Global oral anticoagulation use varies by region in patients with recent diagnosis of atrial fibrillation: the GLORIA-AF Phase III registry

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Journal of the American Heart Association

ORIGINAL RESEARCH

Global Oral Anticoagulation Use Varies by Region in Patients With Recent Diagnosis of Atrial Fibrillation: The GLORIA-AF Phase III Registry

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BACKGROUND: Effective stroke prevention with oral anticoagulants (OAC) is recommended for some patients with atrial fibrillation (AF). We aimed to describe OAC use by geographical region and type of site in patients with recent-onset AF enrolled in a large global registry.

METHODS AND RESULTS: Eligible participants were recruited into GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation), a prospective observational cohort study from 2014 to 2016 in 4 international regions: North America, Europe, Asia, and Latin America. Cumulative incidence functions were generated for direct OACs (DOAC), vitamin K antagonists, and antiplatelet drugs considering competing risks, stratified by region and type of site. Time-to-treatment initiation after AF diagnosis was analyzed with Fine-Gray subdistribution hazard models. A total of 21 237 patients eligible for analysis were identified. By 30 days after AF diagnosis, 40%, 16%, and 8.6% of patients had DOAC, vitamin K antagonists, and antiplatelet drugs initiated, respectively. Earlier initiation of DOACs was observed in Europe, with Asia and Latin America having lower hazard rates of DOAC time-to-treatment initiation than Europe (hazard ratio [HR], 0.66; 95% CI, 0.62–0.70 and HR, 0.79; 95% CI, 0.73–0.85, respectively). DOAC initiation was highest in community hospitals, vitamin K antagonists in outpatient health care centers/anticoagulation clinics, and antiplatelet drugs in primary care clinics.

CONCLUSIONS: Important geographic variability exists with the use of OACs for patients with AF. Differences in the time-to-treatment initiation of OAC by type of site suggests suboptimal implementation of guideline recommendations and could result in less benefit and more harm. Optimizing OAC use for patients with AF may improve outcomes and reduce health care costs.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifiers: NCT01468701, NCT01671007.

Key Words: atrial fibrillation ■ direct-acting oral anticoagulants ■ oral anticoagulation ■ stroke prevention ■ vitamin K antagonists

Oral anticoagulation (OAC) is recommended to manage patients with nonvalvular atrial fibrillation (AF) at risk for stroke. Effective options include vitamin K antagonists (VKA) and direct-acting OACs (DOAC).[1–4] However, effective VKA therapy requires regular monitoring of international normalized ratio

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This manuscript was sent to N.A. Mark Estes III, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Presented in part at the American College of Cardiology Scientific Session, May 17, 2021.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023907

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This study provides an up-to-date global and regional overview of contemporary antithrombotic treatment strategies for stroke prevention in patients with recently diagnosed atrial fibrillation.

What Are the Clinical Implications?

- The significant geographic variability in the use of oral anticoagulants and differences in the time-to-treatment initiation after atrial fibrillation diagnosis by type of site calls for the implementation of consistent guideline recommendations and simplified atrial fibrillation treatment pathways.
- Better education and awareness to optimize oral anticoagulant use may improve outcomes and reduce health care costs.

Nonstandard Abbreviations and Acronyms

CIF	cumulative incidence function
DOAC	direct-acting oral anticoagulants
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation
HR	hazard ratio
OAC	oral anticoagulant
TTI	time-to-initiation
VKA	vitamin K antagonist

and time in the therapeutic range >70%.[5] Thus, DOAC use has increased because of its favorable risk-benefit profile versus VKA[6–11] with fixed-dosing and because it does not require monitoring of anticoagulation targets.[12,13] However, regional heterogeneities in OAC use may exist.[12,13]

Time-to-initiation (TTI) of an OAC after AF detection is an important factor to consider in preventing AF-related thromboemboli. Data from the Riks-Stroke Registry of 94 000 patients post-ischemic stroke showed that 33.4% of patients were diagnosed with AF, but only 16% were prescribed OACs within 6 months of the stroke, leaving a large proportion unprotected.[14] Data from US Medicare beneficiaries (2011–2012) showed another missed opportunity; <20% of patients with AF at high risk of stroke diagnosed in the emergency department were prescribed an OAC.[15]

The GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) is a large, global, "real-world," prospective registry that includes OAC prescribing data in routine clinical practice for patients with AF. This analysis explores whether regional disparities and those driven by type of site exist in long-term treatment with OAC therapy in patients with recent-onset AF enrolled in GLORIA-AF.

METHODS

Data Sharing Agreement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the International Committee of Medical Journal Editors criteria.

Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary article in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/.

Before providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can also be requested via the link https://trials.boehringer-ingelheim.com/. All requests will be governed by a Document Sharing Agreement.

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

Design

The GLORIA-AF registry[16] enrolled patients prospectively in 38 countries comprising 4 international regions with recently diagnosed nonvalvular AF (<3 months before baseline visit; <4.5 months in Latin America) and ≥1 stroke risk-factor based on the CHA_2DS_2-VASc score.[17] Participants, recruited and consented from university and community hospitals and primary care

and specialist offices from 2014 to 2016, were followed for 3 years regardless of OAC prescription (through 2020). Centers were selected to reflect physicians who typically identify and manage new AF cases in a given country. Physicians were encouraged to enroll consecutive patients who met the inclusion criteria. Patients were excluded if valve replacement was expected, a mechanical heart valve was present, >60 days of VKA treatment was already used, any other indication for an OAC was necessary, life expectancy was <1 year, or AF was due to a reversible cause.

The rationale and design of the GLORIA-AF Registry have been previously reported.[16] Approvals were obtained from the institutional review boards at participating sites. Informed consent was obtained from all participants. The GLORIA-AF Registry is listed at Clinicaltrials.gov (NCT01937377, NCT01468701, and NCT01671007).

Data Collection

Secure, validated, web-based platforms hosted on secure networks were used for data entry. Study staff collected data using electronic case report forms, which were then reviewed and signed by the overseeing physician who confirmed accuracy. Data quality was monitored frequently via manual and programmed audits evaluating consistency, accuracy, and data collection concerns, such as missing data.

Measures

Baseline characteristics included demographics, region (Asia, Europe, Latin America, and North America), medical setting (site type: general practice/primary care, specialist office, community hospital, university hospital, and "other," which include outpatient health care centers and anticoagulation clinics), and prescribing physician specialty, clinical characteristics of AF and AF management, risk factors for stroke (CHA_2DS_2-VASc score) and bleeding (HAS-BLED score[18]), and prescribed medications.

Statistical Analysis

Categorical variables are reported as absolute frequencies and percentages, and continuous variables are summarized with median and mean±SD values.

The analysis was a time-to-event analysis, where the event of interest was initiation of long-term treatment. Long-term OAC treatment was defined as antithrombotic treatment prescribed for long-term use at the time of the baseline visit by the physician or as any antithrombotic treatments that the patient was already on at the time of the baseline visit that the patient will remain on for long-term use. Long-term OAC treatment classes prescribed or observed at baseline were DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban), VKAs, and antiplatelet drugs (including aspirin). Time between AF diagnosis and initiation of long-term OAC treatment (as prescribed or observed at baseline) was considered time-to-treatment initiation. TTI was analyzed in the survival analysis framework with competing risks. For example, analysis of TTI for DOACs considers VKAs and antiplatelet drugs as competing risks. Patients with "no treatment" prescribed at baseline were encoded as censored in the TTI analysis. Patients with OAC combinations were excluded (10 patients). Patients prescribed long-term treatment before AF diagnosis were also excluded.

The TTI was analyzed with cumulative incidence function (CIF) curves and Fine-Gray models, while adjusting for covariates. CIF curves were generated for each long-term treatment class (DOAC, VKA, antiplatelet drugs) in the presence of competing risks, to estimate the probability of long-term treatment initiation after AF diagnosis. For example, the CIF for DOAC at 30 days after AF diagnosis estimated the proportion of patients initiating DOAC at that time. For each long-term treatment class, CIF curves were stratified by region and type of site. For example, the CIF for DOAC was generated for each region, estimating the probability of initiating DOAC/region.

TTI was also assessed using 3 separate Fine-Gray subdistribution hazard models,[19,20] adjusted for region, demographics, comorbidities, site type, physician specialty, HAS-BLED score, CHA_2DS_2-VASc score, AF type, treatment reimbursement, rhythm control interventions (cardioversion or AF ablation), and number of baseline medications.

