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*the GLORIA-AF registry program*

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*Published in:*
Clinical Cardiology

*DOI (link to publication from Publisher):*
10.1002/clc.22936



*Publication date:*
2018

*Document Version*
Publisher's PDF, also known as Version of record

Received: 25 October 2017 | Revised: 23 February 2018 | Accepted: 25 February 2018

DOI: 10.1002/clc.22936

PREVENTION WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

# Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program

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**Funding information**
The GLORIA-AF study was funded by Boehringer Ingelheim

**Background:** Antithrombotic prophylaxis with oral anticoagulation (OAC) substantially reduces stroke and mortality in patients with atrial fibrillation (AF).

**Hypothesis:** Analysis of data in the Global Registry on Long-Term Antithrombotic Treatments in Patients With Atrial Fibrillation (GLORIA-AF), an international, observational registry of patients with newly diagnosed AF, can identify factors associated with treatment decisions and outcomes.

**Methods:** Multivariable regression identified patient, physician, and temporal factors associated with OAC prescription, compared with management with antiplatelet drugs or no antithrombotic drugs in North American patients enrolled between November 2011 and February 2014.

**Results:** Of 3320 eligible patients (mean age, 71 ± 11 years; 1879 males with $CHA_2DS_2$-VASc ≥1 and 1441 females with $CHA_2DS_2$-VASc ≥2), 79.3%, 12.5%, and 7.4% received OAC, antiplatelet drugs, or no antithrombotic therapy, respectively. Of those prescribed OAC, 66.4% received non–vitamin K antagonist oral anticoagulation and 24.5% received concomitant therapy with antiplatelet drugs. Independent predictors of OAC therapy were nonparoxysmal AF (odds ratio, 95% confidence interval: 2.02, 1.56–2.63), prior stroke/transient ischemic attack (2.00, 1.37–2.92), specialist care (1.50, 1.04–2.17), more concomitant medications (1.47, 1.13–1.92), commercial insurance (1.41, 1.07–1.85), and heart failure (1.44, 1.07–1.92). Antiplatelet drugs (0.18, 0.14–0.23), prior falls (0.41, 0.27–0.63), and prior bleeding (0.50, 0.35–0.72) were inversely associated with OAC prescription.

**Conclusions:** In GLORIA-AF, 20% of the population comprising males with $CHA_2DS_2$-VASc ≥1 and females with $CHA_2DS_2$-VASc ≥2 did not receive OAC therapy. Patient characteristics associated with a lower likelihood of OAC prescription were use of antiplatelet drugs, paroxysmal pattern of AF, history of falls, and prior bleeding.

KEYWORDS

Atrial Fibrillation, Oral Anticoagulation, Stroke

## 1 | INTRODUCTION

Atrial fibrillation (AF) is a major cause of death and disability and is associated with a 4- to 5-fold increase in the risk of ischemic stroke.[1,2] With appropriate patient selection, antithrombotic prophylaxis with oral anticoagulation (OAC) therapy reduces the risks of stroke and all-cause mortality by approximately 64% and 26%, respectively.[3]

For decades, vitamin K antagonists (VKAs) and antiplatelet drugs were the only treatment choices for stroke prevention in patients with AF. Although VKAs are superior to antiplatelet drugs for stroke prevention,[3,4] they have many food and drug interactions[5] and require frequent laboratory monitoring.[6] The non-VKA oral anticoagulants (NOACs) were developed to address some of these shortcomings. The direct thrombin inhibitor dabigatran and factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are currently approved for use in the

United States and Canada.[7–10] Compared with warfarin, the NOACs display similar efficacy for stroke prevention and have a generally superior safety profile for bleeding risks, especially for intracranial bleeds.[7–10]

As stroke-prevention therapies have advanced, criteria used to select patients for OAC have also evolved. Current guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) recommend OAC for patients with a $CHA_2DS_2$-VASc score ≥2.[11] These guidelines also state that in patients with a $CHA_2DS_2$-VASc score of 1, any OAC, aspirin, or no antithrombotic are reasonable. The Canadian Cardiovascular Society (CCS) currently recommends OAC for patients with 1 $CHA_2DS_2$-VASc risk factor other than female sex or vascular disease, and the European Society of Cardiology (ESC) recommends OAC therapy for all males with a $CHA_2DS_2$-VASc score ≥1 and females with a $CHA_2DS_2$-VASc score ≥2.[12,13] As the global burden of AF has increased, patients are increasing in age, number, and complexity, and there is variability in OAC prescription practice that may, in part, reflect regional practice differences and guidelines.[14,15] Maximizing the guideline-based use of OAC is an important goal. The recent IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation (IMPACT-AF) study demonstrated that educational interventions were able to increase the appropriate use of OAC in patients with AF, and that this was associated with a corresponding reduction in the rate of stroke.[16]

Contemporary registries have reported rates of OAC among at-risk patients ranging from 44% to 80%, and regional differences have been observed in global registries.[17–26] Although these registries have demonstrated an increase over time in the number of patients receiving OAC and the proportion of those receiving a NOAC, there has been limited exploration of clinical factors associated with decisions to provide OAC treatment. Identification of factors inversely associated with OAC prescription could help focus targeted education or inform further research, as appropriate. Therefore, the objective of the present study was to identify patient, physician, and temporal factors associated with the stroke-prevention strategy prescribed for North American patients in the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation (GLORIA-AF).

