Journal of the American Heart Association

ORIGINAL RESEARCH

Incidence and Risk Factors for Residual Adverse Events Despite Anticoagulation in Atrial Fibrillation: Results From Phase II/III of the GLORIA-AF Registry

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BACKGROUND: Residual risk of ischemic stroke despite anticoagulation in patients with atrial fibrillation (AF) represents a significant clinical issue that remains unaddressed. We aimed to evaluate the incidence and risk factors for residual adverse events in AF.

METHODS AND RESULTS: Using data from phase II/III of the prospective GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) registry, we studied anticoagulated patients with newly diagnosed AF and an increased risk of stroke (CHA_2DS_2-VASc ≥1). The primary outcome of interest was ischemic stroke. Secondary outcomes were all-cause death, cardiovascular death and myocardial infarction. A total of 22 410 patients were included; median age 65 (interquartile range 71–78) and 10 044 (44.8%) were female. During a median follow-up period of 3.0 (interquartile range 2.2–3.1) years, the incidence of ischemic stroke was 0.60 (95% CI, 0.54–0.67) per 100-PYs, all-cause death 3.22 (95% CI, 3.08–3.37) per 100-PYs, cardiovascular death 1.08 (95% CI, 1.00–1.16) per 100-PYs and myocardial infarction 0.59 (95% CI, 0.53–0.66) per 100-PYs. Using multivariable Cox proportional hazards analysis, independent predictors of residual ischemic stroke were age (HR 1.05 [95% CI, 1.03–1.07]), diabetes (HR 1.42 [95% CI, 1.08–1.87]), prior thromboembolism (HR 2.27 [95% CI, 1.73–2.98]) and use of antiarrhythmic drugs (HR 0.66 [95% CI, 0.47–0.92]). The incidence of ischemic stroke was comparable among patients treated with nonvitamin K antagonist oral anticoagulants versus vitamin K antagonist; however, there were differences in the independent predictors between both groups.

CONCLUSIONS: Patients with AF remain at significant residual risk of developing complications including ischemic stroke despite anticoagulation therapy. Further efforts among these patients should be directed at the management of modifiable risk factors that contribute to this risk.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifiers: NCT01468701, NCT01671007 and NCT01937377.

Key Words: adverse events ■ anticoagulation ■ ischemic stroke ■ newly diagnosed atrial fibrillation ■ predictors ■ residual risk ■ residual stroke

Atrial fibrillation (AF) is linked to an excess risk of ischemic stroke,[1] through various pathophysiological mechanisms that contribute to thromboembolic complications.[2] Therefore, the management of patients with AF emphasizes stroke prevention with oral anticoagulation therapy in all patients

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026410

For Sources of Funding and Disclosures, see page 8.

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

CLINICAL PERSPECTIVE

What Is New?

- The residual risk of ischemic stroke among anticoagulated patients with atrial fibrillation and a median CHA_2DS_2-VASc score of 4 was 0.60 per 100 PYs.
- Predictors of residual ischemic stroke were prior thromboembolism, age, persistent atrial fibrillation, diabetes, chronic obstructive pulmonary disease and nonuse of antiarrhythmic drugs.

What Are the Clinical Implications?

- The findings from this study emphasize the need for optimization of risk factors in atrial fibrillation beyond mere anticoagulation.

Nonstandard Abbreviations and Acronyms

GLORIA-AF	Global Registry on Long-Term Oral Anti-thrombotic Treatment in Patients With Atrial Fibrillation
NOAC	nonvitamin K antagonist oral anticoagulation
PYs	person-years
VKA	vitamin K antagonist

unless they are at low-risk.[3–6] However, it is recognized that anticoagulation alone does not negate the risk of ischemic stroke but merely reduces the probability of this occurrence. As such, a proportion of patients with AF will suffer from residual ischemic stroke despite receiving adequate anticoagulation therapy.[7] Attention to other comorbidities is therefore recommended, as part of the holistic approach to AF care,[8] given the improved outcomes evident with adherence to such an approach.[9]

Presently, the residual risk of ischemic stroke in patients with AF treated with anticoagulation therapy remains poorly defined though estimates of a broader complication of thromboembolism (includes stroke and systemic embolism) associated with warfarin use was 1.66% per year.[10] The authors reported an increased risk of thromboembolism with additional risk factors based on the simple $CHADS_2$ score; however, it should be noted that the $CHADS_2$ risk stratification schema which was developed to assess stroke risk in nonanticoagulated patients with AF has not been validated for this purpose.[11] Furthermore, in clinical practice, the management of these patients remains a significant challenge as there are limited studies for the basis of any treatment decisions. Overall, research focused on the clinically relevant topic of residual risk of ischemic stroke in AF is lacking. This is important given the increasing prevalence of AF, with its associated increasing health care costs.[12]

Herein, we aimed to evaluate the incidence and risk factors for residual adverse events including ischemic stroke in a contemporary global cohort of anticoagulation patients with AF using the prospective GLORIA-AF (Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation) registry.

METHODS

Study Design and Population

GLORIA-AF is a prospective, observational, global registry program of patients from 935 centers across 38 participating countries in Asia, Europe, North America, Latin America, and Africa/Middle East. The study design has previously been described.[13] In brief, adults with newly diagnosed AF (<3 months before baseline visit) and an increased risk of stroke (CHA_2DS_2-VASc ≥1) were enrolled. This study comprised patients from GLORIA-AF phase II and III, enrolled between 2011 and 2020. Eligible patients who were treated with anticoagulation and had follow-up data were included. Main exclusion criteria were presence of mechanical heart valve or valvular disease requiring valve replacement, previous oral anticoagulation with vitamin K oral antagonist over 60 days, a reversible cause of AF, indication for anticoagulation other than AF, and life expectancy under 1 year. Ethics approval was obtained from local institutional review boards, informed consent was obtained from patients, and the study was performed in accordance with the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection and Definition

Data on demographics, comorbidities and therapies were collected at enrollment with standardized, prospectively designed data collection tools. Creatinine clearance was calculated using the Cockcroft-Gault equation.[14] AF classification was defined according to the European Society of Cardiology recommendations.[15] Severity of AF-related symptoms was ascertained using the European Heart Rhythm Association classification.[16] $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores were determined as previously described.[11,17,18]

Study Outcomes and Follow-Up

The primary outcome of interest was the pre-specified event of ischemic stroke. Secondary outcomes of interest were all-cause death, cardiovascular death and myocardial infarction. Stroke was defined as an acute

onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more, or resulting in death. The categorization of ischaemic cause was established using computed tomography or magnetic resonance scanning, or autopsy. Myocardial infarction was defined as the development of significant Q-waves in at least 2 adjacent electrocardiogram leads, or at least 2 of the following 3 criteria: (1) typical prolonged severe chest pain of at least 30 minutes; (2) electrocardiographic changes suggestive of myocardial infarction including ST-changes or T wave inversion in the electrocardiogram; (3) elevation of troponin or creatinine kinase-MB to more than upper level of normal or, if creatinine kinase-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level. In phase II, follow-up for the dabigatran cohort was performed for 2 years, with scheduled visits at 3, 6, 12, and 24 months. In phase III, follow-up for all patients was conducted for 3 years, with scheduled visits at 6, 12, 24, and 36 months.

