



Universiteit
Leiden
The Netherlands

Incidence and risk factors for residual adverse events despite anticoagulation in atrial fibrillation: results from phase II/III of the GLORIA-AF Registry

Ding, W.Y.; Lane, D.A.; Gupta, D.; Huisman, M.V.; Lip, G.Y.H.; GLORIA-AF Investigators

Citation

Ding, W. Y., Lane, D. A., Gupta, D., Huisman, M. V., & Lip, G. Y. H. (2022). Incidence and risk factors for residual adverse events despite anticoagulation in atrial fibrillation: results from phase II/III of the GLORIA-AF Registry. *Journal Of The American Heart Association Cardiovascular And Cerebrovascular Disease*, 11(15). doi:10.1161/JAHA.122.026410

Version: Publisher's Version





License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3566953>

Note: To cite this publication please use the final published version (if applicable).

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

Wern Yew Ding , MBChB; Deirdre A. Lane , PhD; Dhiraj Gupta , MD; Menno V. Huisman, PhD^{*,†}; Gregory Y. H. Lip , MD^{*,†}; on behalf of the GLORIA-AF Investigators[‡]

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 Anti-thrombotic Treatment in Patients With Atrial Fibrillation) registry, we studied anticoagulated patients with newly diagnosed AF and an increased risk of stroke (CHA₂DS₂-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

Correspondence to: Gregory Y. H. Lip, MD, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, United Kingdom. Email: gregory.lip@liverpool.ac.uk

*M. V. Huisman and G. Y. H. Lip and co-chairs of the GLORIA-AF registry and joint senior authors.

†M. V. Huisman and G. Y. H. Lip are co-senior authors.

‡GLORIA-AF Investigators are listed in Supplemental Material.

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.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

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 CHA₂DS₂-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 CHADS₂ score; however, it should be noted that the CHADS₂ 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 (CHA₂DS₂-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 CHADS₂, CHA₂DS₂-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=22049)	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 (mmHg), 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)	16833 (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 ₂ DS 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 100PYs in the NOAC subgroup and 0.62 (95% CI, 0.49–0.76) per 100PYs 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=22049)	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 CHA₂DS₂-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 CHA₂DS₂-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 CHADS₂ 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

Risk factor	Univariate		Multivariate			
			Model 1*		Model 2†	
	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 CHA₂DS₂-VASc score compared with those on NOAC which may have attenuated the findings. Interestingly, predictors of