## 2 | METHODS

The Global Registry on Long-Term Antithrombotic Treatments in Patients With Atrial Fibrillation (GLORIA-AF) is an international, disease-based registry program enrolling patients with newly diagnosed nonvalvular AF who are at risk for stroke.[27] This analysis comprises North American patients enrolled from November 2011 (1 year following the approval of dabigatran in the United States and Canada) through February 2014. The present analysis uses data from phase 2 of the GLORIA-AF Registry program.

The GLORIA-AF registry enrolls patients age ≥18 years with a $CHA_2DS_2$-VASc score ≥1 and nonvalvular AF diagnosed at a maximum of 3 months prior to their baseline visit. This analysis excluded females with a $CHA_2DS_2$-VASc score of 1.[12,13] The registry recruits from a broad cross-section of clinical practice settings, including academic and community hospitals as well as the offices of specialists and primarycare providers. Recruiting centers were encouraged to enroll consecutive patients to minimize selection bias. Exclusion criteria included mechanical heart valves, valve disease expected to require valve replacement during the course of the registry, >60 days of VKA treatment for any indication in their lifetime, AF with a generally reversible cause, life expectancy <1 year, or an indication for OAC other than AF.

Clinical and demographic characteristics, type of AF, and medical therapies were recorded using standard electronic case-report forms. Clinical data were collected using a validated web-based system.

### 2.1 | Statistical analysis

Demographic data are summarized by mean ± SD and/or median and interquartile ranges for continuous variables, and by frequencies and percentages for categorical variables. Statistical analysis was performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

In the primary analysis, patient characteristics and comorbidities, prescriber characteristics, and temporal trends for use of OACs (NOAC or VKA) vs antiplatelet drugs, or no therapy were compared using multivariable logistic regression models. We selected variables a priori based on potential factors that might be related to the decision to provide OAC (Table 1). These variables were selected from those collected in case-report forms and included the components of the $CHA_2DS_2$-VASc and HAS-BLED scores, sociodemographic factors, other major comorbidities, and patient characteristics believed to potentially influence OAC prescription practices. In the secondary analysis, a similar approach was used to compare patients receiving NOAC vs VKA therapy.

Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were estimated using multivariable logistic regression models based on the following preselected variables representing comorbidities and demographic data: sex, medical history (heart failure [HF], hypertension, diabetes mellitus [DM], prior stroke/transient ischemic attack [TIA], prior bleeding, alcohol abuse, number of concomitant medications above the cohort median, concomitant therapy with antiplatelet drugs, liver disease, history of falls, cancer, chronic obstructive pulmonary disease, peripheral artery disease, coronary artery disease, smoking), insurance status (statutory or federal, commercial, or self-pay), pattern of AF (paroxysmal vs persistent/permanent), specialty of prescribing physician, and type of enrolling site. To analyze temporal trends, the study period was divided into quartiles of approximately equal length (November 14, 2011, to June 8, 2012; June 9, 2012, to January 1, 2013; January 2, 2013, to July 27, 2013; and July 28, 2013, to February 19, 2014). To assess for nonlinear associations, quadratic terms were entered into the model for continuous variables (age, height, weight, and creatinine clearance).

For both descriptive and multivariable regression analyses, missing data points for continuous variables were excluded from the individual analysis in question. Missing data points for categorical variables (eg, medical history) were combined with the "No" category. The actual numbers of missing data points are listed in the corresponding tables.