Statistical Analysis

Continuous variables were presented as median and interquartile range, and measured for differences with Kruskal-Wallis test. Categorical variables were presented as count and percentage, and measured for differences with chi-squared test. The incidence rates (number of events per 100 person-years [PYs] at risk) and incidence rate ratio with 95% CIs for the outcomes of interest were calculated using previously described methods.[19–21] Risk factors for residual ischemic stroke despite anticoagulation in patients with AF were identified using Cox proportional hazards analyses. Multivariable models were used to account for potential confounders. Model 1 included covariates with a $P<0.10$ in the univariate analysis. Model 2 (primary) included the following covariates which have been reported to influence the outcome: age, sex, systolic blood pressure, body mass index, creatinine clearance, type of AF, hypertension, hypercholesterolemia, diabetes, coronary artery disease, heart failure, left ventricular hypertrophy, prior thromboembolism, peripheral artery disease, AF ablation, antiplatelet use, antiarrhythmic drug therapy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and statin therapy. Plots of Kaplan–Meier curves were used to compare the primary outcome of interest between patients who were treated with nonvitamin K antagonist oral anticoagulation (NOAC) and vitamin K antagonist (VKA), and survival distributions were tested with log-rank test. Further subgroup analyses were performed to determine if risk factors differed according to anticoagulation agent. A 2-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed using RStudio (Version 1.3.1093).

RESULTS

A total of 22 410 patients with newly diagnosed AF were included in this study (Figure S1). The median age was 65 (interquartile range 71–78) and 10 044 (44.8%) were female. Baseline characteristics of patients who suffered an ischemic stroke compared with those without an ischemic stroke during the study period are shown in Table 1. Patients who had an ischemic stroke were significantly older with higher systolic blood pressure, lower body mass index and creatinine clearance, more advanced forms of AF, and greater comorbidities including hypercholesterolemia, prior thromboembolism, prior stroke and chronic obstructive pulmonary disease. The prevalence of hypertension, diabetes, coronary artery disease, heart failure, left ventricular hypertrophy, prior bleeding and peripheral artery disease were comparable between the groups.

Patients with an ischemic stroke were less likely to have been treated with an antiarrhythmic drug at enrollment and more likely to have received statin therapy (Table 2). The choice of anticoagulation agent and use of AF ablation, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, digoxin, and diuretic therapy were not statistically different between both groups.

Incidence of Adverse Events

During a median follow-up period of 3.0 (interquartile range 2.2–3.1) years, there were 361 (1.6%) ischemic stroke events, 1918 (8.6%) all-cause death, 648 (3.0%) cardiovascular death and 357 (1.6%) myocardial infarction. Despite anticoagulation therapy, the incidence of ischemic stroke was 0.60 (95% CI, 0.54–0.67) per 100 PYs, all-cause death 3.22 (95% CI, 3.08–3.37) per 100 PYs, cardiovascular death 1.08 (95% CI, 1.00–1.16) per 100 PYs and myocardial infarction 0.59 (95% CI, 0.53–0.66) per 100 PYs.

In the primary prevention subgroup of patients with no prior history of stroke, the incidence of ischemic stroke was 0.49 (95% CI, 0.44–0.56) per 100 PYs while among the secondary prevention subgroup of patients with prior stroke, the incidence was 1.54 (95% CI, 1.25–1.88) per 100 PYs. The incidence rate ratio of ischemic stroke between the secondary versus primary prevention subgroups was 3.12 (95% CI, 2.44–3.96) per 100 PYs.

Risk Factors for Residual Ischemic Stroke

Using univariate Cox proportional hazards analyses, risk factors for residual ischemic stroke among anticoagulated patients were age, systolic blood pressure, body mass index, creatinine clearance, AF classification, hypercholesterolemia, diabetes, prior thromboembolism,

Table 1. Baseline Characteristics

Baseline characteristics	Ischemic stroke (n=361)	No ischemic stroke (n=22 049)	*P* value
Age (y), median (IQR)	76 (70–81)	71 (65–78)	<0.001
Female sex, n (%)	171 (47.4)	9873 (44.8)	0.353
Heart rate (bpm), median (IQR)	77 (65–90)	76 (65–90)	0.851
sBP (mm Hg), median (IQR)	134 (121–145)	130 (120–142)	0.029
BMI (kg/m^2), median (IQR)	27.1 (23.8–31.0)	27.8 (24.8–31.8)	0.003
CrCl (mL/min), median (IQR)	64.9 (48.7–87.0)	75.6 (57.4–98.5)	<0.001
AF classification, n (%)			0.026
Paroxysmal	168 (46.5)	11 718 (53.1)	
Persistent	142 (39.3)	7905 (35.9)	
Permanent	51 (14.1)	2426 (11.0)	
EHRA classification, n (%)			<0.001
I	153 (44.1)	7523 (36.4)	
II	94 (27.1)	7793 (37.7)	
III	70 (20.2)	4117 (19.9)	
IV	30 (8.7)	1214 (5.9)	
Comorbidities, n (%)			
Hypertension	286 (79.2)	16 833 (76.5)	0.254
Hypercholesterolemia	167 (47.4)	9023 (42.1)	0.049
Diabetes	101 (28.0)	5184 (23.5)	0.055
Coronary artery disease	73 (20.7)	3919 (18.3)	0.259
Congestive heart failure	85 (23.8)	4958 (22.7)	0.657
Left ventricular hypertrophy	72 (20.7)	4262 (20.3)	0.884
Prior thromboembolism	116 (32.1)	3230 (14.6)	<0.001
Prior stroke	95 (26.3)	2295 (10.4)	<0.001
Prior bleeding	21 (5.9)	1097 (5.1)	0.573
Peripheral artery disease	17 (4.7)	636 (2.9)	0.062
COPD	33 (9.1)	1352 (6.2)	0.029
$CHADS_2$ score, median (IQR)	2 (2–3)	2 (1–3)	<0.001
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	3 (2–4)	<0.001
HAS-BLED score, median (IQR)	1 (1–2)	1 (1–2)	<0.001

AF indicates atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; EHRA, European Heart Rhythm Association; IQR, interquartile range; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; and sBP, systolic blood pressure.

peripheral artery disease, chronic obstructive pulmonary disease, nonuse of antiarrhythmic drug and use of statin therapy (Table 3). After adjusting for the various confounders in Model 1, independent predictors of residual ischemic stroke were age, diabetes, prior thromboembolism, chronic obstructive pulmonary disease and nonuse of an antiarrhythmic drug. In Model 2, the independent predictors were age, persistent AF, diabetes, prior thromboembolism and nonuse of antiarrhythmic drug (Figure). Female sex, systolic blood pressure, body mass index, hypertension, hypercholesterolemia, coronary artery disease, heart failure, left ventricular hypertrophy, peripheral artery disease, AF ablation, antiplatelet, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, digoxin and statin therapy were not found to be associated with residual ischemic stroke.