The Fine-Gray model is similar to the Cox model for survival analysis, considering the occurrence of events that compete with the event of interest (in this case, DOAC, VKA, and antiplatelet treatment are competing risks). A model was built for each treatment class where the other 2 classes were considered competing risks. The Fine-Gray model for long-term DOAC treatment initiation considered VKA and antiplatelet drugs as competing risks. The Fine-Gray model calculated subdistribution hazard ratios (HR) in the presence of competing risks and was used to evaluate variables associated with TTI. Univariate and multivariate models were fit to evaluate observed and adjusted HR together with 95% CIs; variables associated with TTI (ie, whose 95% CI does not include 1) were highlighted. For simplicity, "hazard rate" instead of "subdistribution hazard rate" is used in the following analyses. The hazard rate is the instantaneous rate of prescription/initiation; the hazard ratio is the ratio of hazard rates and is assumed to be constant. Missing data for baseline characteristics were imputed using multiple imputation. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

The GLORIA-AF Phase III registry comprised 21 591 patients enrolled at 935 sites in 38 countries, of whom 21 237 (age 70.5±10.6 years; 44.9% female) were eligible for analysis. The majority came from Europe (48.4%), then North America (24%), Asia (19.9%), and Latin America (7.6%). Demographics and characteristics are summarized in Table 1.

The most common comorbidities were hypertension (74.5%) and diabetes (23.3%). Patients prescribed antiplatelet drugs had the highest proportion of prior stroke (12%), prior bleeding (6.9%), and coronary artery disease (24.3%). Congestive heart failure was 19.6% among DOAC, 28.6% among VKA, and 20.0% among antiplatelet drugs users. Patients treated with VKA had the highest proportion of permanent (14.1%) and persistent (40.8%) AF.

VKAs were prescribed to 4828 (22.7%) and DOACs to 12 636 (59.5%) participants with the remaining 3773 (17.8%) prescribed antiplatelet drugs (2370 patients) or no treatment (1403 patients). Patients prescribed VKA had 24.2±23.9 days from AF diagnosis to initiation of VKA (median of 16 days). Patients initiated DOAC 25.6±25.9 days after AF diagnosis (median of 17 days). The 3773 patients prescribed antiplatelet drugs or no treatment initiated this class of treatment 19.3±24.5 days after AF diagnosis (median of 7 days).

Most patients prescribed OACs were from Europe as they represented the largest population in GLORIA-AF: 50.9% in the DOAC group and 56.9% in the VKA group were from Europe (Table 1). DOACs were prescribed most frequently in every region (42.7% in Asia, 62.6% in Europe, 69.2% in North America, and 53.1% in Latin America). The second most frequent drug class prescribed was VKA in Europe (26.7%) and Latin America (33.8%), and antiplatelet drugs in North America (16.4%) and Asia (38.5%).

TTI of Antithrombotic Strategy (CIF Curves)

By 30 days after AF diagnosis, CIF curves for TTI demonstrated 40% of patients were prescribed DOACs, whereas 16% and 8.6% were prescribed VKAs and antiplatelet drugs, respectively (Figure). DOACs were most commonly prescribed throughout and incorporated earliest compared with VKAs and antiplatelet drugs. Thus, DOACs dominated the antithrombotic treatment classes. By 90 days after AF diagnosis, 63% were prescribed DOACs, 24% VKAs, and 11.7% antiplatelet drugs. After 90 days, curves plateaued. The median time to starting long-term treatment was 49 days for a DOAC (the time 50% of patients started DOACs). The median time to starting long-term treatment was not reached for a VKA nor for an antiplatelet drug (the CIF curves for VKA and antiplatelet drugs were <50%). Ultimately, 63.8% of patients were prescribed DOACs. The TTI for antithrombotic treatment varied between region (Figures S1 through S3) and site type (Figures S4 through S6).

CIF Stratified by Region

DOAC initiation was fastest in Europe (46% of patients from Europe being prescribed DOAC at 30 days), with North America having the largest proportion of patients ultimately prescribed DOACs, 72% (Figure S1). Regions reached 50% of their population prescribed DOAC, at 38 days for Europe, 43 days for North America, and 88 days for Asia and Latin America. Early initiation of VKAs was the fastest in Europe (with 19% of patients from Europe being prescribed DOAC at 30 days), with Latin America ultimately having the largest proportion prescribed VKAs, 35% (Figure S2). Asia initiated antiplatelet drugs early and had the greatest proportion of patients prescribed antiplatelet drugs overall, 27% (Figure S3). The CIF curves stratified by region for VKA and antiplatelet drugs were <50%, so no region reached 50% prescription for these OACs.

CIF Stratified by Type of Site

Early DOAC initiation was led by community hospitals, with 50% initiating a DOAC at 35 days (followed by specialist offices at 41 days); community hospitals also had the largest proportions of patients prescribed DOACs, 70.5% (Figure S4). Outpatient health care offices/anticoagulation clinics were the fastest to incorporate VKAs, with 25% VKA initiation at 28 days. They also had the greatest proportion of patients prescribed VKAs, 41% (Figure S5). The TTI of antiplatelet drugs was fastest among general practice/primary care and outpatient health care offices/anticoagulation clinics. General practice/primary care had the greatest proportion of patients prescribed antiplatelets, 20% (Figure S6).

Factors Influencing the TTI of Antithrombotic Strategy (Fine-Gray Models)

TTI of DOAC

In the multivariable Fine-Gray model for *time-to-initiation of DOAC,* considering competing risks (Table 2), Asia and Latin America had a lower hazard rate of DOAC TTI than Europe (HR,0.66; 95% CI, 0.62–0.70 and HR, 0.79; 95% CI, 0.73–0.85, respectively). Specialist offices and community hospitals had an increase in hazard rate of DOAC TTI (HR, 1.27; 95% CI, 1.21–1.33; and HR, 1.40; 95% CI, 1.34–1.47), respectively,

Table 1. Baseline Characteristics

Variable	Overall* (n=21 237) (100%)	DOAC (n=12 636) (59.5%)	VKA (n=4828) (22.7%)	No OAC† (n=3773) (17.8%)
Age, y				
Median (IQR)	71.0 (64.0–78.0)	72.0 (65.0–78.0)	72.0 (65.0–79.0)	69.0 (61.0–77.0)
Mean (SD)	70.5 (10.6)	71.0 (10.2)	71.1 (10.4)	68.2 (12.0)
Female sex, n (%)	9544 (44.9)	5703 (45.1)	2147 (44.5)	1694 (44.9)
Race/ethnicity, n (%)				
American Indian/Alaskan Native	126 (0.6)	79 (0.6)	34 (0.7)	13 (0.3)
Black	394 (1.9)	236 (1.9)	84 (1.7)	74 (2.0)
White	14 772 (70.0)	9300 (73.6)	3597 (74.5)	1875 (49.7)
Asian	4127 (19.4)	1754 (13.8)	765 (15.8)	1608 (42.6)
Native Hawaiian/other Pacific Islander	3 (0.0)	1 (0.0)	0 (0.0)	2 (0.1)
Arab/Middle East	29 (0.1)	16 (0.1)	7 (0.1)	6 (0.2)
African	11 (0.1)	6 (0.0)	2 (0.0)	3 (0.1)
Other‡	603 (2.8)	382 (3.0)	133 (2.8)	88 (2.3)
Missing	1181 (5.6)	871 (6.9)	206 (4.3)	104 (2.8)
Region, n (%)				
Asia	4237 (19.9)	1810 (14.3)	798 (16.5)	1629 (43.2)
Europe	10 277 (48.4)	6435 (50.9)	2747 (56.9)	1095 (29.0)
North America	5097 (24.0)	3527 (27.9)	734 (15.2)	836 (22.2)
Latin America	1626 (7.6)	864 (6.8)	549 (11.4)	213 (5.6)
Type of site, n (%)				
General practitioner/primary care	1318 (6.2)	683 (5.4)	254 (5.3)	381 (10.1)
Specialist office	6215 (29.3)	4090 (32.4)	1107 (22.9)	1018 (27.0)
Community hospital	6250 (29.4)	4167 (33.0)	1243 (25.7)	840 (22.3)
University hospital	6755 (31.8)	3401 (26.9)	1947 (40.3)	1407 (37.3)
Outpatient health care center	335 (1.6)	100 (0.8)	163 (3.4)	72 (1.9)
Anticoagulation clinics	118 (0.6)	45 (0.4)	57 (1.2)	16 (0.4)
Other	246 (1.2)	150 (6.8)	57 (1.2)	39 (1.0)
Physician speciality, n (%)				
General practitioner/primary care physician/geriatrician	1085 (5.1)	574 (4.5)	255 (4.7)	256 (6.8)
Cardiologist	18 052 (85.0)	10 839 (85.8)	3939 (81.6)	3274 (86.8)
Neurologist	524 (2.5)	383 (3.0)	70 (1.4)	71 (1.9)
Internist	820 (3.9)	414 (3.3)	324 (6.7)	82 (2.2)
Angiologist	3 (0.0)	2 (0.0)	1 (0.0)	0 (0.0)
Other‡	779 (3.7)	422 (3.3)	267 (5.5)	90 (2.4)
Missing	4 (0.0)	2 (0.0)	2 (0.0)	0 (0.0)
Medical treatment reimbursed by, n (%)				
Private insurance	3083 (14.5)	2063 (16.3)	489 (10.1)	531 (14.1)
Statutory/federal insurance	15 721 (74.0)	9062 (71.7)	3811 (78.9)	2848 (75.5)
Self-pay/no coverage	1014 (4.8)	623 (4.9)	221 (4.6)	170 (4.5)
Unknown	1419 (6.7)	888 (7.0)	307 (6.4)	224 (5.9)
Body mass index, n (%)				
<18.5	267 (1.3)	141 (1.1)	58 (1.2)	68 (1.8)
18.5 to <25	5900 (27.8)	3195 (25.3)	1288 (26.7)	1417 (37.6)
25 to <30	7970 (37.5)	4735 (37.5)	1863 (38.6)	1372 (36.4)
30 to <35	4121 (19.4)	2605 (20.6)	954 (19.8)	562 (14.9)
≥35	2734 (12.9)	1795 (14.2)	621 (12.9)	318 (8.4)
Missing	245 (1.2)	165 (1.3)	44 (0.9)	36 (1.0)