**TABLE 1** Characteristics of study participants by prescribed stroke-prevention strategy

| | VKA, n = 885 (26.7) | NOAC, n = 1748 (52.7) | ASA, n = 414 (12.5) | None, n = 246 (7.4) | Overall[a,b], N = 3320 |
|---|---|---|---|---|---|
| Demographics | | | | | |
| $CHA_2DS_2$-VASc score | 3.6 ± 1.5 | 3.2 ± 1.5 | 2.7 ± 1.5 | 3.3 ± 1.5 | 3.3 ± 1.5 |
| HAS-BLED score | 1.5 ± 0.9 | 1.4 ± 0.9 | 2.0 ± 0.8 | 1.2 ± 0.8 | 1.5 ± 0.9 |
| Age, y | 72 ± 11 | 71 ± 10 | 67 ± 13 | 71 ± 12 | 71 ± 11 |
| Weight, kg | 91.8 ± 26.7 | 91.3 ± 24.0 | 88.6 ± 23.9 | 85.6 ± 23.6 | 90.6 ± 24.7 |
| CrCl, mL/min | 84.0 ± 46.0 | 89.8 ± 42.7 | 95.8 ± 50.5 | 80.0 ± 38.7 | 88.2 ± 44.7 |
| Female sex | 398 (45.0) | 725 (41.5) | 187 (45.2) | 118 (48.0) | 1441 (43.4) |
| Medical history | | | | | |
| HF | 246 (27.8) | 316 (18.1) | 62 (15.0) | 40 (16.3) | 669 (20.2) |
| HTN | 749 (84.6) | 1437 (82.2) | 321 (77.5) | 202 (82.1) | 2732 (82.3) |
| DM | 301 (34.0) | 465 (26.6) | 79 (19.1) | 67 (27.2) | 921 (27.7) |
| Prior stroke/TIA | 136 (15.4) | 233 (13.3) | 18 (4.3) | 27 (11.0) | 422 (12.7) |
| Prior bleed | 66 (7.5) | 117 (6.7) | 44 (10.6) | 28 (11.4) | 260 (7.8) |
| Alcohol ≥8 U/wk | 52 (5.9) | 136 (7.8) | 44 (10.6) | 12 (4.9) | 246 (7.4) |
| No. of concomitant meds | 4.1 ± 1.9 | 3.8 ± 2.0 | 3.4 ± 2.0 | 3.5 ± 2.1 | 3.9 ± 2.0 |
| Use of antiplatelet drugs | 238 (26.9) | 408 (23.3) | 414 (100) | 0 (0) | 1080 (32.5) |
| Liver disease | 18 (2.0) | 20 (1.1) | 9 (2.2) | 7 (2.8) | 54 (1.6) |
| Falls | 48 (5.4) | 71 (4.1) | 27 (6.5) | 20 (8.1) | 171 (5.2) |
| Cancer | 157 (17.7) | 303 (17.3) | 57 (13.8) | 48 (19.5) | 568 (17.1) |
| COPD/emphysema | 109 (12.3) | 166 (9.5) | 39 (9.4) | 20 (8.1) | 338 (10.2) |
| PAD | 43 (4.9) | 81 (4.6) | 20 (4.8) | 19 (7.7) | 167 (5.0) |
| CAD | 259 (29.3) | 479 (27.4) | 96 (23.2) | 70 (28.5) | 919 (27.7) |
| Current smoking | 80 (9.0) | 112 (6.4) | 46 (11.1) | 27 (11.0) | 267 (8.0) |
| Pattern of AF | | | | | |
| Paroxysmal | 558 (63.1) | 1080 (61.8) | 331 (80.0) | 187 (76.0) | 2175 (65.5) |
| Persistent | 273 (30.8) | 583 (33.4) | 75 (18.1) | 50 (20.3) | 989 (29.8) |
| Permanent | 54 (6.1) | 85 (4.9) | 8 (1.9) | 9 (3.7) | 156 (4.7) |
| Insurance | | | | | |
| Government | 596 (67.3) | 1070 (61.2) | 239 (57.7) | 163 (66.3) | 2088 (62.9) |
| Commercial | 186 (21.0) | 570 (32.6) | 145 (35.0) | 67(27.2) | 974 (29.3) |
| None | 103 (11.6) | 108 (6.2) | 30 (7.2) | 16 (6.5) | 258 (7.8) |
| Clinical care setting | | | | | |
| Community hospital | 79 (8.9) | 124 (7.1) | 65 (15.7) | 15 (6.1) | 285 (8.6) |
| University hospital | 77 (8.7) | 136 (7.8) | 26 (6.3) | 11 (4.5) | 253 (7.6) |
| Specialist office | 578 (65.3) | 1250 (71.5) | 242 (58.5) | 156 (63.4) | 2245 (67.6) |
| GP/PCP | 136 (15.4) | 211 (12.1) | 79 (19.1) | 57 (23.2) | 485 (14.6) |
| Outpatient healthcare/anticoagulant clinic | 15 (1.7) | 27 (1.5) | 2 (0.5) | 7 (2.8) | 52 (1.6) |
| Prescribers | | | | | |
| Primary care | 123 (13.9) | 184 (10.5) | 59 (14.3) | 45 (18.3) | 414 (12.5) |
| Cardiologist | 734 (82.9) | 1500 (85.8) | 348 (84.1) | 198 (80.5) | 2802 (84.4) |
| Neurologist | 21 (2.4) | 52 (3.0) | 2 (0.5) | 1 (0.4) | 77 (2.3) |

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid (aspirin); CAD, coronary artery disease; $CHA_2DS_2$-VASc, CHF, HTN, age >75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (female); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DM, diabetes mellitus; GP, general practitioner; HAS-BLED, HTN, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly age (>65 years); HF, heart failure; HTN, hypertension; INR, international normalized ratio; NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulant; PAD, peripheral arterial disease; PCP, primary-care provider; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist. Data are presented as n (%) or mean ± SD.