Additional and Subgroup Analysis

There were 17 574 (78.4%) patients on NOAC and 4836 (21.6%) on VKA therapy. Baseline characteristics and medication use/therapies based on the type of anticoagulation at enrollment are described in Tables S1 and S2, respectively. The incidence of ischemic stroke was 0.59 (95% CI, 0.53–0.67) per 100 PYs in the NOAC subgroup and 0.62 (95% CI, 0.49–0.76) per 100 PYs in the VKA subgroup.

Using Kaplan–Meier survival analysis, there was no significant difference in the primary outcome of ischemic stroke between patients who were treated with NOAC versus VKA therapy (log-rank *P*=0.73).

Table 2. Medication Use and Therapies at Enrollment

Medication use and therapies	Ischemic stroke (n=361)	No ischemic stroke (n=22 049)	*P* value
Atrial fibrillation ablation	4 (1.1%)	398 (1.8%)	0.419
Anticoagulation agent, n (%)			0.190
Apixaban	83 (23.0)	4422 (20.1)	
Dabigatran	119 (33.0)	8603 (39.0)	
Edoxaban	7 (1.9)	325 (1.5)	
Rivaroxaban	67 (18.6)	3948 (17.9)	
Vitamin K antagonist	85 (23.5)	4751 (21.5)	
Antiplatelet, n (%)	69 (19.1)	3855 (17.5)	0.460
Antiarrhythmic drug, n (%)	62 (17.2)	5849 (26.5)	<0.001
Angiotensin-converting enzyme inhibitor, n (%)	119 (33.0)	7047 (32.0)	0.727
Angiotensin receptor blocker, n (%)	85 (23.5)	5835 (26.5)	0.235
Beta blocker, n (%)	233 (64.5)	14 201 (64.4)	1.000
Digoxin, n (%)	41 (11.4)	1895 (8.6)	0.079
Diuretic, n (%)	145 (40.2)	8780 (39.8)	0.937
Statin, n (%)	189 (52.4)	9861 (44.7)	0.005

Among NOAC-treated patients with AF, predictors for residual ischemic stroke were age, diabetes, prior thromboembolism and chronic obstructive pulmonary disease (Table S3). Meanwhile, predictors for residual ischemic stroke among VKA-treated patients with AF were age, prior thromboembolism, and use of antiplatelet therapy, angiotensin receptor blocker and digoxin (Table S4).

DISCUSSION

In this study of patients from the large, global, prospective GLORIA-AF registry with newly diagnosed AF and a median CHA_2DS_2-VASc score of 4, the incidence of ischemic stroke was 0.60 per 100 PYs despite anticoagulation therapy with a higher incidence among patients who were on secondary prevention therapy. Second, prior thromboembolism was the greatest risk factor for residual ischemic stroke with a 2.3-fold increase in risk, while other predictors of residual ischemic stroke were age, persistent AF, diabetes, chronic obstructive pulmonary disease and nonuse of antiarrhythmic drug. Third, the residual risk of ischemic stroke was comparable between patients treated with NOAC versus VKA therapy though independent predictors of events differed according to the choice of anticoagulation. The novelty of this study lies in the contemporary nature of the study cohort, inclusion of patients treated with NOAC therapy, and in-depth examination of various comorbidities and therapeutic aspects.

The incidence of residual ischemic stroke among anticoagulated patients with AF in this study was lower compared with previous landmark randomized controlled trials on NOAC therapy,[22–25] likely reflecting the patient characteristics with less comorbidities in this study, better contemporary management of diseases and the inclusion of patients with newly diagnosed AF who have less advanced forms of the condition and who may be at lower risk of adverse outcomes.[26,27] Previous observational studies in patients with AF reported a higher incidence of all-cause death (6.3 per 100 PYs), predominantly from cardiovascular causes,[28] and myocardial infarction (1.2 per 100 PYs)[29] compared with this study. Differences in the results may be attributed to the low uptake (<20%) of anticoagulation in both these studies, though the patients were generally younger and with less comorbidities. Notably, the study by Lee et al was performed using data from the Korean National Health Insurance Service which were identified using *ICD-10* codes.[28] Interestingly, our incidence of myocardial infarction closely resembled that of patients without AF (0.6 per 100 PYs).[29] A meta-analysis of 30 cohort studies with over 4 million patients found that the pooled event rates for all cause death was 1.8 per 100 PYs for the entire cohort while cardiovascular death was 1.0 per 100 PYs (men) and 0.6 per 100 PYs (women), stroke was 0.3 per 100 PYs for the entire cohort, and coronary heart disease was 0.6 per 100 PYs (men) and 0.3 per 100 PYs (women).[30]

Risk factors of residual ischemic stroke in AF remains poorly defined and previous studies have suggested that although there is a degree of overlap with traditional risk factors among nonanticoagulated patients with AF, there are important differences to consider. A retrospective cohort study of 11 848 patients with AF using health check-ups and insurance claims data of Japanese health insurance companies found that older age, hypertension, hyperlipidemia and greater CHA_2DS_2-VASc score were independent predictors of residual thromboembolism.[31] Post hoc analysis of the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) randomized controlled trial demonstrated that permanent AF, worsening renal function, prior stroke and prior coronary artery disease were independently associated with a residual risk of the composite outcome of thromboembolism and cardiovascular death.[32] A meta-analysis of 6 randomized controlled trials comprised of 58 883 patients found that age ≥75 years, female sex, previous stroke or transient ischemic attack, VKA naïve status, renal failure, previous aspirin use, Asian race and greater $CHADS_2$ score contributed to a higher risk of residual stroke in AF.[33] Another meta-analysis demonstrated that female sex was linked to a higher risk of thromboembolism in patients on VKA therapy but not NOAC.[34]

In this study, we found that increasing age, persistent AF, diabetes, prior thromboembolism, chronic

Table 3. Risk Factors for Residual Risk of Ischemic Stroke in Anticoagulated Patients With AF

