior reports [13] although current clinical practice guidelines recommend that patients with AF at a high risk of bleeding should generally continue anticoagulation with frequent visits and close monitoring [21]. A history of AF ablation in multimorbid AF patients was associated with more frequent OAC prescription as per guidelines [21] and consistent with other studies [22].

Younger age (≤75 years) was associated with greater OAC prescription and more frequent selection of VKAs compared to practice patterns for older patients. Several studies have suggested that increasing age is a barrier to implementing OAC use [23, 24]. Importantly, stroke risk increases with age, and the absolute benefit of OACs is clearly increased for older patients with AF [25]. In one report, when adjusted for comorbidity, age was not an important determinant of anticoagulation [26].
Table 5. Multivariable log-binomial analysis for factors associated with prescription of OAC therapy (no OAC vs OAC).

| Factor | Relative Risk (95% CI) For Prescription of No OAC Globally |
|--------|----------------------------------------------------------|
| Age    |                                                          |
| <65    | 1.05 (0.95–1.16)                                         |
| 65–74  | 0.90 (0.83–0.99)                                         |
| ≥75    | 1.0 (ref)                                                |
| BMI class |                                                   |
| <18.5  | 0.98 (0.77–1.24)                                         |
| 18.5–24| 1.0 (ref)                                                |
| 25–29  | 0.85 (0.79–0.91)                                         |
| 30–34  | 0.77 (0.69–0.87)                                         |
| ≥35    | 0.70 (0.60–0.81)                                         |
| Gender |                                                          |
| Male   | 1.0 (ref)                                                |
| Female | 1.05 (0.97–1.13)                                         |
| Current smoker | 1.14 (1.03–1.25)                                       |
| Past smoker | 0.91 (0.84–0.99)                                       |
| Categorization of AF |                                |
| EHRA I | 1.0 (ref)                                                |
| EHRA II | 1.04 (0.96–1.12)                                        |
| EHRA III | 0.99 (0.91–1.07)                                       |
| EHRA IV | 1.07 (0.95–1.20)                                        |
| Type of AF |                                               |
| Paroxysmal | 1.67 (1.42–1.97)                                      |
| Persistent | 1.20 (1.02–1.43)                                      |
| Permanent | 1.0 (ref)                                               |
| Hypertension | 0.89 (0.83–0.97)                                      |
| Coronary artery disease | 1.42 (1.31–1.53)                                     |
| Myocardial infarction | 1.18 (1.08–1.28)                                     |
| Congestive heart failure | 1.01 (0.94–1.08)                                     |
| Diabetes mellitus | 0.95 (0.88–1.02)                                     |
| Previous TIA or stroke | 0.81 (0.68–0.97)                                     |
| Bleeding after diagnosis of AF | 1.60 (1.42–1.79)                                     |
| Peripheral artery disease | 1.13 (0.96–1.34)                                     |
| Cancer | 1.00 (0.90–1.12)                                         |
| Functional dyspepsia | 0.85 (0.56–1.27)                                     |
| Gastric ulcer | 0.91 (0.69–1.21)                                     |
| Gastritis or duodenitis | 0.95 (0.82–1.10)                                     |
| COPD | 1.03 (0.90–1.19)                                         |
| Hyperthyroidism | 0.96 (0.79–1.17)                                     |
| Hepatic disease | 1.05 (0.87–1.27)                                     |
| Dementia | 1.09 (0.76–1.56)                                     |
| AF cardioversion | 0.96 (0.89–1.04)                                     |
| Creatinine clearance (mL/min) |                                           |
| <30    | 1.09 (0.94–1.26)                                         |
| 30–59  | 0.88 (0.79–0.97)                                         |
| 60–79  | 0.91 (0.83–1.00)                                         |
| ≥80    | 1.0 (ref)                                                |

(Continued)
Multimorbid AF patients with paroxysmal or persistent AF were less often prescribed OACs in particular VKAs than those with permanent AF. NOACs should be preferred in patients with multimorbidity and polypharmacy given their lower number of drug–drug interactions compared with VKAs [27]. Ischemic stroke may occur as frequently in paroxysmal AF as in permanent AF, especially with multiple risk factors [28]. Moreover, the use of OACs should be based on stroke risk assessment according to the CHA
subscript2
DS
subscript2
-VASc risk score [21].

The pattern of AF seems to be related to patient profiles characterized by age, concomitant diseases, symptoms, and risk factors for stroke and bleeding [13]. Patients with higher European Heart Rhythm Association symptom scores were more often prescribed VKAs than those who were asymptomatic.