(*Continued*)

Table 1. (Continued)

Variable	Overall* (n=21 237) (100%)	DOAC (n=12 636) (59.5%)	VKA (n=4828) (22.7%)	No OAC† (n=3773) (17.8%)
Smoking, n (%)				
Nonsmoker	12 152 (57.2)	7143 (56.5)	2756 (57.1)	2253 (59.7)
Current smoker	2027 (9.5)	1105 (8.7)	444 (9.2)	478 (12.7)
Past smoker	6429 (30.2)	3979 (31.5)	1488 (30.8)	962 (25.5)
Unknown	629 (3.0)	409 (3.2)	140 (2.9)	80 (2.1)
Type of AF, n (%)				
Paroxysmal	11 969 (56.3)	7139 (56.5)	2179 (45.1)	2651 (70.3)
Persistent	7248 (34.1)	4333 (34.3)	1968 (40.8)	947 (25.1)
Permanent	2020 (9.5)	1164 (9.2)	681 (14.1)	175 (4.6)
Medical history, n (%)				
Congestive heart failure	4616 (21.7)	2480 (19.6)	1381 (28.6)	755 (20.0)
History of hypertension	15 830 (74.5)	9640 (76.3)	3640 (75.4)	2550 (67.6)
Diabetes	4939 (23.3)	2931 (23.2)	1229 (25.5)	779 (20.6)
Previous stroke	2243 (10.6)	1330 (10.5)	461 (9.5)	452 (12.0)
Coronary artery disease	3966 (18.7)	2129 (16.8)	921 (19.1)	916 (24.3)
Prior bleeding	1124 (5.3)	614 (4.9)	248 (5.1)	262 (6.9)
Creatinine clearance, mL/min				
Median (IQR)	75.2 (56.7–98.3)	76.0 (57.9–99.2)	72.2 (53.4–95.0)	76.3 (56.8–99.6)
Mean (SD)	83.7 (152.4)	86.9 (194.2)	76.8 (35.5)	81.6 (37.5)
Chronic concomitant medications, n (%)				
Antiplatelet	5423 (25.5)	2165 (17.1)	888 (18.4)	2370 (62.8)
Cardioversion, n (%)				
Yes	3840 (18.1)	2495 (19.7)	690 (14.3)	655 (17.4)
No	17 173 (80.9)	10 006 (79.2)	4098 (84.9)	3069 (81.3)
Unknown	224 (1.1)	135 (1.1)	40 (0.8)	49 (1.3)
AF ablation, n (%)				
Yes	382 (1.8)	254 (2.0)	84 (1.7)	44 (1.2)
No	20 676 (97.4)	12 273 (97.1)	4703 (97.4)	3700 (98.1)
Unknown	179 (0.8)	109 (0.9)	41 (0.8)	29 (0.8)
Chronic gastrointestinal disease, n (%)				
Yes	2814 (13.2)	1740 (13.8)	564 (11.7)	510 (13.5)
No	18 148 (85.4)	10 700 (84.7)	4212 (87.2)	3236 (85.8)
Unknown	275 (1.3)	196 (1.6)	52 (1.1)	27 (0.7)
Cancer, n (%)				
Yes	2112 (9.9)	1318 (10.4)	478 (9.9)	316 (8.4)
No	18 820 (88.6)	11 124 (88.0)	4281 (88.7)	3415 (90.5)
Unknown	305 (1.4)	194 (1.5)	69 (1.4)	42 (1.1)
Number of medications at baseline, n (%)				
Low (nb <3)	7367 (34.7)	4035 (31.9)	1505 (31.2)	1827 (48.4)
High (nb ≥3)	13 870 (65.3)	8601 (68.1)	3323 (68.8)	1946 (51.6)
CHA_2DS_2-VASc score, mean (SD)	3.2 (1.5)	3.2 (1.5)	3.3 (1.5)	2.9 (1.6)
HAS-BLED score, mean (SD)	1.4 (0.9)	1.3 (0.9)	1.3 (0.9)	1.7 (1.0)
HAS-BLED risk score ≥3, n (%)	1970 (9.3)	909 (7.2)	370 (7.7)	691 (18.3)

AF indicates atrial fibrillation; DOAC, direct-acting oral anticoagulants; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; IQR, interquartile range; nb, number of medications at baseline; OAC, oral anticoagulant; and VKA, vitamin K antagonists.

*This analysis excluded patients with OAC combinations, and those that initiated long term treatment before AF diagnosis.

†No OAC: patients not treated with oral anticoagulants (antiplatelet agents or no treatment).

‡"Other" refers to any other race not mentioned in the above categories.

versus university hospitals, the reference. Other sites (including outpatient health care offices and anticoagulation clinics) had a reduced hazard rate of DOAC TTI versus the reference (HR, 0.75; 95% CI, 0.66–0.84).

Variables associated with an increased hazard rate of DOAC TTI were neurologists (versus cardiologists), AF ablation (versus no ablation), cardioversion, and medical treatment reimbursement (self-pay or no coverage versus private or federal insurance) (Table 2). Variables associated with a decreased hazard rate of DOAC TTI included smoking (current or past smoker versus nonsmoker), "internist" or "other" (versus cardiologist), HAS-BLED risk score ≥3 (versus <3), CHA_2DS_2-VASc score (low [1 if female and 0 if male] or moderate [2 if female and 1 if male] versus high score [≥3 if female, ≥2 if male], and permanent AF [versus paroxysmal AF]).

TTI of VKA

In the multivariable Fine-Gray model for TTI of VKA, considering competing risks (Table 3), Asia and North America had a lower hazard rate of VKA TTI than Europe (HR, 0.75; 95% CI, 0.68–0.82; and HR, 0.55; 95% CI, 0.50–0.60, respectively). General practice/primary care, specialist offices, and community hospitals had a reduced hazard rate of VKA TTI versus university hospitals (HR, 0.67; 95% CI, 0.59–0.78; HR, 0.67; 95% CI, 0.61–0.72; and HR, 0.59; 95% CI, 0.55–0.63, respectively). Other variables associated with a reduced hazard rate of VKA TTI were neurologists (versus cardiologists), a HAS-BLED score ≥3 (versus HAS-BLED score <3), a moderate CHA_2DS_2-VASc score (2 for men and 1 for women) (versus a high CHA_2DS_2-VASc score [≥2 for men and ≥3 for women]), cardioversion, and reimbursement (self-pay or no coverage compared with private or federal insurance). On the contrary, "internist" or "other" (versus cardiologists), a high number (≥3) of baseline medications (versus <3), and persistent or permanent AF (versus paroxysmal AF) were associated with an increased hazard rate of VKA TTI.