[a] The numbers of patients from treatment groups do not add up to the overall column because 27 patients treated with an antiplatelet drug other than ASA or a combination of OACs were not presented.

[b] For OAC treatment (VKA or NOAC), numbers of patients with missing/unknown values for the following characteristics are: HAS-BLED score (n = 211), CrCl (n = 636), HF (n = 15), HTN (n = 1), prior stroke/TIA (n = 1), prior bleeding (n = 61), alcohol ≥8 U/wk (n = 102), liver disease (n = 16), prior falls (n = 65), cancer (n = 7), COPD/emphysema (n = 12), PAD (n = 12), CAD (n = 28), and prescribers (n = 19). For non-OAC treatment (aspirin or none), numbers of patients with missing/unknown values for the following characteristics are: HAS-BLED score (n = 59), CrCl (n = 157), HF (n = 3), HTN (n = 2), prior stroke/TIA (n = 1), prior bleeding (n = 10), alcohol ≥8 U/wk (n = 32), liver disease (n = 6), prior falls (n = 21), cancer (n = 0), COPD/emphysema (n = 2), PAD (n = 3), CAD (n = 12), and prescribers (n = 7).

## 3 | RESULTS

From November 2011 through February 2014, 3320 eligible patients were enrolled from 292 centers. A total of 2934 (88.4%) patients were enrolled from 265 centers in the United States and 386 (11.6%) from 27 centers in Canada. The majority of patients were enrolled from specialist offices (67.6%), followed by primary-care offices (14.6%). Most prescribing physicians were cardiologists (84.4%). The mean age of the study population was 71 ± 11 years, the mean $CHA_2DS_2$-VASc score was 3.3 ± 1.5, and the mean HAS-BLED score was 1.5 ± 0.9. Patient demographics and medical history are summarized in Table 1, grouped according to prescribed therapy.

Use of antithrombotic therapy according to age, stroke risk, and bleeding risk is depicted in Figures 1 and 2. In patients with a $CHA_2DS_2$-VASc score ≥2, the rate of OAC was significantly lower in those with a HAS-BLED score of ≥3 compared with those with a HAS-BLED score ≤2 (74.0% vs 83.0%, respectively; $P < 0.0001$). This was accompanied by a significant increase in the proportion of patients managed with aspirin alone (21.7% vs 9.3%, respectively; $P < 0.0001$).

The results of the multivariable models of factors associated with the choice of OAC prescription as opposed to non-OAC management (antiplatelet drugs or no antithrombotic treatment) are displayed in Table 2 and in Supporting Information, Table 1, in the online version of this article. Independent predictors of OAC therapy prescription were nonparoxysmal AF, prior stroke/TIA, greater number of concomitant medications, commercial insurance coverage, a history of HF, and care by a specialist. There was also a positive correlation between increasing age and OAC prescription. Antiplatelet drug use, history of falls, and prior bleeding were inversely associated with OAC. There was a significant, "U-shaped" relationship in the odds of receiving OAC vs no OAC across the 4 time quartiles (overall $P = 0.004$; see Supporting Information, Table 1, in the online version of this article).

The results of the multivariable prediction models for the selection of NOAC as opposed to VKA therapy in the 2633 patients who received OAC are presented in Table 3 and in Supporting Information, Table 2, in the online version of this article. Having commercial insurance coverage and being enrolled at a specialist's office were each significantly associated with a greater likelihood of NOAC use. Factors associated with VKA use included HF, lack of commercial insurance coverage, DM, and additional therapy with antiplatelet drugs. There was a significant "U-shaped" relationship in the odds of receiving