	Univariate		Multivariate			
			Model 1*		Model 2†	
Risk factor	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value
Age (per y)	1.05 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001	1.05 (1.03–1.07)	<0.001
Female sex	1.10 (0.89–1.36)	0.370			0.98 (0.76–1.26)	0.873
Heart rate (per bpm)	1.00 (0.99–1.00)	0.740				
Systolic blood pressure (per mmHg)	1.01 (1.00–1.01)	0.043	1.01 (1.00–1.01)	0.095	1.01 (1.00–1.01)	0.067
BMI (per kg/m^2)	0.97 (0.96–0.99)	0.006	0.99 (0.97–1.02)	0.586	0.99 (0.97–1.02)	0.525
CrCl (per mL/min)	0.99 (0.99–0.99)	<0.001	1.00 (0.99–1.00)	0.663	1.00 (1.00–1.00)	0.953
AF classification						
Paroxysmal	Reference		Reference		Reference	
Persistent	1.29 (1.03–1.62)	0.029	1.24 (0.96–1.60)	0.093	1.34 (1.03–1.75)	0.030
Permanent	1.54 (1.12–2.12)	0.008	1.14 (0.78–1.65)	0.503	1.28 (0.87–1.87)	0.214
Hypertension	1.21 (0.93–1.58)	0.150			1.28 (0.91–1.79)	0.158
Hypercholesterolemia	1.29 (1.05–1.60)	0.018	1.19 (0.90–1.55)	0.219	1.18 (0.89–1.57)	0.251
Diabetes	1.31 (1.04–1.66)	0.022	1.42 (1.09–1.85)	0.009	1.42 (1.08–1.87)	0.011
Coronary artery disease	1.22 (0.94–1.58)	0.140			1.03 (0.73–1.43)	0.884
Congestive heart failure	1.11 (0.87–1.42)	0.410			1.24 (0.92–1.68)	0.159
Left ventricular hypertrophy	1.02 (0.78–1.33)	0.870			1.01 (0.74–1.36)	0.967
Prior thromboembolism	2.80 (2.23–3.50)	<0.001	2.32 (1.79–3.00)	<0.001	2.27 (1.73–2.98)	<0.001
Prior bleeding	1.23 (0.79–1.91)	0.360				
Peripheral artery disease	1.79 (1.10–2.91)	0.020	1.32 (0.78–2.25)	0.299	1.15 (0.64–2.08)	0.643
COPD	1.60 (1.11–2.31)	0.011	1.53 (1.04–2.26)	0.031		
AF ablation	0.45 (0.15–1.41)	0.170			0.88 (0.28–2.77)	0.823
Antiplatelet	1.08 (0.82–1.41)	0.590			0.91 (0.66–1.27)	0.593
Antiarrhythmic drug	0.55 (0.41–0.73)	<0.001	0.70 (0.51–0.96)	0.025	0.66 (0.47–0.92)	0.013
ACE-i	1.03 (0.82–1.29)	0.800			0.83 (0.62–1.11)	0.201
Angiotensin receptor blocker	0.86 (0.67–1.10)	0.230			0.76 (0.56–1.05)	0.098
Beta-blocker	1.03 (0.82–1.28)	0.810				
Digoxin	1.38 (0.99–1.93)	0.057	1.39 (0.95–2.02)	0.086		
Diuretic	1.03 (0.83–1.27)	0.810				
Statin	1.39 (1.13–1.72)	0.002	1.04 (0.79–1.37)	0.797	1.12 (0.84–1.50)	0.445

ACE-i indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; and HR, hazard ratio.

*Adjusted for risk factors with *P*<0.10 on univariate analysis; includes age, systolic blood pressure, BMI, CrCl, type of AF, hypercholesterolemia, diabetes, prior thromboembolism, peripheral artery disease, COPD, antiarrhythmic drug therapy, digoxin, and statin therapy.

†Adjusted for age, sex, systolic blood pressure, BMI, CrCl, type of AF, hypertension, hypercholesterolemia, diabetes, coronary artery disease, heart failure, left ventricular hypertrophy, prior thromboembolism, peripheral artery disease, AF ablation, antiplatelet use, antiarrhythmic drug therapy, ACE-i, angiotensin receptor blocker and statin therapy.

obstructive pulmonary disease and nonuse of antiarrhythmic drugs were independent predictors of residual ischemic stroke. Compared with aforementioned studies, we undertook a rigorous assessment to identify potential risk factors and studied the effects of additional variables such as body mass index, chronic obstructive pulmonary disease, AF ablation and antiarrhythmic drug therapy. In contrast to previous reports,[35–37] we were unable to demonstrate the benefit of AF ablation in terms of stroke prevention among anticoagulated patients. This discrepancy may be explained by the low number of patients (1.8%) who received AF ablation in our cohort as those who were treated with an antiarrhythmic drug at enrollment had a 30% to 34% reduction in the residual risk of ischemic stroke, thereby confirming the prognostic benefit of early rhythm control therapy in AF.[38]

The superiority of NOACs over VKA therapy in terms of effectiveness and safety has previously been demonstrated,[39–42] although no statistical difference in the risk of ischemic stroke was observed in this study. Of note, patients on VKA therapy had higher CHA_2DS_2-VASc score compared with those on NOAC which may have attenuated the findings. Interestingly, predictors of