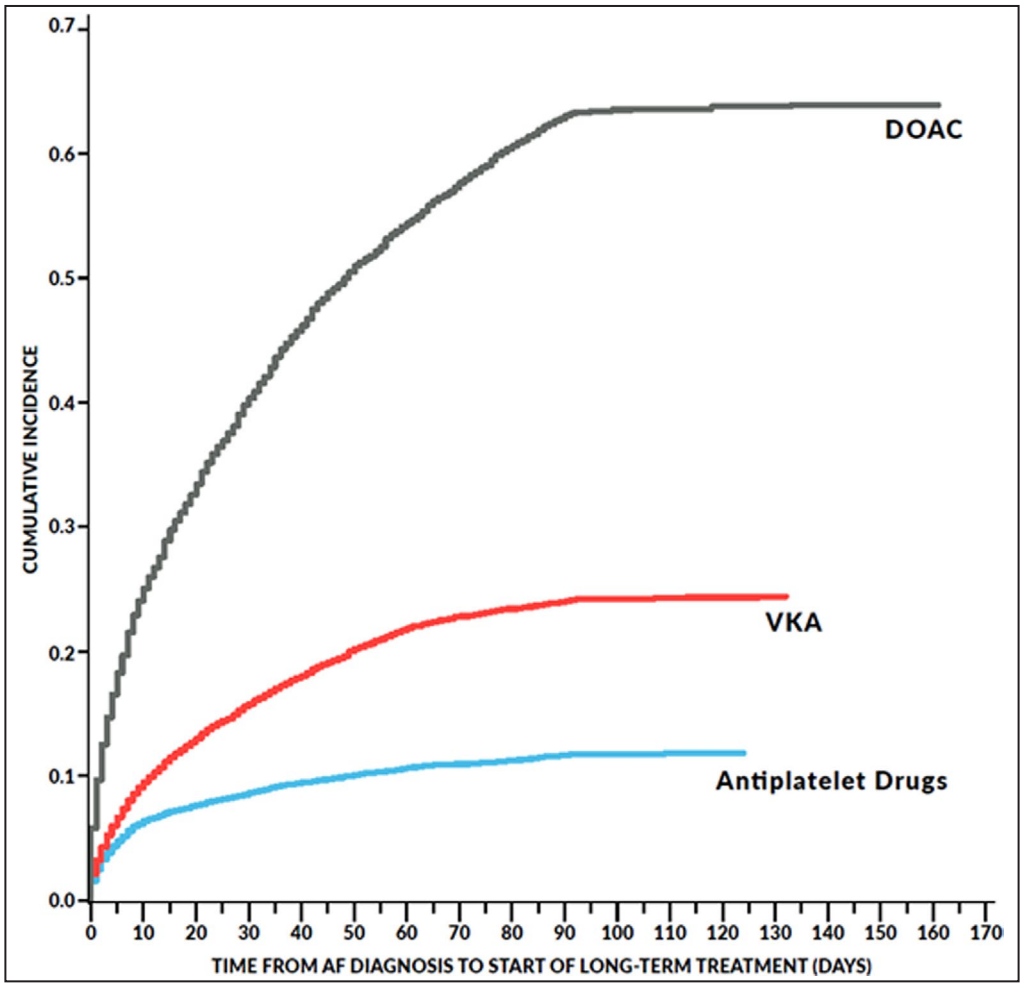

Figure 1. Cumulative incidence function of time-to-initiation by oral anticoagulant type.
AF indicates atrial fibrillation; DOAC, direct-acting oral anticoagulants; and VKA, vitamin K antagonists.

Table 2. The Multivariable Fine-Gray Model for Time-to-Initiation of DOAC in the Presence of Competing Risks

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Region						
Asia	4237	1810 (42.7)	0.602	0.572, 0.635	0.657	0.621, 0.695
Europe	10 277	6435 (62.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
North America	5097	3527 (69.2)	1.021	0.982, 1.061	1.027	0.979, 1.078
Latin America	1626	864 (53.1)	0.705	0.657, 0.756	0.787	0.730, 0.849
Type of site						
GP/primary care	1318	683 (51.8)	0.927	0.859, 1.000	1.003	0.922, 1.091
Specialist office	6215	4090 (65.8)	1.373	1.312, 1.436	1.268	1.206, 1.333
Community hospital	6250	4167 (66.7)	1.497	1.430, 1.567	1.402	1.338, 1.470
University hospital	6755	3401 (50.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Other	699	295 (42.2)	0.706	0.628, 0.794	0.746	0.661, 0.843
Body mass index class						
<18.5	284	152 (53.5)	0.927	0.791, 1.086	0.933	0.797, 1.093
18.5 to <25	5948	3227 (54.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25 to <30	8051	4789 (59.5)	1.110	1.061, 1.160	1.029	0.984, 1.077
30 to <35	4183	2647 (63.3)	1.172	1.114, 1.233	1.023	0.971, 1.079
≥35	2771	1822 (65.8)	1.218	1.152, 1.289	1.023	0.964, 1.086
Smoking status						
Nonsmoker	12 535	7396 (59.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Current smoker	2089	1142 (54.7)	0.898	0.843, 0.957	0.918	0.861, 0.978
Past smoker	6613	4097 (62.0)	1.012	0.975, 1.051	0.959	0.923, 0.997
Physician specialty						
GP/primary care	1058	576 (54.4)	0.834	0.772, 0.901	0.934	0.854, 1.022
Cardiologist	18 053	10 839 (60.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Neurologist	524	383 (73.1)	1.600	1.441, 1.775	1.717	1.544, 1.910
Internist	820	414 (50.5)	0.754	0.682, 0.833	0.782	0.709, 0.862
Other	782	424 (54.2)	0.842	0.765, 0.926	0.819	0.743, 0.902
Cardioversion						
Yes	3872	2515 (65.0)	1.094	1.050, 1.140	1.051	1.009, 1.096
No	17 365	10 121 (58.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
AF ablation						
Yes	384	255 (66.4)	1.016	0.915, 1.127	1.271	1.140, 1.418
No	20 853	12 381 (59.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Chronic gastrointestinal disease						
Yes	2857	1773 (62.1)	1.004	0.957, 1.052	0.971	0.925, 1.019
No	18 380	10 863 (59.1)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
HAS–BLED (imputed) risk score class						
Low (score <3)	19 028	11 618 (61.1)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (score ≥3)	2209	1018 (46.1)	0.651	0.609, 0.695	0.634	0.593, 0.678
CHA_2DS_2–VASc score class						
Low (score=1 for F)	488	168 (34.4)	0.544	0.467, 0.634	0.533	0.455, 0.623
Moderate (score=1 for men or score=2 for women)	3965	2228 (56.2)	0.896	0.857, 0.937	0.868	0.828, 0.910
High (score ≥2 for men or score ≥3 for women)	16 784	10 240 (61.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

(*Continued*)

Table 2. Continued

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Type of AF						
Paroxysmal AF	11 969	7139 (59.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Persistent AF	7248	4333 (59.8)	0.990	0.954, 1.028	0.987	0.950, 1.026
Permanent AF	2020	1164 (57.6)	0.896	0.843, 0.953	0.909	0.853, 0.969
Cancer						
Yes	2142	1336 (62.4)	1.052	0.996, 1.111	0.977	0.923, 1.034
No	19 096	11 300 (59.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medical treatment reimbursed by						
Not self-pay	20 161	11 976 (59.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Self-pay/no coverage	1076	660 (61.3)	1.040	0.959, 1.127	1.175	1.078, 1.279
Number of medications at baseline, nb						
Low (nb <3)	8357	4683 (56.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (nb ≥3)	12 880	7953 (67.7)	1.060	1.023, 1.099	0.989	0.952, 1.027

AF indicates atrial fibrillation; DOAC, direct-acting oral anticoagulants; GP, general practice; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; nb, number of medications at baseline; and ref, reference.

TTI of Antiplatelet Drugs

In the multivariable Fine-Gray model for TTI of antiplatelet drugs, considering competing risks (Table 4), Asia, North America, and Latin America had a higher hazard rate of antiplatelet drug TTI than Europe (HR, 3.92; 95% CI, 3.51–4.39; HR,1.69; 95% CI, 1.49–1.92; and HR, 1.29; 95% CI, 1.05–1.58, respectively). Also, general practice/primary care and other types of sites (outpatient health care offices and anticoagulation clinics) had an increased hazard rate of antiplatelet drug TTI versus university hospitals (HR, 1.36; 95% CI, 1.16–1.60; and HR, 1.93; 95% CI, 1.52–2.44). Community hospitals had a reduced hazard rate of antiplatelet drug TTI versus university hospitals (HR, 0.85; 95% CI, 0.76–0.95).

Other variables associated with an increased hazard rate of antiplatelet drug TTI were current smoker (versus nonsmoker), a HAS-BLED score ≥3 (which increased antiplatelet drug TTI hazard rate 4.2 times versus HAS-BLED score <3). Other variables associated with reduced hazard rates of antiplatelet drug TTI were community hospital (versus university hospital), body mass index ≥35 (versus 18.5 to <25), past smokers (versus nonsmokers), neurologists, internists, and others (versus cardiologists), type of AF (persistent and permanent versus paroxysmal), AF ablation, chronic gastrointestinal disease, cancer, reimbursement (self-pay or no coverage compared with private or federal insurance), and a high number (≥3) of baseline medications (versus <3 medications).

DISCUSSION

From the large, prospective, global GLORIA-AF registry, (1) the majority of patients (59.5%) were treated with DOACs; (2) regional differences exist in use of DOACs, VKAs, and antiplatelet drugs; and (3) TTI by treatment class vary by region and site type. DOACs were the largest proportion of prescribed treatments for AF. Europe led early initiation of DOACs and VKA, and Asia was the fastest to initiate antiplatelet drugs. Europe had nearly twice the hazard rate of VKA TTI versus North America, whereas Latin America had the largest proportion prescribed VKA.

Differences seen might result from systemwide differences in management among regions because pf local AF guidelines, health care systems, or socioeconomic factors.[12,13,21] The high use of antiplatelet drugs in patients from Asia was previously reported.[22–25] Reasons are likely multifactorial. However, the risk of ischemic stroke in patients from Asia may be even greater, reaching the OAC treatment threshold at age ≥55.[26,27]

Asia had slower uptake of DOAC use, but patient numbers grew steadily. Data from a Korean-based cohort study showed that OAC prescription increased from 34.7% to 50.6% between 2008 and2015; and 50% of OAC prescriptions were DOACs.[28] Of note, the GLORIA-AF registry recruited patients between 2014 and 2016; reimbursement varies by country and may limit the overall use of DOACs in some locales.