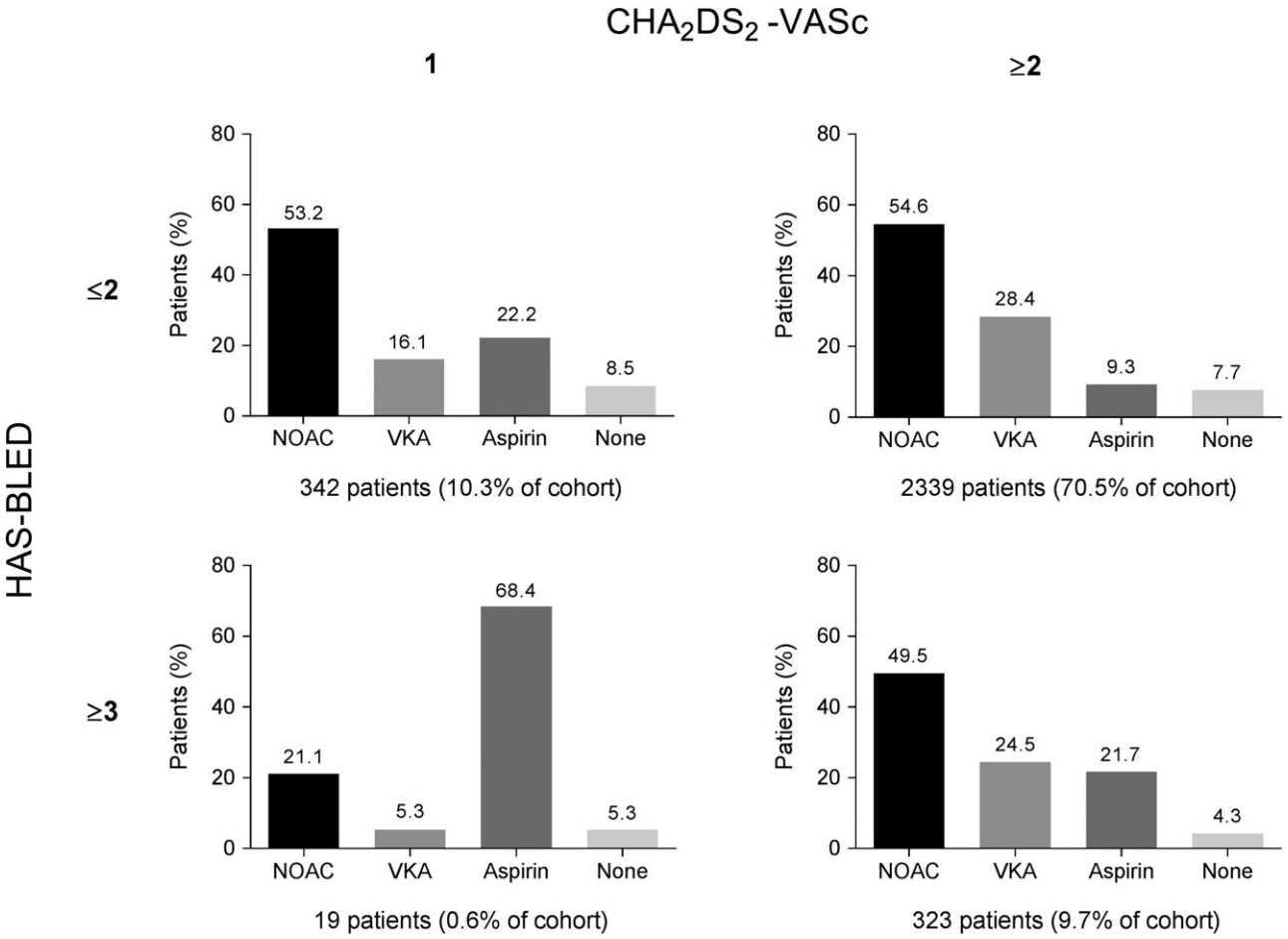


**FIGURE 1** Prescribing patterns for NOAC, VKA, aspirin, or no antithrombotic according to HAS-BLED and $CHA_2DS_2$-VASc scores. Among the 3320 eligible patients, 273 patients missing HAS-BLED scores and/or 27 patients who were prescribed other treatments (eg, antiplatelet drugs except aspirin or treatment combinations) were not included in the figure. Abbreviations: $CHA_2DS_2$-VASc, CHF, HTN, age >75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (F); CHF, congestive heart failure; DM, diabetes mellitus; F, female; HAS-BLED, HTN, abnormal renal and liver function, stroke, bleeding history or predisposition, labile INR, elderly age (>65 years); HTN, hypertension; INR, international normalized ratio; NOAC, non-VKA oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonist