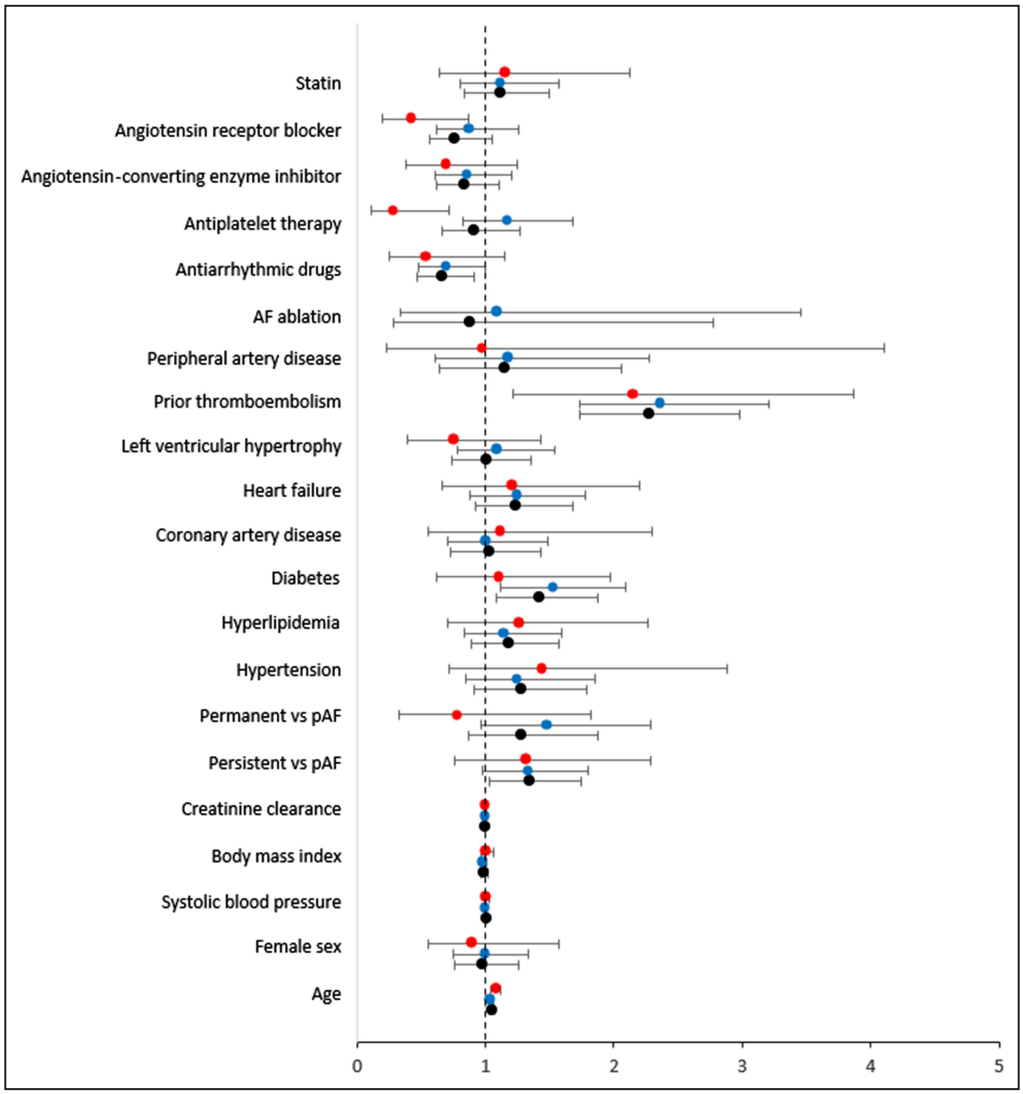

Figure. Risk factors for residual risk of ischemic stroke among anticoagulated patients with atrial fibrillation.
Black dot=overall cohort; blue dot=NOAC subgroup; red dot=VKA subgroup. AF indicates atrial fibrillation; NOAC, nonvitamin K antagonist oral anticoagulant; pAF, paroxysmal AF; and VKA, vitamin K antagonist.

residual ischemic stroke varied according to the choice of anticoagulation (NOAC versus VKA) but there was no influence of sex, as previously reported.[34] Notably, in patients who may suffer from residual ischemic stroke, NOACs have been found to be more effective and safer for secondary stroke prevention compared with warfarin.[43]

Limitations

The main limitations of this study are related to possible misclassification and selection biases because of its observational nature. We performed extensive model adjustment to account for possible confounders to the residual risk of ischemic stroke in AF. However, we are unable to confirm a cause-effect relationship as residual unmeasured confounders may exist. The current study does not account for possible changes in anticoagulation status during follow-up. As the GLORIA-AF registry enrolled patients with newly diagnosed AF, the results presented here may not be applicable to the wider AF population. Furthermore, because of the low number of events in the VKA subgroup and potential overfitting in the multivariable Cox proportional hazards model, the results of this subgroup analysis may have occurred by chance. Finally, we did not explore the residual risk of ischemic stroke in patients with a prior history of stroke.

CONCLUSIONS

Patients with AF remain at significant risk of ischemic stroke despite anticoagulation therapy. Risk factors for residual ischemic stroke were prior thromboembolism,

age, persistent AF, diabetes, chronic obstructive pulmonary disease and nonuse of antiarrhythmic drug therapy. This emphasizes the need to treat these risk factors, if modifiable, beyond antithrombotic therapy.

ARTICLE INFORMATION

Received April 29, 2022; accepted June 27, 2022.

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Acknowledgments

The authors thank the patients who participated in this registry, their families, the investigators, study co-ordinators, and study teams. The authors also extend a special thanks to Dr Christine Teutsch. This publication is based on research using data from data contributors Boehringer Ingelheim that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Sources of Funding

The GLORIA-AF registry was sponsored by Boehringer Ingelheim GmbH. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Disclosures

Lane has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS), has been a speaker for Bayer, Boehringer Ingeheim, and BMS/Pfizer and has consulted for BMS, and Boehringer Ingelheim. Gupta: Speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Biosense Webster and Boston Scientific. Proctor for Abbott. Research Grants from Medtronic, Biosense Webster and Boston Scientific. Huisman: Research grants from Dutch Healthcare Fund, Dutch Heart Foundation, Bayer Health Care, Pfizer-BMS and Leo Pharma, and consulting fees from Boehringer Ingelheim, Bayer Health Care and Pfizer-BMS. Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Other authors declare no conflict of interest.

Supplemental Material

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Hugh McIntyre
Brent McLaurin
Feliz Alvaro Medina Palomino
Francesco Melandri
Hiroshi Meno
Dhananjai Menzies
Marco Mercader
Christian Meyer
Beat j. Meyer
Jacek Miarka
Frank Mibach
Dominik Michalski
Patrik Michel
Rami Mihail Chreih
Ghiath Mikdadi
Milan Mikus
Davor Milicic
Constantin Militaru
Sedi Minaie
Bogdan Minescu
Iveta Mintale
Tristan Mirault
Michael J. Mirro
Dinesh Mistry
Nicoleta Violeta Miu
Naomasa Miyamoto
Tiziano Moccetti
Akber Mohammed
Azlisham Mohd Nor
Michael Mollerus
Giulio Molon
Sergio Mondillo
Patrícia Moniz
Lluis Mont
Vicente Montagud
Oscar Montaña
Cristina Monti
Luciano Moretti
Kiyoo Mori
Andrew Moriarty
Jacek Morka
Luigi Moschini
Nikitas Moschos
Andreas Mügge
Thomas J. Mulhearn
Carmen Muresan
Michela Muriago
Wlodzimierz Musial
Carl W. Musser
Francesco Musumeci
Thuraia Nageh
Hidemitsu Nakagawa
Yuichiro Nakamura
Toru Nakayama
Gi-Byoung Nam
Michele Nanna
Indira Natarajan
Hemal M. Nayak
Stefan Naydenov
Jurica Nazlić
Alexandru Cristian Nechita