Most guidelines recommend the CHA_2DS_2-VASc score for stroke risk assessment, where OACs (preferably, DOACs) are recommended for patients with AF who had a CHA_2DS_2-VASc score ≥1 (men) or ≥2 (women)[1,2,4] or CHA_2DS_2-VASc score ≥2 (men) or ≥3 (women).[3] Our analysis showed that patients with low CHA_2DS_2-VASc scores had half the adjusted hazard rate for DOAC TTI versus those with a high CHA_2DS_2-VASc score, which aligns with the guidelines.

Table 3. The Multivariable Fine-Gray Model for Time-to-Initiation of VKA in the Presence of Competing Risks

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Region						
Asia	4237	798 (18.8)	0.727	0.672, 0.787	0.746	0.683, 0.815
Europe	10 277	2747 (26.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
North America	5097	734 (14.4)	0.485	0.447, 0.526	0.546	0.496, 0.600
Latin America	1626	549 (33.8)	1.249	1.144, 1.364	1.097	0.993, 1.212
Type of site						
GP/primary care	1318	254 (19.3)	0.613	0.539, 0.697	0.674	0.586, 0.775
Specialist office	6215	1107 (17.8)	0.552	0.513, 0.594	0.665	0.611, 0.724
Community hospital	6250	1243 (19.9)	0.633	0.590, 0.680	0.590	0.549, 0.634
University hospital	6755	1947 (28.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Other	699	277 (39.6)	1.402	1.238, 1.588	1.089	0.955, 1.243
Body mass index class						
<18.5	284	60 (21.1)	0.955	0.736, 1.239	1.006	0.775, 1.305
18.5 to <25	5948	1293 (21.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25 to <30	8051	1878 (23.3)	1.055	0.983, 1.133	1.015	0.944, 1.091
30 to <35	4183	967 (23.1)	1.023	0.941, 1.111	0.998	0.915, 1.088
≥35	2771	630 (22.7)	0.990	0.901, 1.089	1.051	0.951, 1.162
Smoking status						
Nonsmoker	12 535	2840 (22.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Current smoker	2089	456 (21.8)	0.973	0.880, 1.073	1.028	0.929, 1.138
Past smoker	6613	1532 (28.1)	1.002	0.941, 1.067	1.064	0.999, 1.135
Physician specialty						
GP/primary care	1058	226 (21.4)	0.992	0.870, 1.133	0.881	0.586, 0.896
Cardiologist	18 053	3940 (21.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Neurologist	524	70 (13.4)	0.601	0.473, 0.765	0.493	0.188, 0.375
Internist	820	324 (39.5)	1.970	1.764, 2.201	1.657	1.181, 1.621
Other	782	268 (34.3)	1.645	1.461, 1.854	1.287	1.140, 1.454
Cardioversion						
Yes	3872	695 (17.9)	0.718	0.663, 0.779	0.725	0.667, 0.787
No	17 365	4133 (23.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
AF ablation						
Yes	384	85 (22.1)	0.939	0.759, 1.162	1.097	0.878, 1.370
No	20 853	4743 (22.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Chronic gastrointestinal disease						
Yes	2857	570 (20.0)	0.825	0.756, 0.899	0.959	0.878, 1.047
No	18 380	4258 (23.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
HAS–BLED (imputed) risk score class						
Low (score <3)	19 028	4403 (23.1)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (score ≥3)	2209	425 (19.2)	0.803	0.726, 0.889	0.807	0.728, 0.895
CHA_2DS_2–VASc score class						
Low (score=1 for women)	488	73 (15.0)	0.674	0.538, 0.845	0.815	0.650, 1.023
Moderate (score=1 for men or score=2 for women)	3965	759 (19.1)	0.799	0.740, 0.863	0.866	0.799, 0.939
High (score ≥2 for men or score ≥3 for women)	16 784	3996 (23.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

(*Continued*)

Table 3. Continued

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Type of AF						
Paroxysmal AF	11 969	2179 (18.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Persistent AF	7248	1968 (27.2)	1.558	1.466, 1.656	1.402	1.318, 1.491
Permanent AF	2020	681 (33.7)	1.925	1.770, 2.094	1.479	1.357, 1.612
Cancer						
Yes	2142	484 (22.6)	0.985	0.896, 1.082	1.074	0.976, 1.181
No	19 096	4344 (22.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medical treatment reimbursed by						
Not self-pay	20 161	4592 (22.8)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Self-pay/no coverage	1076	236 (21.9)	0.946	0.825, 1.084	0.854	0.739, 0.988
Number of medications at baseline, nb						
Low (nb <3)	8357	1702 (20.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (nb ≥3)	12 880	3126 (24.3)	1.160	1.094, 1.230	1.150	1.081, 1.225

AF indicates atrial fibrillation; DOAC, direct-acting oral anticoagulants; GP, general practice; nb, number of medications at baseline; ref, reference; and VKA, vitamin K antagonists.

Although of smaller magnitude, a similar association was observed for CHA_2DS_2-VASc score and VKA, whereas for antiplatelet drugs it was reversed (low CHA_2DS_2-VASc score has almost 3 times the hazard rate of those with a high-risk score for antiplatelet drug TTI). A similar pattern for CHA_2DS_2-VASc and treatment classes was observed for HAS-BLED. A high HAS-BLED score has a 4-fold increase in hazard rate for antiplatelet drug TTI versus a low HAS-BLED score, perhaps reflecting the misconception that aspirin was safer than OAC for major bleeding and intracerebral hemorrhage.[29]

Patients treated with antiplatelets were younger, with higher HAS-BLED scores, and higher prevalence of prior stroke, bleeding, coronary artery disease, and paroxysmal AF versus patients treated with OACs. Similarly, previous cohort studies revealed factors associated with nonuse of OACs in the "DOAC era," for example, female sex, vascular disease, or prior intracerebral hemorrhage.[28,30]

Data from previous registries show variability in treatment at the regional or country level and locally, for example, at the state level (in the United States) in the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) program.[31] Koziel et al. discuss the prescription patterns in the GLORIA registry compared with other registries (Eurobservational Research Programme Atrial Fibrillation, ORBIT-AF, and GARFIELD-AF).[31–33] Treatment disparities and prescribing patterns may result from local practice variation rather than worldwide guidelines. Understanding this heterogeneity may improve the global quality of care for patients with AF.[34] Furthermore, TTI of OACs may be considered a novel quality indicator reflecting the "actual" status of AF therapy. Future research is necessary to assess the impact on clinical outcomes of different prescribing patterns and time to treatment initiation for anticoagulation drugs.

Limitations

The GLORIA-AF Registry, one of the largest *prospective* global studies of consecutive patients with recently diagnosed AF, is complementary to published trial data and retrospective reports from single countries.[35–37] This article presents a post hoc, exploratory analysis based on the GLORIA-AF Registry, which may pose a limitation. Generalizability of our results may be limited as the study population included only those with a CHA_2DS_2-VASc score ≥1. In this observational study, long-term OAC treatment was defined as either observed or prescribed at baseline. We analyzed neither changes/switches in treatment nor compliance nor the duration of the long-term OAC treatment. Furthermore, data contribution between regions were unbalanced, that is, nearly 50% of the cohort was enrolled in Europe and a relatively few patients were enrolled in Africa/Middle East and Latin America. Large global, heterogeneous cohorts, grouped into continental regions, may not reflect regional characteristics that modify the effect of site type on TTI and OAC use. Data on the quality of anticoagulation are not available.

A limitation of the Fine-Gray subdistribution hazard models is that the risk set includes patients who are currently event free as well as those who have previously experienced a competing event; only patients who experience the event of interest and those who are censored are removed from the risk set.

Table 4. The Multivariable Fine-Gray Model for Time-to-Initiation of Antiplatelet in the Presence of Competing Risks