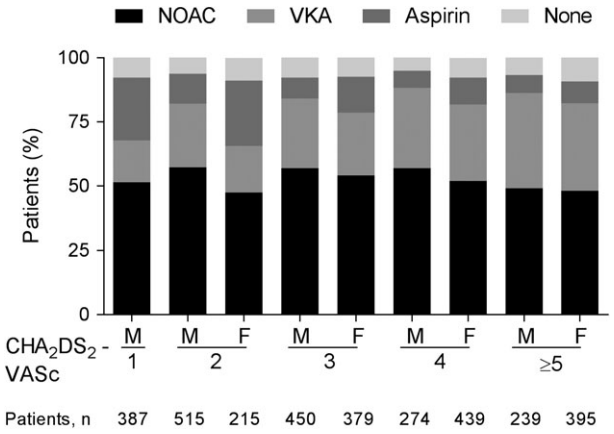


**FIGURE 2** Stroke prevention strategy according to stroke risk. Among the 3320 eligible patients, 3293 were included in this analysis (27 patients treated with antiplatelet drugs except aspirin or combinations of OACs were excluded). Abbreviations: $CHA_2DS_2$-VASc, CHF, HTN, age >75 y, DM, stroke/TIA, vascular disease, age 65–74 y, sex category (F); CHF, congestive heart failure; DM, diabetes mellitus; F, female; HTN, hypertension; M, male; NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonist

NOAC vs VKA across the 4 time quartiles (overall $P < 0.0001$; see Supporting Information, Table 2, in the online version of this article).

## 4 | DISCUSSION

In this cohort of high-risk North American patients (males with a $CHA_2DS_2$-VASc score ≥1 and females with a $CHA_2DS_2$-VASc score ≥2) with newly diagnosed nonvalvular AF, 20% of the analysis population did not receive OAC therapy. Nonparoxysmal AF, prior stroke/TIA, more concomitant medications, commercial insurance coverage, HF, being seen at a specialist office, and advanced age were associated with use of OAC. Conversely, treatment with antiplatelet drugs, history of falls, and prior bleeding were associated with a lower likelihood of OAC. This analysis suggests that patient characteristics and conditions affect selection of an antithrombotic treatment strategy. This is the first study to examine patient, physician, and temporal factors associated with the stroke-prevention strategy prescribed for North American patients with AF.

OAC in our cohort (79.3%) is at the higher end of the range reported in other contemporary registries. Differences in OAC rates among registries may reflect different inclusion criteria; whereas other major registries include all patients, GLORIA-AF includes patients with a $CHA_2DS_2$-VASc score ≥1.[17,20,28] In a report from the US-based Practice Innovation and Clinical Excellence (PINNACLE) registry (enrollment January 2008 to December 2012), among patients with a mean $CHA_2DS_2$-VASc score of 3.7, only 44.9% of patients received OAC and 31.4% were placed on therapy with antiplatelet drugs.[17] This registry sampled exclusively from cardiology practices and did not report the components of the HAS-BLED score.

In a publication from the most recent cohort (2014–2015) of the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF), among patients with a median $CHA_2DS_2$-VASc score of 3.0, 71.1% were taking OAC and 16.6% were taking antiplatelet drug monotherapy.[20] In a 2015 report from the EURO-Observational Research Programme on Atrial Fibrillation (EORP-AF) registry (enrollment February 2012 to March 2013), OAC was prescribed to 79.8% and 81.5% of females and males, respectively.[28] Data from the GARFIELD-AF registry indicate that appropriate OAC has increased over time and this is largely driven by increased use of NOACs.[20] The most recent publication has highlighted factors underpinning the decision between VKA and NOAC. NOACs were chosen more often than VKAs among men, the elderly (age >65 years), patients of Asian ethnicity, those with dementia, those using nonsteroidal anti-inflammatory drugs, and current smokers. VKAs were chosen more often than NOACs among patients with cardiac, vascular, and/or renal comorbidities.

Differences in patient characteristics and the rates of medication usage between North American patients and other patients in the global GLORIA-AF registry program have been reported previously.[26] Globally, 80% of patients with a $CHA_2DS_2$-VASc score ≥1 were prescribed OAC and 12% were prescribed therapy with antiplatelet drugs alone.[19,26] North American patients make up 22.5% of the global cohort and medication usage rates are similar to the overall global trends. Rates of OAC were highest in Europe, where 90% of patients received OAC and 6% were given antiplatelet drugs alone. Slightly

**TABLE 2** Independent categorical predictors of OAC vs non-OAC prescription

| | Adjusted OR (95% CI)[a,b] | *P* Value[c] |
|---|---|---|
| Medical history | | |
| No/missing | 1.00 (Ref) | — |
| HF | 1.44 (1.07–1.92) | 0.015 |
| Prior stroke/TIA | 2.00 (1.37–2.92) | 0.0003 |
| No. of concomitant meds > median[d] | 1.47 (1.13–1.92) | 0.005 |
| Prior bleed | 0.50 (0.35–0.72) | 0.0002 |
| Use of antiplatelet drug | 0.18 (0.14–0.23) | <0.0001 |
| History of falls | 0.41 (0.27–0.63) | <0.0001 |
| Pattern of AF | | |
| Paroxysmal | 1.00 (Ref) | — |
| Persistent/permanent | 2.02 (1.56–2.63) | <0.0001 |
| Insurance | | |
| Statutory/federal | 1.00 (Ref) | — |
| Commercial | 1.41 (1.07–1.85) | 0.016 |
| Clinical care setting[e] | | |
| Community hospital | 1.00 (Ref) | — |
| Specialist | 1.50 (1.04–2.17) | 0.032 |

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; OAC, oral anticoagulant; OR, odds ratio; Ref, reference; TIA, transient ischemic attack.