Libor Nechvatal
Sandra Adela Negron
James Neiman
Fernando Carvalho Neuenschwander
David Neves
Anna Neykova
Ricardo Nicolás Miguel
George Nijmeh
Alexey Nizov
Rodrigo Noronha Campos
Janko Nossan
Tatiana Novikova
Ewa Nowalany-Kozielska
Emmanuel Nsah
Juan Carlos Nunez Fragoso
Svetlana Nurgalieva
Dieter Nuyens
Ole Nyvad
Manuel Odin de Los Rios Ibarra
Philip O'Donnell
Martin O'Donnell
Seil Oh
Yong Seog Oh
Dongjin Oh
Gilles O'Hara
Kostas Oikonomou
Claudia Olivares
Richard Oliver
Rafael Olvera Ruiz
Christoforos Olympios
Anna omaszuk-Kazberuk
Joaquín Osca Asensi
eena Padayattil jose
Francisco Gerardo Padilla Padilla
Victoria Padilla Rios
Giuseppe Pajes
A. Shekhar Pandey
Gaetano Paparella
F Paris
Hyung Wook Park
Jong Sung Park
Fragkiskos Parthenakis
Enrico Passamonti
Rajesh J. Patel
Jaydutt Patel
Mehool Patel
Janice Patrick
Ricardo Pavón Jimenez
Analía Paz
Vittorio Pengo
William Pentz
Beatriz Pérez
Alma Minerva Pérez Ríos
Alejandro Pérez-Cabezas
Richard Perlman
Viktor Persic
Francesco Perticone
Terri K. Peters
Sanjiv Petkar
Luis Felipe Pezo
Christian Pflücke
David N. Pham
Roland T. Phillips
Stephen Phlaum
Denis Pieters
Julien Pineau
Arnold Pinter
Fausto Pinto
R. Pisters
Nediljko Pivac
Darko Pocanic
Cristian Podoleanu
Alessandro Politano
Zdravka Poljakovic
Stewart Pollock
Jose Polo Garcéa
Holger Poppert
Maurizio Porcu
Antonio Pose Reino
Neeraj Prasad
Dalton Bertolim Précoma
Alessandro Prelle
John Prodafikas
Konstantin Protasov
Maurice Pye
Zhaohui Qiu
Jean-Michel Quedillac
Dimitar Raev
Carlos Antonio Raffo Grado
Sidiqullah Rahimi
Arturo Raisaro
Bhola Rama
Ricardo Ramos
Maria Ranieri
Nuno Raposo
Eric Rashba
Ursula Rauch-Kroehnert
Ramakota Reddy
Giulia Renda
Shabbir Reza
Luigi Ria
Dimitrios Richter
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Nadezda Rozkova
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Frank Rubalcava
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Matthieu Pierre Rutgers
Karin Rybak
Samir Said
Tamotsu Sakamoto
Abraham Salacata
Adrien Salem
Rafael Salguero Bodes
Marco A. Saltzman
Alessandro Salvioni
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Marcelo Sanmartín Fernández
Wladmir Faustino Saporito
Kesari Sarikonda
Taishi Sasaoka
Hamdi Sati
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Pierre-Jean Scala
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Carlos Scherr
Lisa Schmitz
Karl-Heinz Schmitz
Bettina Schmitz
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Norbert Schön
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Anil Shah
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Vijay Kumar Sharma
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Hideki Shimomura
Dong-Gu Shin
Eun-Seok Shin
Junya Shite
Gerolamo Sibilio
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Iveta Sime
Tim A. Simmers
Narendra Singh
Peter Siostrzonek
Didier Smadja
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Dario Sobral Filho
Hassan Soda
Carl Sofley
Adam Sokal
Yannie Soo Oi Yan
Rodolfo Sotolongo
Olga Ferreira de Souza
Jon Arne Sparby
Jindrich Spinar
David Sprigings
Alex C. Spyropoulos
Dimitrios Stakos
Clemens Steinwender
Georgios Stergiou
Ian Stiell
Marcus Stoddard
Anastas Stoikov
Witold Streb
Ioannis Styliadis
Guohai Su
Xi Su
Wanda Sudnik
Kai Sukles
Xiaofei Sun
H. Swart
Janko Szavits-Nossan
Jens Taggeselle
Yuichiro Takagi
Amrit Pal Singh Takhar
Angelika Tamm
Katsumi Tanaka
Tanyanan Tanawuttiwat
Sherman Tang
Aylmer Tang
Giovanni Tarsi
Tiziana Tassinari
Ashis Tayal
Muzahir Tayebjee
J.M. ten Berg
Dan Tesloianu
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Dierk Thomas
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Hiroshi Tsutsui
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Ype Tuininga
Minang Turakhia
Samir Turk
Wayne Turner
Arnljot Tveit
Richard Tytus
C Valadão
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Philippe van de Borne
B.J. van den Berg
C van der Zwaan
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Peter Vanacker
Dimo Vasilev
Vasileios Vasilikos
Maxim Vasilyev
Srikar Veerareddy
Mario Vega Miño
Asok Venkataraman
Paolo Verdecchia
Francesco Versaci
Ernst Günter Vester
Hubert Vial
Jason Victory
Alejandro Villamil
Marc Vincent
Anthony Vlastaris
Jürgen vom Dahl
Kishor Vora
Robert B. Vranian
Paul Wakefield
Ningfu Wang
Mingsheng Wang
Xinhua Wang
Feng Wang
Tian Wang
Alberta L. Warner
Kouki Watanabe
Jeanne Wei
Christian Weimar
Stanislav Weiner
Renate Weinrich
Ming-Shien Wen
Marcus Wiemer
Preben Wiggers
Andreas Wilke
David Williams
Marcus L. Williams
Bernhard Witzenbichler
Brian Wong
Ka Sing Lawrence Wong
Beata Wozakowska-Kaplon
Shulin Wu
Richard C. Wu
Silke Wunderlich
Nell Wyatt
John (Jack) Wylie
Yong Xu
Xiangdong Xu
Hiroki Yamanoue
Takeshi Yamashita
Ping Yen Bryan Yan
Tianlun Yang
Jing Yao
Kuo-Ho Yeh
Wei Hsian Yin
Yoto Yotov
Ralf Zahn
Stuart Zarich
Sergei Zenin
Elisabeth Louise Zeuthen

Huanyi Zhang
Donghui Zhang
Xingwei Zhang
Ping Zhang
Jun Zhang
Shui Ping Zhao
Yujie Zhao
Zhichen Zhao
Yang Zheng
Jing Zhou
Sergio Zimmermann
Andrea Zini
Steven Zizzo
Wenxia Zong
L Steven Zukerman

Table S1. Baseline characteristics based on type of anticoagulation at enrolment

Baseline characteristics	NOAC (n=17574)	VKA (n=4836)	p value
Age (years), median (IQR)	71 (65 - 78)	72 (65 - 78)	0.006
Female sex, n (%)	7892 (44.9%)	2152 (44.5%)	0.625
Heart rate (bpm), median (IQR)	76 (65 - 90)	78 (66 - 90)	<0.001
sBP (mmHg), median (IQR)	130 (120 - 143)	130 (120 - 141)	<0.001
BMI (kg/m^2), median (IQR)	27.8 (24.8 - 31.9)	27.5 (24.6 - 31.5)	<0.001
CrCl (mL/min), median (IQR)	76.3 (58.3 - 99.2)	72.2 (53.4 - 95.2)	<0.001
AF classification, n (%)			<0.001
Paroxysmal	9712 (55.3%)	2174 (45.0%)	
Persistent	6070 (34.5%)	1977 (40.9%)	
Permanent	1792 (10.2%)	685 (14.2%)	
EHRA classification, n (%)			<0.004
I	6100 (37.8%)	1576 (32.6%)	
II	6249 (38.7%)	1638 (33.9%)	
III	2968 (18.4%)	1219 (25.2%)	
IV	841 (5.2%)	403 (8.3%)	
Comorbidities, n (%)			
Hypertension	13467 (76.8%)	3652 (75.8%)	0.139
Hypercholesterolaemia	7335 (42.9%)	1855 (39.5%)	<0.001
Diabetes mellitus	4052 (23.1%)	1233 (25.5%)	<0.001
Coronary artery disease	3076 (17.9%)	916 (19.6%)	0.009
Congestive heart failure	3669 (21.0%)	1374 (28.7%)	<0.001
Left ventricular hypertrophy	3281 (19.5%)	1053 (23.3%)	<0.001
Prior thromboembolism	2697 (15.3%)	649 (13.4%)	0.001
Prior stroke	1928 (11.0%)	462 (9.6%)	0.005
Prior bleeding	867 (5.0%)	251 (5.3%)	0.566
Peripheral artery disease	498 (2.9%)	155 (3.2%)	0.172
COPD	1066 (6.1%)	319 (6.7%)	0.213
$CHADS_2$ score, median (IQR)	2 (1 - 3)	2 (1 - 3)	<0.001*
CHA_2DS_2-VASc score, median (IQR)	3 (2 - 4)	3 (2 - 4)	<0.001*
HAS-BLED score, median (IQR)	1 (1 - 2)	1 (1 - 2)	0.170