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Region						
Asia	4237	1031 (24.3)	5.119	4.622, 5.669	3.924	3.509, 4.389
Europe	10 277	586 (5.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
North America	5097	619 (12.1)	2.133	1.906, 2.386	1.691	1.487, 1.923
Latin America	1626	135 (8.3)	1.448	1.202, 1.745	1.286	1.045, 1.583
Type of site						
GP/primary care	1318	248 (18.8)	1.634	1.418, 1.883	1.363	1.162, 1.597
Specialist office	6215	718 (11.6)	0.933	0.845, 1.032	1.091	0.970, 1.226
Community hospital	6250	501 (8.0)	0.646	0.578, 0.722	0.847	0.755, 0.950
University hospital	6755	804 (11.9)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Other	699	100 (14.3)	1.184	0.960, 1.460	1.927	1.522, 2.439
Body mass index class						
<18.5	284	44 (15.5)	1.082	0.795, 1.473	1.074	0.787, 1.465
18.5 to <25	5948	865 (14.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
25 to <30	8051	876 (10.9)	0.718	0.653, 0.789	0.945	0.858, 1.041
30 to <35	4183	369 (8.8)	0.569	0.504, 0.643	0.909	0.797, 1.036
≥35	2771	216 (7.8)	0.493	0.425, 0.572	0.837	0.714, 0.983
Smoking status						
Nonsmoker	12 535	1417 (11.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Current smoker	2089	327 (15.7)	1.439	1.274, 1.624	1.315	1.160, 1.492
Past smoker	6613	627 (9.5)	0.816	0.743, 0.897	0.903	0.818, 0.996
Physician specialty						
GP/primary care	1058	140 (13.2)	1.157	0.977, 1.370	1.207	0.999, 1.459
Cardiologist	18 053	2106 (11.7)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Neurologist	524	37 (7.1)	0.600	0.433, 0.832	0.616	0.440, 0.862
Internist	820	49 (6.0)	0.489	0.368, 0.649	0.677	0.505, 0.907
Other	782	39 (5.0)	0.410	0.299, 0.563	0.652	0.473, 0.898
Cardioversion						
Yes	3872	431 (11.1)	0.990	0.891, 1.100	1.038	0.934, 1.153
No	17 365	1940 (11.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
AF ablation						
Yes	384	23 (6.0)	0.509	0.338, 0.767	0.207	0.136, 0.314
No	20 853	2348 (11.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Chronic gastrointestinal disease						
Yes	2857	321 (11.2)	0.989	0.880, 1.111	0.869	0.771, 0.980
No	18 380	2050 (11.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
HAS–BLED (imputed) risk score class						
Low (score <3)	19 028	1713 (9.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (score ≥3)	2209	658 (29.8)	3.707	3.388, 4.057	4.219	3.824, 4.654
CHA_2DS_2–VASc score class						
Low (score=1 for women)	488	118 (24.2)	2.901	2.426, 3.468	2.663	2.188, 3.241
Moderate (score=1 for men or score=2 for women)	3965	594 (15.0)	1.582	1.441, 1.736	1.744	1.578, 1.928
High (score ≥2 for men or score ≥3 for women)	16 784	1659 (9.9)	1 (ref)	1 (ref)	1 (ref)	1 (ref)

(*Continued*)

Table 4. Continued

Variable	Total, n (100%)	DOAC, n (%)	Univariate		Multivariate	
			Hazard ratio	95% CI	Hazard ratio	95% CI
Type of AF						
Paroxysmal AF	11 969	1715 (14.3)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Persistent AF	7248	552 (7.6)	0.510	0.463, 0.561	0.584	0.531, 0.643
Permanent AF	2020	104 (5.1)	0.333	0.273, 0.405	0.471	0.387, 0.573
Cancer						
Yes	2142	184 (8.6)	0.731	0.629, 0.849	0.796	0.682, 0.929
No	19 096	2187 (11.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medical treatment reimbursed by						
Not self-pay	20 161	2253 (11.2)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Self-pay/no coverage	1076	118 (11.0)	0.975	0.808, 1.177	0.801	0.659, 0.974
Number of medications at baseline, nb						
Low (nb <3)	8357	1084 (13.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
High (nb ≥3)	12 880	1287 (10.0)	0.725	0.669, 0.786	0.874	0.801, 0.954

AF indicates atrial fibrillation; DOAC, direct-acting oral anticoagulants; GP, general practice; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; and nb, number of medications at baseline.

Several of the CIF curves cross, and therefore the proportional hazards assumption was violated in those cases. The hazard ratios from the Fine-Grey model, though not independent of time, can still be interpreted as an average hazard ratio over time. This article has not investigated how differences in timing of initiation of OAC affect clinical outcomes.

CONCLUSIONS

Regional differences in OAC use for stroke prevention in patients with AF exist. The TTI of OACs in patients with recently diagnosed AF varies by location and site type. DOACs were initiated in larger proportions in Europe and North America than in Latin America and Asia. Significant geographic variability in OAC use and differences in the TTI of OAC by type of site calls for implementation of consistent guideline recommendations and simplified AF treatment pathways. These should include education and awareness by targeting local health care models to improve outcomes and reduce health care costs.

ARTICLE INFORMATION

Received September 13, 2021; accepted January 6, 2022.

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Acknowledgments

Author contributions: Bayer, Kotalczyk, and Kea take responsibility for the integrity of the work as a whole, from inception to published article. Bayer, Kotalczyk, Kea, Teutsch, Larsen, Button, Huisman, Lip, and Olshansky made substantial contributions to the design of the work, data analysis or interpretation, drafted and critically revised for important intellectual content, approved the final version for publication, and agree to be accountable for the accuracy and integrity of the work. Bayer had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

This study was supported by Boehringer Ingelheim. The study sponsor was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and, review, or approval of the article.

Disclosures

Bayer is an employee of Boehringer Ingelheim. Kea is a site investigator for Abbott, Siemens, and Beckman. No fees are received personally. Teutsch is an employee of Boehringer Ingelheim Huisman has received research grants from Dutch Healthcare Fund, Dutch Heart Foundation, Bayer Health Care, Pfizer-BMS, Leo Pharma, and consulting fees from Boehringer Ingelheim, Bayer Health Care, Pfizer-BMS, to the LUMC. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Olshansky is a US co-coordinator for GLORIA-AF, DSMB Amarin, Consultant Sanofi, and a consultant for Lundbeck. The remaining authors have no disclosures to report.

Supplemental Material

Appendix S1
Figures S1–S6

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SUPPLEMENTAL MATERIAL

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Fernando Carvalho Neuenschwander	Beatriz Pérez	Shabbir Reza
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Anna Neykova	Alejandro Pérez-Cabezas	Dimitrios Richter
Ricardo Nicolás Miguel	Richard Perlman	Hans Rickli
George Nijmeh	Viktor Persic	Werner Rieker

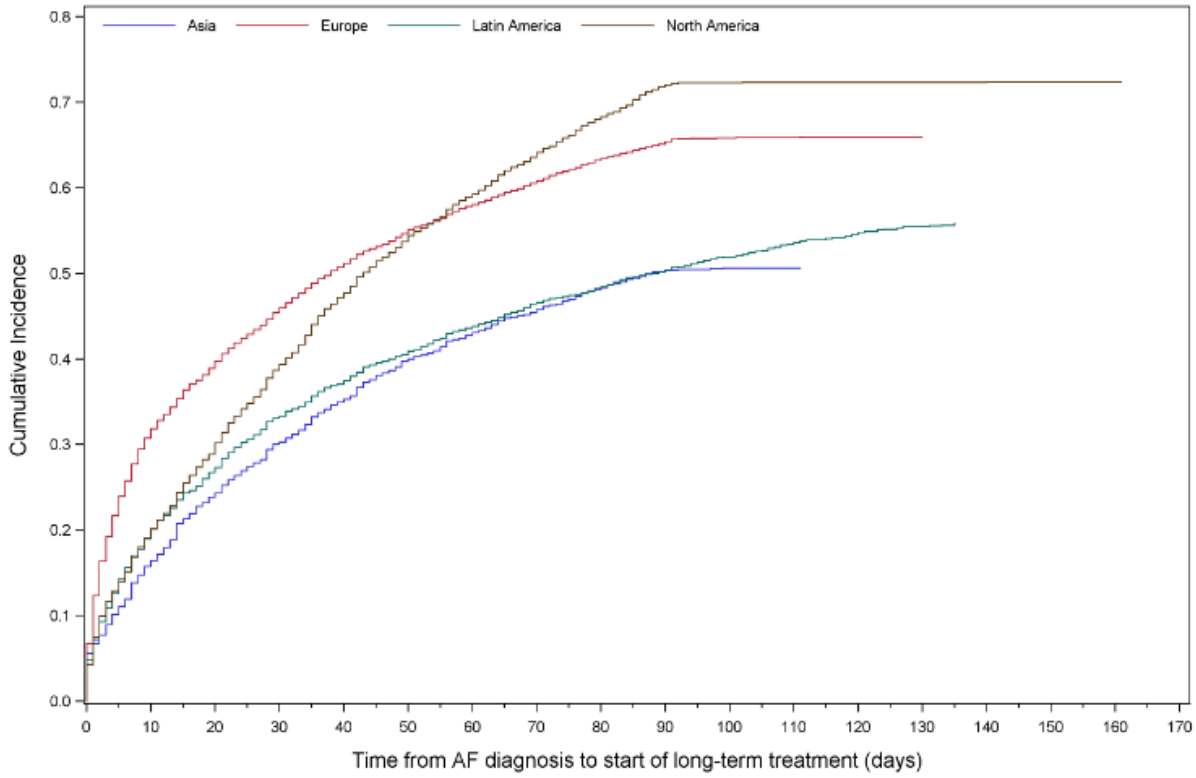
Alexey Nizov	Francesco Perticone	Tomas Ripolil Vera
Rodrigo Noronha Campos	Terri K. Peters	Luiz Eduardo Ritt
Janko Nossan	Sanjiv Petkar	Douglas Roberts
Tatiana Novikova	Luis Felipe Pezo	Ignacio Rodriguez Briones
Ewa Nowalany-Kozielska	Christian Pflücke	Aldo Edwin Rodriguez Escudero
Emmanuel Nsah	David N. Pham	Carlos Rodríguez Pascual
Juan Carlos Nunez Fragoso	Roland T. Phillips	Mark Roman
Svetlana Nurgalieva	Stephen Phlaum	Francesco Romeo
Dieter Nuyens	Denis Pieters	E. Ronner
Ole Nyvad	Julien Pineau	Jean-Francois Roux
Manuel Odin de Los Rios Ibarra	Arnold Pinter	Nadezda Rozkova
Philip O'Donnell	Fausto Pinto	Miroslav Rubacek
Martin O'Donnell	R. Pisters	Frank Rubalcava
Seil Oh	Nediljko Pivac	Andrea M. Russo
Yong Seog Oh	Darko Pocanic	Matthieu Pierre Rutgers
Dongjin Oh	Cristian Podoleanu	Karin Rybak
Gilles O'Hara	Alessandro Politano	Samir Said
Kostas Oikonomou	Zdravka Poljakovic	Tamotsu Sakamoto
Claudia Olivares	Stewart Pollock	Abraham Salacata
Richard Oliver	Jose Polo Garcéa	Adrien Salem
Rafael Olvera Ruiz	Holger Poppert	Rafael Salguero Bodes
Christoforos Olympios	Maurizio Porcu	Marco A. Saltzman
Anna omaszuk-Kazberuk	Antonio Pose Reino	Alessandro Salvioni
Joaquín Osca Asensi	Neeraj Prasad	Gregorio Sanchez Vallejo