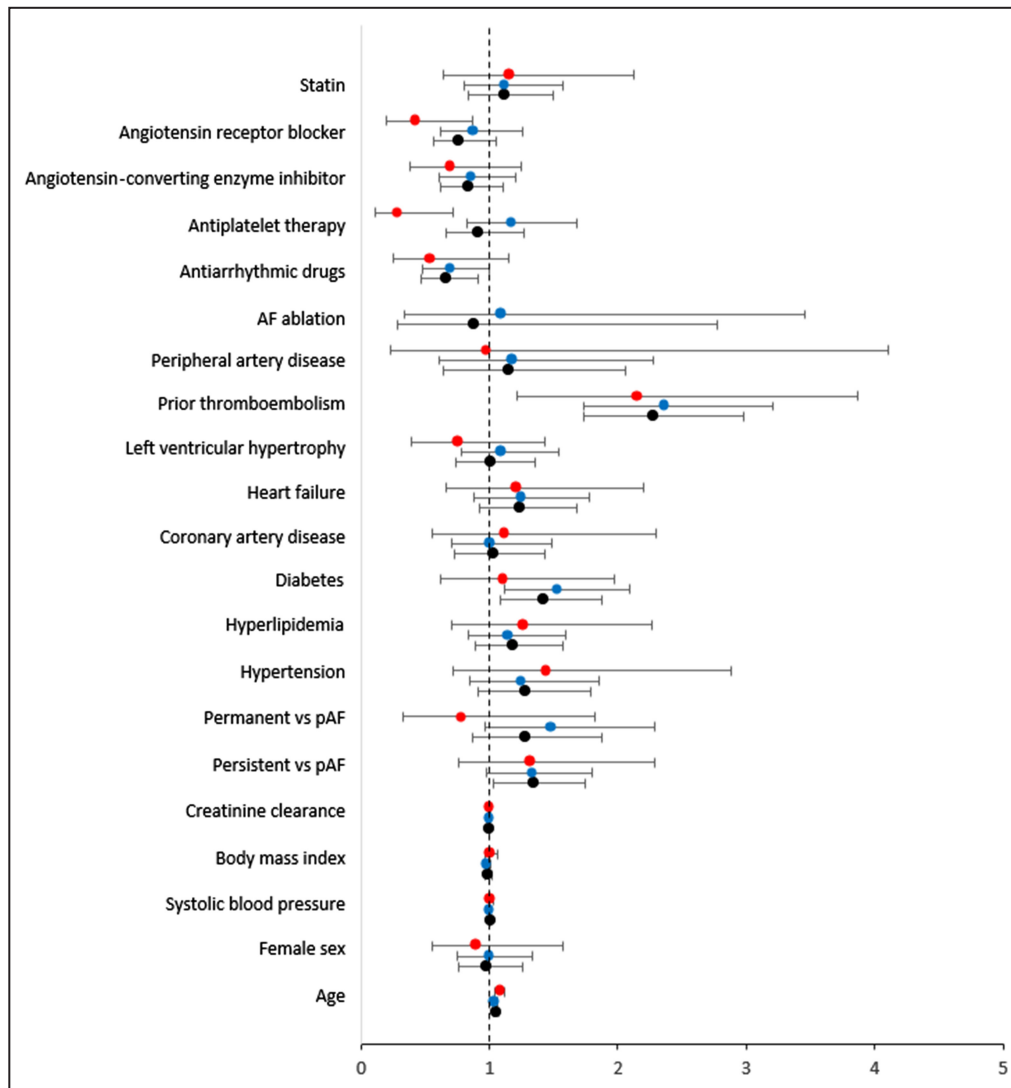


Figure. Risk factors for residual risk of ischemic stroke among anticoagulated patients with atrial fibrillation.

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.

Affiliations

Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK (W.Y.D., D.A.L., D.G., G.Y.H.L.); Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (D.A.L., G.Y.H.L.); and Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands (M.V.H.).

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 Ingelheim, 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