* Significantly higher in the VKA group. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; EHRA, European Heart Rhythm Association; IQR, interquartile range; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulant; sBP, systolic blood pressure; VKA, vitamin K antagonist.

Table S2. Medication use and therapies based on type of anticoagulation at enrolment

Medication use and therapies	NOAC (n=17574)	VKA (n=4836)	p value
AF ablation	315 (1.8%)	87 (1.8%)	1.000
Antiplatelet, n (%)	3011 (17.1%)	913 (18.9%)	0.005
Anti-arrhythmic drug, n (%)	4717 (26.8%)	1194 (24.7%)	0.003
ACE-i, n (%)	5553 (31.6%)	1613 (33.4%)	0.021
Angiotensin receptor blocker, n (%)	4679 (26.6%)	1241 (25.7%)	0.185
Beta-blocker, n (%)	11273 (64.1%)	3161 (65.4%)	0.121
Digoxin, n (%)	1417 (8.1%)	519 (10.7%)	<0.001
Diuretic, n (%)	6792 (38.6%)	2133 (44.1%)	<0.001
Statin, n (%)	7877 (44.8%)	2173 (44.9%)	0.903

AF, atrial fibrillation; ACE-i, angiotensin-converting enzyme inhibitor; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Table S3. Risk factors for residual risk of ischaemic stroke in NOAC-treated patients with atrial fibrillation

	Univariate		Multivariate			
			Model 1 *		Model 2 †	
Risk Factor	HR (95% CI)	p value	aHR (95% CI)	p value	aHR (95% CI)	p value
Age (per year)	1.05 (1.04 - 1.07)	<0.001	1.04 (1.02 - 1.06)	<0.001	1.04 (1.02 - 1.06)	<0.001
Female sex	1.10 (0.89 - 1.36)	0.370			1.00 (0.75 - 1.33)	0.977
Heart rate (per bpm)	1.00 (0.99 - 1.00)	0.740				
Systolic blood pressure (per mmHg)	1.01 (1.00 - 1.01)	0.043	1.00 (1.00 - 1.01)	0.235	1.00 (1.00 - 1.01)	0.217
BMI (per kg/m^2)	0.97 (0.96 - 0.99)	0.006	0.98 (0.96 - 1.01)	0.260	0.98 (0.96 - 1.01)	0.243
CrCl (per mL/min)	0.99 (0.99 - 0.99)	<0.001	1.00 (0.99 - 1.01)	0.853	1.00 (1.00 - 1.00)	0.940
AF classification						
Paroxysmal	reference		reference		reference	
Persistent	1.36 (1.05 - 1.76)	0.021	1.30 (0.97 - 1.74)	0.080	1.33 (0.98 - 1.80)	0.065
Permanent	1.62 (1.11 - 2.34)	0.011	1.39 (0.92 - 2.12)	0.122	1.49 (0.97 - 2.29)	0.070
Hypertension	1.21 (0.93 - 1.58)	0.150			1.25 (0.85 - 1.85)	0.255
Hypercholesterolaemia	1.29 (1.05 - 1.60)	0.018	1.15 (0.84 - 1.58)	0.370	1.15 (0.83 - 1.59)	0.414
Diabetes mellitus	1.31 (1.04 - 1.66)	0.022	1.55 (1.15 - 2.10)	0.004	1.53 (1.12 - 2.09)	0.008
Coronary artery disease	1.22 (0.94 - 1.58)	0.140			1.01 (0.70 - 1.48)	0.941
Congestive heart failure	1.11 (0.87 - 1.42)	0.410			1.25 (0.88 - 1.78)	0.213
Left ventricular hypertrophy	1.02 (0.78 - 1.33)	0.870			1.09 (0.78 - 1.54)	0.609
Prior thromboembolism	2.80 (2.23 - 3.50)	<0.001	2.35 (1.75 - 3.16)	<0.001	2.36 (1.73 - 3.21)	<0.001
Prior bleeding	1.23 (0.79 - 1.91)	0.360				
Peripheral artery disease	1.79 (1.10 - 2.91)	0.020	1.36 (0.75 - 2.47)	0.308	1.18 (0.61 - 2.27)	0.618
COPD	1.60 (1.11 - 2.31)	0.011	1.79 (1.16 - 2.75)	0.008		
AF ablation	0.45 (0.15 - 1.41)	0.170			1.09 (0.34 - 3.46)	0.882
Antiplatelet	1.08 (0.82 - 1.41)	0.590			1.17 (0.82 - 1.68)	0.389
Anti-arrhythmic drug	0.55 (0.41 - 0.73)	<0.001	0.74 (0.52 - 1.06)	0.096	0.69 (0.48 - 1.00)	0.051
ACE-i	1.03 (0.82 - 1.29)	0.800			0.86 (0.61 - 1.20)	0.361
Angiotensin receptor blocker	0.86 (0.67 - 1.10)	0.230			0.88 (0.62 - 1.26)	0.484
Beta-blocker	1.03 (0.82 - 1.28)	0.810				

Digoxin	1.38 (0.99 - 1.93)	0.057	1.19 (0.75 - 1.90)	0.465		
Diuretic	1.03 (0.83 - 1.27)	0.810				
Statin	1.39 (1.13 - 1.72)	0.002	1.08 (0.78 - 1.48)	0.655	1.12 (0.80 - 1.57)	0.504

[*] Adjusted for risk factors with $p < 0.10$ on univariate analysis; includes age, systolic blood pressure, BMI, CrCl, type of AF, hypercholesterolaemia, diabetes mellitus, prior thromboembolism, peripheral artery disease, COPD, anti-arrhythmic drug therapy, digoxin and statin therapy. [†] Adjusted for age, sex, systolic blood pressure, BMI, CrCl, type of AF, hypertension, hypercholesterolaemia, diabetes mellitus, coronary artery disease, heart failure, left ventricular hypertrophy, prior thromboembolism, peripheral artery disease, AF ablation, antiplatelet use, anti-arrhythmic drug therapy, ACE-i, angiotensin receptor blocker and statin therapy. ACE-i, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio.