[a] OR >1 favors OAC; OR <1 favors antiplatelet drug or no OAC.

[b] This analysis included 3313 patients.

[c] See Supporting Information, Table 1, in the online version of this article for the full information and results of the associated multivariable prediction model.

[d] Median no. of concomitant medications excluding antithrombotic drugs.

[e] There is a trend for greater likelihood of OAC in the university hospital clinical setting (OR: 1.66, 95% CI: 0.97–2.83, $P = 0.063$).

**TABLE 3** Independent categorical predictors of NOAC vs VKA prescription

| | Adjusted OR (95% CI)[a,b] | *P* Value[c] |
|---|---|---|
| Medical history | | |
| No/missing | 1.00 (Ref ) | — |
| HF | 0.55 (0.44–0.70) | <0.0001 |
| DM | 0.78 (0.62–0.99) | 0.037 |
| Use of additional antiplatelet drug | 0.79 (0.63–0.99) | 0.043 |
| Insurance | | |
| Statutory/federal | 1.00 (Ref ) | — |
| Commercial | 1.72 (1.34–2.22) | <0.0001 |
| Self-pay/no coverage/unknown | 0.64 (0.45–0.92) | 0.015 |
| Clinical care setting[d] | | |
| Community hospital | 1.00 (Ref ) | — |
| Specialist office | 1.61 (1.12–2.32) | 0.010 |

Abbreviations: CI, confidence interval; DM, diabetes mellitus; GP, general practitioner; HF, heart failure; NOAC, non-VKA oral anticoagulant; OR, odds ratio; PCP, primary-care provider; Ref, reference; VKA, vitamin K antagonist.

[a] OR >1 favors NOAC; OR <1 favors VKA.

[b] This analysis included 2633 patients.

[c] See Supporting Information, Table 2, in the online version of this article for the full information and results of the associated multivariable prediction model.

[d] There is a trend for greater likelihood of NOAC use in the GP/PCP clinical setting (OR: 1.52, 95% CI: 0.98–2.37, $P = 0.063$).

higher rates of OAC use in Europe may be driven by the fact that ESC guidelines more strongly suggest OAC for patients with a single $CHA_2DS_2$-VASc risk factor (other than sex) than do guidelines from the United States.[11,13]

In this study, use of antiplatelet drugs, history of falls, prior bleeding, and paroxysmal AF (vs persistent/permanent AF) were identified as potential reasons for not prescribing OAC. In the present cohort, approximately 1 in 4 patients who received OAC also received antiplatelet drugs. The practice of combining antiplatelet drugs and OAC has been associated with increased bleeding without reduction in thrombotic outcomes.[29,30] Additionally, discontinuing therapy with antiplatelet drugs is one of the modifiable elements of the HAS-BLED score.[31] Outside of specific transient indications such as recent acute coronary syndrome or coronary stent, prescribing concomitant therapy with antiplatelet drugs in patients receiving OAC for AF should be avoided.[12,13]

Falls remain a controversial risk factor for bleeding in patients with AF;[32–34] however, there is no clear evidence to support falls or a predisposition thereto as a contraindication to OAC. The ESC guidelines recommend withholding therapy only in patients with a predisposition to severe, uncontrolled falls.[13]

It is not surprising that patients in this cohort with a history of bleeding were significantly less likely to receive OAC. The approach to stroke prevention in patients with AF and a history of bleeding is challenging. Observational data suggest that in patients who have bled on OAC, resumption of OAC after an appropriate interval impacts positively on stroke and mortality, even after an intracranial bleed.[35–37] However, many questions remain with respect to the safety, timing, and circumstances under which to initiate or resume OAC after a bleeding event, and randomized studies are required to provide guidance.[13]