Multimorbid AF patients with a history of cardioversion were less often prescribed VKAs than those without prior cardioversion. NOACs were preferred in multimorbid AF patients after cardioversion. A similar pattern was found in another study where rhythm control strategy was associated with selection of NOAC [14].

### OAC prescription in multimorbid AF patients regionally

In this study, multimorbidity influenced ATT use within particular regions. In Europe, younger patients (age <65 years) were less likely to be prescribed OACs than those with permanent AF. NOACs should be preferred in patients with multimorbidity and polypharmacy given their lower number of drug–drug interactions compared with VKAs [27]. Ischemic stroke may occur as frequently in paroxysmal AF as in permanent AF, especially with multiple risk factors [28]. Moreover, the use of OACs should be based on stroke risk assessment according to the CHA
subscript2
DS
subscript2
-VASc risk score [21]. The pattern of AF seems to be related to patient profiles characterized by age, concomitant diseases, symptoms, and risk factors for stroke and bleeding [13]. Patients with higher European Heart Rhythm Association symptom scores were more often prescribed VKAs than those who were asymptomatic.

Multimorbid AF patients with a history of cardioversion were less often prescribed VKAs than those without prior cardioversion. NOACs were preferred in multimorbid AF patients after cardioversion. A similar pattern was found in another study where rhythm control strategy was associated with selection of NOAC [14].

### Table 5. (Continued)

| Factor | Relative Risk (95% CI) For Prescription of No OAC Globally |
|--------|----------------------------------------------------------|
| AF ablation | 0.30 (0.20–0.45) |
| Region | |
| Asia | 3.17 (2.88–3.49) |
| Europe | 1.0 (ref) |
| North America | 1.24 (1.11–1.39) |
| Latin America | 1.14 (0.96–1.37) |
| Medical treatment reimbursed by | |
| Self-pay/no coverage | 0.82 (0.69–0.96) |
| Not self-pay | 1.0 (ref) |
| Type of site | |
| Specialist office | 1.26 (1.14–1.39) |
| Community hospital | 1.0 (ref) |
| University hospital | 1.28 (1.17–1.40) |

*A few other variables (alcohol abuse, psychosocial factors, biological heart valve implant, valve repair, and peptic ulcer) are included in the multivariable log-binomial regression analysis model and are presented in the S1 File.

**AF** = atrial fibrillation; **BMI** = body mass index; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **EHRA** = European Heart Rhythm Association; **OAC** = oral anticoagulant; **ref** = reference; **TIA** = transient ischemic attack.

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younger multimorbid AF patients (age <65 years) were less likely to be prescribed OACs than older patients (age ≥75 years). Multimorbid AF patients with diabetes were more likely to receive OACs, due to their association with higher thromboembolic risk, as well as higher all-cause, cardiovascular, and noncardiovascular mortality [29]. AF patients with multimorbidity and cancer in North America were less likely to receive OAC.

Asia and North America were associated with decreased OAC prescription. In Asia, OACs are less commonly prescribed in nonvalvular AF patients than in Europe, possibly because of suspicion of the risk of bleeding during treatment [30]. Also, NOACs are not reimbursed in some Asian countries.

Strengths

It is one the largest prospective global cohort of consecutive AF patients receiving different antithrombotic treatments. Initiation of Phase III was region-specific, once relevant baseline characteristics of patients initiating dabigatran and VKA therapy in Phase II overlapped based on propensity score comparisons. After the baseline visit, all patients in this Phase III were managed according to local clinical practice and were followed for 3 years, regardless of prescribed antithrombotic therapy. This study had regular follow-up with physicians, alongside on-site monitoring, multiple standards for data quality assurance and review.

Limitations

Although the GLORIA-AF study was designed to capture all outcome events, this analysis did not consider follow-up data. The following limitations exist in our study: we have no data on patient and prescriber treatment preferences; similarly, reasons for OAC nonprescription were not reported. Furthermore, this study reflects single, initial-treatment decisions during a period when prescribing patterns may have been changing, and the analysis was based on prescription pattern shortly after entry into the registry (baseline). Neither have we accounted for quality of anticoagulation or changes in clinical practice patterns over time.

Conclusion

AF patients with multimorbidity who were prescribed NOACs were relatively healthier, more likely to have paroxysmal AF, and had fewer prevalent comorbidities than AF multimorbid patients on VKAs. Multimorbidity may determine the antithrombotic therapy prescription pattern within AF patients. Several factors are related to increased OAC prescription in multimorbid AF patients, including younger age, hypertension, prior TIA or stroke, and AF ablation. Pattern of AF (paroxysmal and persistent AF), CAD, MI, history of bleeding, and region (Asia, North America) were inversely associated with OAC prescription.

Supporting information

S1 File.
(PDF)

S2 File.
(ODT)

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