Marcelo Sanmartín Fernández	Adam Sokal	Tian Ming Tu
Wladmir Faustino Saporito	Yannie Soo Oi Yan	Ype Tuininga
Kesari Sarikonda	Rodolfo Sotolongo	Minang Turakhia
Taishi Sasaoka	Olga Ferreira de Souza	Samir Turk
Hamdi Sati	Jon Arne Sparby	Wayne Turner
Irina Savelieva	Jindrich Spinar	Arnljot Tveit
Pierre-Jean Scala	David Sprigings	Richard Tytus
Peter Schellinger	Alex C. Spyropoulos	C Valadão
Carlos Scherr	Dimitrios Stakos	P.F.M.M. van Bergen
Lisa Schmitz	Clemens Steinwender	Philippe van de Borne
Karl-Heinz Schmitz	Georgios Stergiou	B.J. van den Berg
Bettina Schmitz	Ian Stiell	C van der Zwaan
Teresa Schnabel	Marcus Stoddard	M. Van Eck
Steffen Schnupp	Anastas Stoikov	Peter Vanacker
Peter Schoeniger	Witold Streb	Dimo Vasilev
Norbert Schön	Ioannis Styliadis	Vasileios Vasilikos
Peter Schwimmbeck	Guohai Su	Maxim Vasilyev
Clare Seamark	Xi Su	Srikar Veerareddy
Greg Searles	Wanda Sudnik	Mario Vega Miño
Karl-Heinz Seidl	Kai Sukles	Asok Venkataraman
Barry Seidman	Xiaofei Sun	Paolo Verdecchia
Jaroslaw Sek	H. Swart	Francesco Versaci
Lakshmanan Sekaran	Janko Szavits-Nossan	Ernst Günter Vester
Carlo Serrati	Jens Taggeselle	Hubert Vial
Neerav Shah	Yuichiro Takagi	Jason Victory
Vinay Shah	Amrit Pal Singh Takhar	Alejandro Villamil
Anil Shah	Angelika Tamm	Marc Vincent

Shujahat Shah	Katsumi Tanaka	Anthony Vlastaris
Vijay Kumar Sharma	Tanyanan Tanawuttiwat	Jürgen vom Dahl
Louise Shaw	Sherman Tang	Kishor Vora
Khalid H. Sheikh	Aylmer Tang	Robert B. Vranian
Naruhito Shimizu	Giovanni Tarsi	Paul Wakefield
Hideki Shimomura	Tiziana Tassinari	Ningfu Wang
Dong-Gu Shin	Ashis Tayal	Mingsheng Wang
Eun-Seok Shin	Muzahir Tayebjee	Xinhua Wang
Junya Shite	J.M. ten Berg	Feng Wang
Gerolamo Sibilio	Dan Tesloianu	Tian Wang
Frank Silver	Salem H.K. The	Alberta L. Warner
Iveta Sime	Dierk Thomas	Kouki Watanabe
Tim A. Simmers	Serge Timsit	Jeanne Wei
Narendra Singh	Tetsuya Tobaru	Christian Weimar
Peter Siostrzonek	Andrzej R. Tomasik.	Stanislav Weiner
Didier Smadja	Mikhail Torosoff	Renate Weinrich
David W. Smith	Emmanuel Touze	Ming-Shien Wen
Marcelo Snitman	Elina Trendafilova	Marcus Wiemer
Dario Sobral Filho	W. Kevin Tsai	Preben Wiggers
Hassan Soda	Hung Fat Tse	Andreas Wilke
Carl Sofley	Hiroshi Tsutsui	David Williams

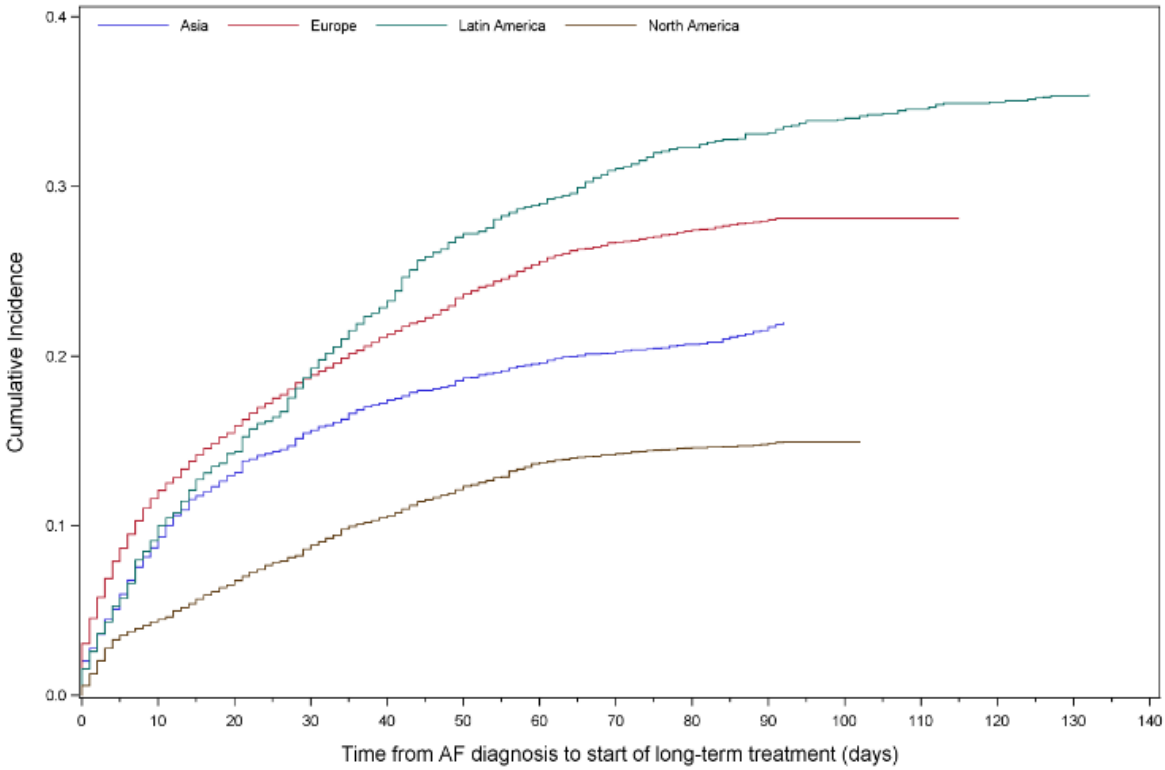
Marcus L. Williams	Ping Yen Bryan Yan	Ping Zhang
Bernhard Witzenbichler	Tianlun Yang	Jun Zhang
Brian Wong	Jing Yao	Shui Ping Zhao
Ka Sing Lawrence Wong	Kuo-Ho Yeh	Yujie Zhao
Beata Wozakowska-Kaplon	Wei Hsian Yin	Zhichen Zhao
Shulin Wu	Yoto Yotov	Yang Zheng
Richard C. Wu	Ralf Zahn	Jing Zhou
Silke Wunderlich	Stuart Zarich	Sergio Zimmermann
Nell Wyatt	Sergei Zenin	Andrea Zini
John (Jack) Wylie	Elisabeth Louise Zeuthen	Steven Zizzo
Yong Xu	Huanyi Zhang	Wenxia Zong
Xiangdong Xu	Donghui Zhang	L Steven Zukerman
Hiroki Yamanoue	Xingwei Zhang	
Takeshi Yamashita		

Figure S1. Time-to-Initiation of DOACs Stratified by Region.