Bleeding risk also influenced choice of stroke prevention strategy in this cohort. Among patients at higher risk of stroke (ie, $CHA_2DS_2$-VASc score ≥2), those at high risk of bleeding (ie, HAS-BLED score ≥3) were significantly less likely to receive OAC and more likely to receive antiplatelet drugs than those at low risk of bleeding (ie, HAS-BLED score ≤2; Figure 1). The superiority of OAC over therapy with antiplatelet drugs for stroke prevention has been well-established in a meta-analysis.[3] The net clinical benefit (balance of stroke and bleeding) of OAC over therapy with antiplatelet drugs has been demonstrated in patients with AF who have additional risk factors for stroke, including those with higher HAS-BLED scores.[38,39] We advocate that a high HAS-BLED score should not preclude the use of OAC; rather, it should help identify patients who need closer follow-up, addressing reversible factors for bleeding.[13,40]

Patients with paroxysmal AF were less likely to receive OAC than those with persistent or permanent AF. However, the balance of current evidence suggests that although patients with permanent AF appear to have a higher risk of stroke, patients with each of the 3 patterns of "clinical" AF (permanent, persistent, or paroxysmal) who have additional stroke risk factors have a sufficiently high risk of stroke to warrant consideration of OAC.[41–44] This position is supported by the AHA/ACC/HRS, ESC, and CCS guidelines, each of which recommend against taking the clinical pattern of AF into account when risk-stratifying patients with AF.[11–13] Patients with paroxysmal AF were included in all major trials of OAC.[7–10]

In our secondary analysis, approximately two-thirds of patients who started OAC therapy received 1 of the NOACs. NOAC use (over VKA) was predicted by having commercial insurance coverage and care from a specialist. Factors that predicted use of a VKA included HF, lack of insurance coverage, DM, and additional therapy with antiplatelet drugs. We found significant "U-shaped" relationships in the odds of receiving OAC and the odds of receiving a NOAC across the 4 time quartiles in our study. These relationships could reflect interactions between a number of physician, patient, and payer factors that impacted prescribing patterns for OACs and NOACs over this timeframe. Overall, our analysis supports the notion that, after an initial latency period, NOAC use is beginning to overtake VKA use in North America and throughout the world.[17–20,45]

## 4.1 | Study limitations

This study enrolled patients from 413 centers in Canada and the United States, encompassing a wide range of healthcare settings in order to represent a broad cross-section of patients treated. Sites were directed by protocol to enroll patients consecutively; however, because GLORIA-AF is not population-based, it may not completely represent the entirety of the AF population. The observed treatment patterns are affected by the sites composing the sample.

Most patients (84.4%) had a cardiologist as the prescribing physician and most (67.6%) were seen in a specialist office. This may have affected the number of patients receiving OAC and increased the proportion receiving a NOAC. It is worth noting that these data were

collected before the arrival of target-specific reversal agents for NOACs; it remains unknown whether the availability of reversal agents would change decisions to offer OAC and/or to offer a NOAC over VKA.

## 5 | CONCLUSION

In this North American cohort of patients with AF, one-fifth of the study population, comprising males with a $CHA_2DS_2$-VASc score ≥1 and females with a $CHA_2DS_2$-VASc score ≥2, did not receive OAC. $CHADS_2$ risk factors generally predicted OAC; however, use of antiplatelet drugs, a history of falling, prior bleeding, and paroxysmal AF were identified as potential reasons to not provide OAC.

### Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. BO, JLH, MVH, and GYHL contributed to the design and conduct of the global registry. WFM, JSH, and DC developed this secondary manuscript with input from the other authors. SL contributed to statistical analysis. All authors contributed to manuscript preparation and have approved the final article.

### Acknowledgement

This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). Editorial support was provided by Daniella Babu, PhD, of Envision Scientific Solutions, which was contracted and compensated by BIPI for these services.

### Conflicts of interest

*The authors received no direct compensation related to the development of the manuscript*. DC has received personal fees from Bayer and Boehringer Ingelheim, grants and personal fees from Daiichi-Sankyo, and grants from Bristol-Myers Squibb/Pfizer. BO received personal fees from during the conduct of the study as well as personal fees from Lundbeck, On-X/Cryolife, and Amarin outside the submitted work. JLH received consulting fees from Boehringer Ingelheim during the conduct of the study; consulting fees were received from Bayer HealthCare, Boehringer Ingelheim, Ortho-McNeil-Janssen (Johnson & Johnson), and Pfizer outside the submitted work. MVH received grants from and has undertaken consulting for Boehringer Ingelheim, Pfizer-BMS, Bayer HealthCare, and Daiichi-Sankyo. GYHL has undertaken consulting for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo, and speaking for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo; no personal fees were received. SL is an employee of Boehringer Ingelheim Pharmaceuticals, Inc. JSH has received research support from Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb/Pfizer, Medtronic, and St. Jude Medical. The authors declare no other potential conflicts of interest.

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## SUPPORTING INFORMATION

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**How to cite this article:** McIntyre WF, Conen D, Olshansky B, et al. Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program. *Clin Cardiol*. 2018;41:744–751. https://doi.org/10.1002/clc.22936