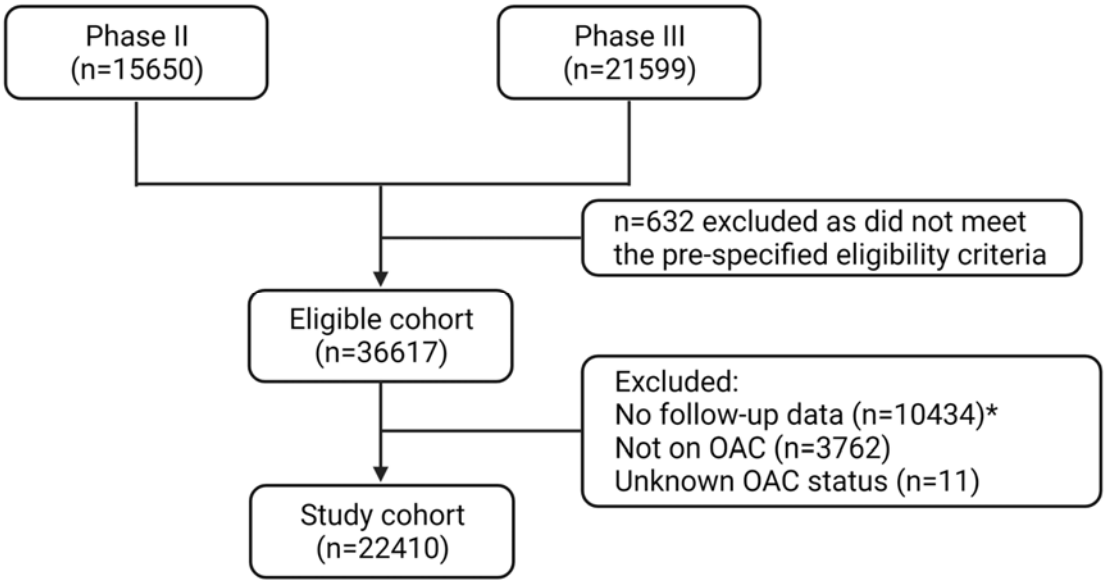
Table S4. Risk factors for residual risk of ischaemic stroke in VKA-treated patients with atrial fibrillation

	Univariate		Multivariate			
			Model 1 *		Model 2 †	
Risk Factor	HR (95% CI)	p value	aHR (95% CI)	p value	aHR (95% CI)	p value
Age (per year)	1.05 (1.04 - 1.07)	<0.001	1.08 (1.04 - 1.12)	<0.001	1.08 (1.04 - 1.12)	<0.001
Female sex	1.10 (0.89 - 1.36)	0.370			0.90 (0.55 - 1.57)	0.784
Heart rate (per bpm)	1.00 (0.99 - 1.00)	0.740				
Systolic blood pressure (per mmHg)	1.01 (1.00 - 1.01)	0.043	1.01 (1.00 - 1.02)	0.226	1.01 (1.00 - 1.03)	0.072
BMI (per kg/m^2)	0.97 (0.96 - 0.99)	0.006	1.02 (0.97 - 1.06)	0.485	1.01 (0.97 - 1.06)	0.618
CrCl (per mL/min)	0.99 (0.99 - 0.99)	<0.001	1.00 (0.99 - 1.01)	0.692	1.00 (0.99 - 1.01)	0.769
AF classification						
Paroxysmal	reference				reference	
Persistent	1.07 (0.67 - 1.73)	0.770			1.32 (0.76 - 2.29)	0.321
Permanent	1.32 (0.71 - 2.45)	0.386			0.78 (0.33 - 1.82)	0.558
Hypertension	1.21 (0.93 - 1.58)	0.150			1.44 (0.72 - 2.88)	0.300
Hypercholesterolaemia	1.29 (1.05 - 1.60)	0.018	1.26 (0.73 - 2.20)	0.409	1.27 (0.71 - 2.26)	0.428
Diabetes mellitus	1.31 (1.04 - 1.66)	0.022	1.07 (0.61 - 1.86)	0.815	1.11 (0.62 - 1.97)	0.733
Coronary artery disease	1.22 (0.94 - 1.58)	0.140			1.12 (0.55 - 2.30)	0.751
Congestive heart failure	1.11 (0.86 - 1.42)	0.410			1.21 (0.66 - 2.20)	0.535
Left ventricular hypertrophy	1.02 (0.78 - 1.33)	0.870			0.76 (0.39 - 1.43)	0.391
Prior thromboembolism	2.80 (2.23 - 3.50)	<0.001	2.33 (1.34 - 4.05)	0.003	2.16 (1.21 - 3.87)	0.010
Prior bleeding	1.23 (0.79 - 1.91)	0.360				
Peripheral artery disease	1.79 (1.10 - 2.91)	0.020	1.37 (0.42 - 4.50)	0.602	0.98 (0.23 - 4.11)	0.980
COPD	1.60 (1.11 - 2.31)	0.011	0.92 (0.37 - 2.33)	0.865		
AF ablation	0.45 (0.15 - 1.41)	0.170			NA	0.995
Antiplatelet	1.08 (0.82 - 1.41)	0.590			0.28 (0.11 - 0.72)	0.008
Anti-arrhythmic drug	0.55 (0.41 - 0.73)	<0.001	0.59 (0.29 - 1.20)	0.144	0.54 (0.25 - 1.15)	0.107
ACE-i	1.03 (0.82 - 1.29)	0.800			0.69 (0.38 - 1.25)	0.220
Angiotensin receptor blocker	0.86 (0.67 - 1.10)	0.230			0.42 (0.20 - 0.87)	0.020
Beta-blocker	1.03 (0.82 - 1.28)	0.810				
Digoxin	1.38 (0.99 - 1.93)	0.057	1.90 (1.01 - 3.58)	0.046		

Diuretic	1.03 (0.83 - 1.27)	0.810				
Statin	1.39 (1.13 - 1.72)	0.002	0.96 (0.55 - 1.69)	0.895	1.16 (0.64 - 2.12)	0.621

[*] Adjusted for risk factors with $p < 0.10$ on univariate analysis; includes age, systolic blood pressure, BMI, CrCl, type of AF, hypercholesterolaemia, diabetes mellitus, prior thromboembolism, peripheral artery disease, COPD, anti-arrhythmic drug therapy, digoxin and statin therapy. [†] Adjusted for age, sex, systolic blood pressure, BMI, CrCl, type of AF, hypertension, hypercholesterolaemia, diabetes mellitus, coronary artery disease, heart failure, left ventricular hypertrophy, prior thromboembolism, peripheral artery disease, AF ablation, antiplatelet use, anti-arrhythmic drug therapy, ACE-i, angiotensin receptor blocker and statin therapy. ACE-i, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HR, hazard ratio; NA, not available.

Figure S1. Flow chart of patient selection



* Due to study design of GLORIA-AF phase II. OAC, oral anticoagulation.