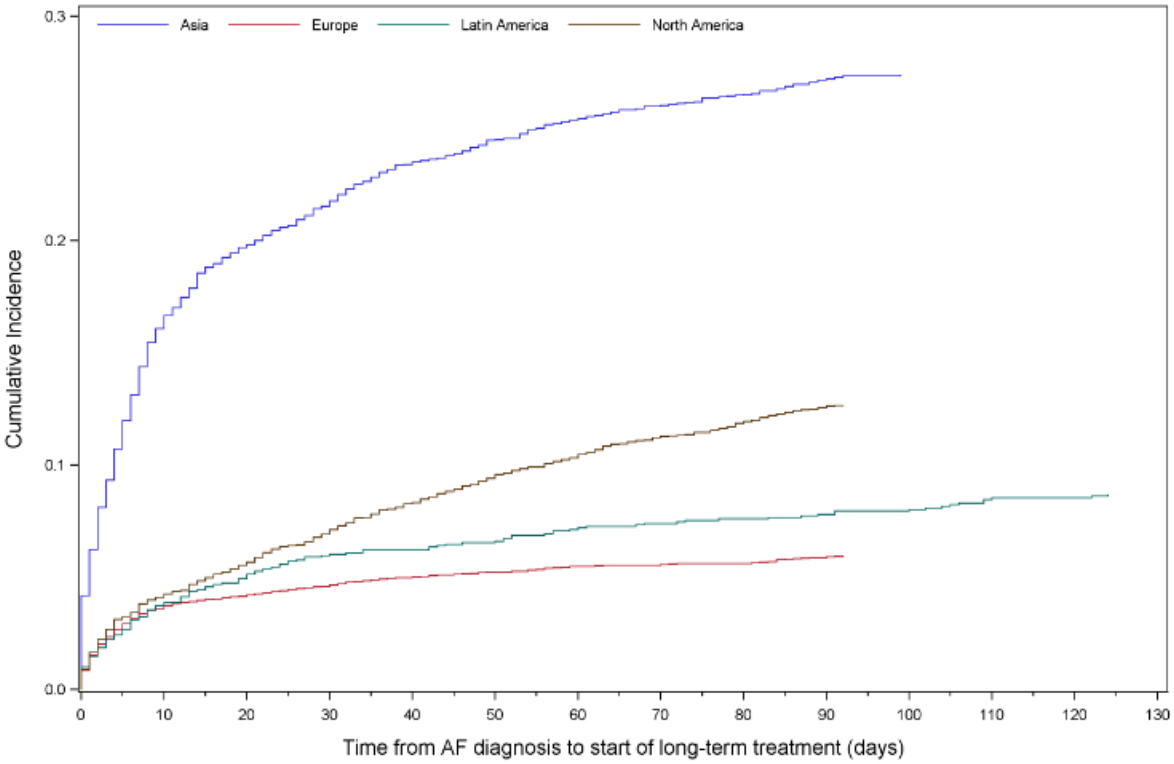
DOAC, direct-acting oral anticoagulants; AF, atrial fibrillation.

Figure S2. Time-to-Initiation of VKAs Stratified by Region.



VKA, vitamin K antagonist; AF, atrial fibrillation.

Figure S3. Time-to-Initiation of Antiplatelets Stratified by Region.



AF – atrial fibrillation

Figure S4. Time-to-Initiation of DOACs stratified by Treatment Site.

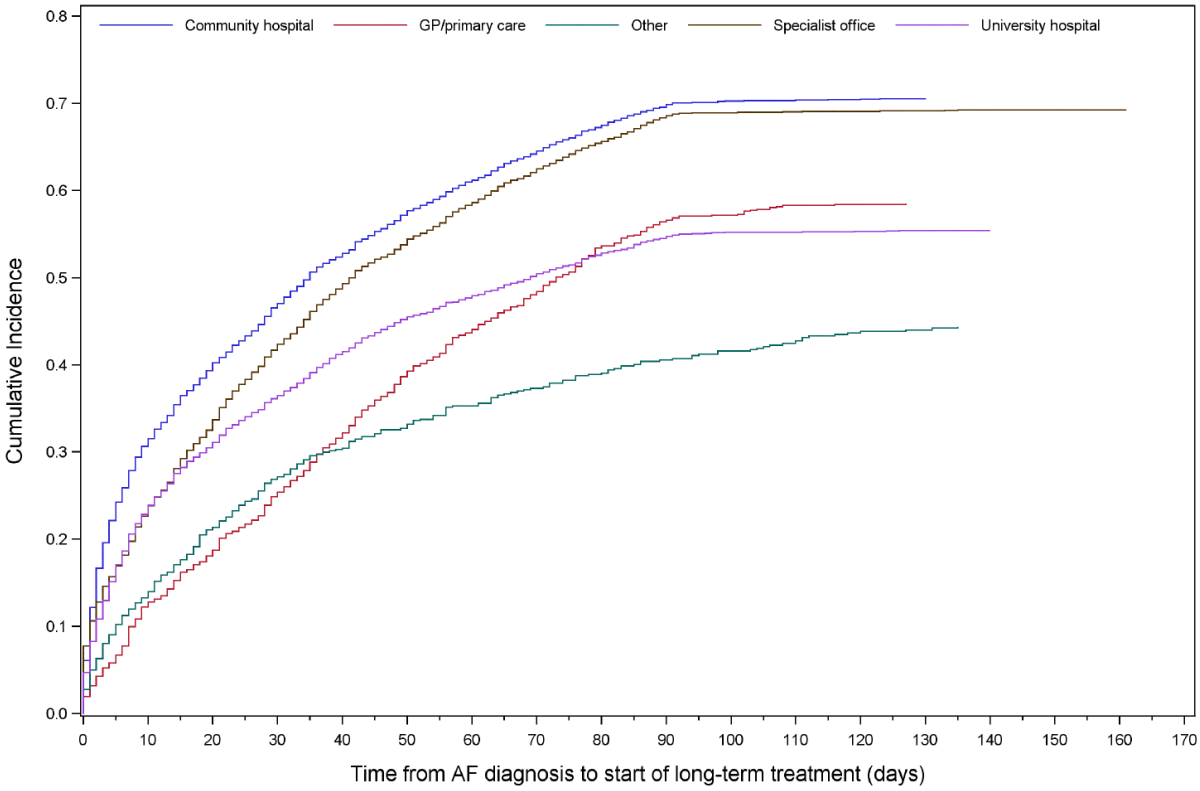


Figure S5. Time-to-Initiation of VKAs stratified by Treatment Site.

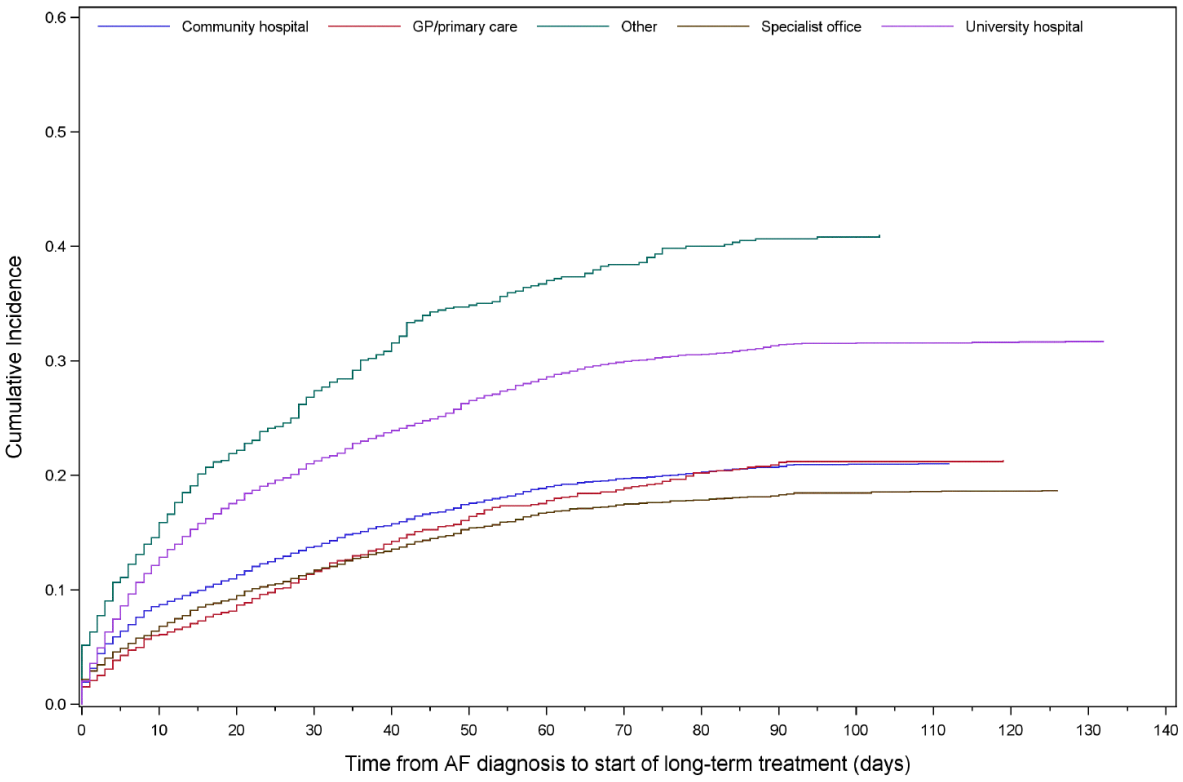


Figure S6. Time-to-Initiation of Antiplatelet Drugs stratified by Treatment Site.