Data S1
Tables S1–S4
Figure S1

REFERENCES

- Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359–364. doi: [10.1016/s0002-9343\(02\)01236-6](https://doi.org/10.1016/s0002-9343(02)01236-6)
- Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart*. 2020;106:1463–1468. doi: [10.1136/heartjnl-2020-316977](https://doi.org/10.1136/heartjnl-2020-316977)
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-AA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42:373–498. doi: [10.1093/eurheartj/ehaa612](https://doi.org/10.1093/eurheartj/ehaa612)
- Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201. doi: [10.1016/j.chest.2018.07.040](https://doi.org/10.1016/j.chest.2018.07.040)
- Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, Guo Y, Sriratanasathavorn C, Oh S, Okumura K, et al. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. *Thromb Haemost*. 2022;122:20–47. doi: [10.1055/s-0041-1739411](https://doi.org/10.1055/s-0041-1739411)
- January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JCJ, Ellorin PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: [10.1161/CIR.0000000000000665](https://doi.org/10.1161/CIR.0000000000000665)
- Ding WY. Residual stroke risk in atrial fibrillation. *Arrhythm Electrophysiol Rev*. 2021;10:147–153. doi: [10.15420/aer.2021.34](https://doi.org/10.15420/aer.2021.34)
- Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;14:627–628. doi: [10.1038/nrcardio.2017.153](https://doi.org/10.1038/nrcardio.2017.153)
- Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, Gumprecht J, Koziel M, Yang P-S, Guo Y, et al. Adherence to the "atrial fibrillation better care" pathway in patients with atrial fibrillation: impact on clinical outcomes—a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost*. 2022;122:406–414. doi: [10.1055/a-1515-9630](https://doi.org/10.1055/a-1515-9630)
- Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. *Arch Intern Med*. 2012;172:623–631. doi: [10.1001/archinternmed.2012.121](https://doi.org/10.1001/archinternmed.2012.121)
- Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870. doi: [10.1001/jama.285.22.2864](https://doi.org/10.1001/jama.285.22.2864)
- Burdett P, Lip GYH. Atrial fibrillation in the United Kingdom: predicting costs of an emerging epidemic recognising and forecasting the cost drivers of atrial fibrillation-related costs. *Eur Heart J Qual Care Clin Outcomes*. 2022;8:187–194. doi: [10.1093/ehjqcco/qcaa093](https://doi.org/10.1093/ehjqcco/qcaa093)
- Huisman MV, Lip GYH, Diener HC, Dubner SJ, Halperin JL, Ma CS, Rothman KJ, Teutsch C, Zint K, Ackermann D, et al. Design and rationale of global registry on long-term oral antithrombotic treatment in patients with atrial fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J*. 2014;167:329–334. doi: [10.1016/j.ahj.2013.12.006](https://doi.org/10.1016/j.ahj.2013.12.006)
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41. doi: [10.1159/000180580](https://doi.org/10.1159/000180580)
- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: [10.1093/eurheartj/ehw210](https://doi.org/10.1093/eurheartj/ehw210)
- Kirchhof P, Auricchio A, Bax J, Crijns W, Camm J, Diener H-C, Goette A, Hindricks G, Hohnloser S, Kappenberger L, et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETWORK and the European Heart Rhythm Association. *Europace*. 2007;9:1006–1023. doi: [10.1093/europace/eum191](https://doi.org/10.1093/europace/eum191)
- Lip GYH, Nieuwlaet R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010;137:263–272. doi: [10.1378/chest.09-1584](https://doi.org/10.1378/chest.09-1584)
- Pisters R, Lane DA, Nieuwlaet R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100. doi: [10.1378/chest.10-0134](https://doi.org/10.1378/chest.10-0134)
- Woodward M. *Epidemiology: Study Design and Data Analysis*. Chapman & Hall/CRC; 2005.
- Kelsey JL, Whittemore AS, Evans AS, Thompson WD (eds). Methods of sampling and estimation of sample size. In: *Methods in Observational Epidemiology*. New York, NY: Oxford University Press; 1996.
- Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol*. 1990;131:373–375. doi: [10.1093/oxfordjournals.aje.a115507](https://doi.org/10.1093/oxfordjournals.aje.a115507)
- Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinler J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. doi: [10.1056/NEJMoa1310907](https://doi.org/10.1056/NEJMoa1310907)
- Granger CB, Alexander JH, McMurray JVV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi: [10.1056/NEJMoa1107039](https://doi.org/10.1056/NEJMoa1107039)

24. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: [10.1056/NEJMoa0905561](https://doi.org/10.1056/NEJMoa0905561)
25. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: [10.1056/NEJMoa1009638](https://doi.org/10.1056/NEJMoa1009638)
26. Cho S, Kim J, Kim J-B, Park J, Park J-K, Kang K-W, Shim J, Choi E-K, Lee YS, Park HW, et al. The difference of burden of ectopic beats in different types of atrial fibrillation and the effect of atrial fibrillation type on stroke risk in a prospective cohort of patients with atrial fibrillation (CODE-AF registry). *Sci Rep*. 2020;10:6319. doi: [10.1038/s41598-020-63370-4](https://doi.org/10.1038/s41598-020-63370-4)
27. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1591–1602. doi: [10.1093/eurheartj/ehw007](https://doi.org/10.1093/eurheartj/ehw007)
28. Lee E, Choi E-K, Han K-D, Lee H, Choe W-S, Lee S-R, Cha M-J, Lim W-H, Kim Y-J, Oh S. Mortality and causes of death in patients with atrial fibrillation: a nationwide population-based study. *PLoS One*. 2018;13:e0209687. doi: [10.1371/journal.pone.0209687](https://doi.org/10.1371/journal.pone.0209687)
29. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med*. 2014;174:107–114. doi: [10.1001/jamainternmed.2013.11912](https://doi.org/10.1001/jamainternmed.2013.11912)
30. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Ouditayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ*. 2016;532:h7013. doi: [10.1136/bmj.h7013](https://doi.org/10.1136/bmj.h7013)
31. Maeda T, Nishi T, Funakoshi S, Tada K, Tsuji M, Satoh A, Kawazoe M, Yoshimura C, Arima H. Residual risks of ischemic stroke and systemic embolism among atrial fibrillation patients with anticoagulation: large-scale real-world data (F-CREATE project). *Heart*. 2021;107:217–222. doi: [10.1136/heartjnl-2020-317299](https://doi.org/10.1136/heartjnl-2020-317299)
32. Senoo K, Lip GYH, Lane DA, Buller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. *Stroke*. 2015;46:2523–2528. doi: [10.1161/STROKEAHA.115.009487](https://doi.org/10.1161/STROKEAHA.115.009487)
33. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GYH. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. *Stroke*. 2013;44:1329–1336. doi: [10.1161/STROKEAHA.113.000883](https://doi.org/10.1161/STROKEAHA.113.000883)
34. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol*. 2014;113:485–490. doi: [10.1016/j.amjcard.2013.10.035](https://doi.org/10.1016/j.amjcard.2013.10.035)
35. Kim M, Yu HT, Kim JY, Kim T-H, Uhm J-S, Joung B, Lee M-H, Pak H-N. Atrial fibrillation and the risk of ischemic strokes or intracranial hemorrhages: comparisons of the catheter ablation, medical therapy, and non-atrial fibrillation population. *Europace*. 2021;23:529–538. doi: [10.1093/europace/euaa235](https://doi.org/10.1093/europace/euaa235)
36. Soglietto A, De Ponti R, Di Biase L, Matta M, Gaita F, Romero J, De Ferrari GM, Anselmino M. Impact of atrial fibrillation catheter ablation on mortality, stroke, and heart failure hospitalizations: a meta-analysis. *J Cardiovasc Electrophysiol*. 2020;31:1040–1047. doi: [10.1111/jce.14429](https://doi.org/10.1111/jce.14429)
37. Yang P-S, Sung J-H, Jang E, Yu HT, Kim T-H, Uhm J-S, Kim J-Y, Pak H-N, Lee M-H, Joung B. Catheter ablation improves mortality and other outcomes in real-world patients with atrial fibrillation. *J Am Heart Assoc*. 2020;9:e015740. doi: [10.1161/JAHA.119.015740](https://doi.org/10.1161/JAHA.119.015740)
38. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;383:1305–1316. doi: [10.1056/NEJMoa2019422](https://doi.org/10.1056/NEJMoa2019422)
39. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GYH. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail*. 2015;17:1192–1200. doi: [10.1002/ejhf.343](https://doi.org/10.1002/ejhf.343)
40. He Q, Sze C-Y, Shum T-Y, Hao G, Wong N-YB, Sin T-H, Wei W, Xia S. Comparing clinical outcomes of NOACs with warfarin on atrial fibrillation with valvular heart diseases: a meta-analysis. *BMC Cardiovasc Disord*. 2019;19:113. doi: [10.1186/s12872-019-1089-0](https://doi.org/10.1186/s12872-019-1089-0)
41. Pan K-L, Singer DE, Ovbiagele B, Wu Y-L, Ahmed MA, Lee M. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005835. doi: [10.1161/JAHA.117.005835](https://doi.org/10.1161/JAHA.117.005835)
42. Zelniker TA, Ruff CT, Antman EM, Giugliano RP. The efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and coronary artery disease: a meta-analysis of randomized trials. *Eur Heart J Acute Cardiovasc Care*. 2019;8:554–561. doi: [10.1177/2048872618796990](https://doi.org/10.1177/2048872618796990)
43. Diener H-C, Hankey GJ, Easton JD, Lip GYH, Hart RG, Caso V. Non-vitamin K oral anticoagulants for secondary stroke prevention in patients with atrial fibrillation. *Eur Heart J Suppl*. 2020;22:113–121. doi: [10.1093/eurheartj/suaa104](https://doi.org/10.1093/eurheartj/suaa104)

SUPPLEMENTAL MATERIAL

Data S1. List of GLORIA-AF Investigators

Dzifa Wosornu Abban	Ermentina Bagni	Jordi Bruguera Cortada
Nasser Abdul	Seth H. Baker	A. Bruni
Atilio Marcelo Abud	Richard Bala	Claude Brunschwig
Fran Adams	Antonio Baldi	Hervé Buathier
Srinivas Addala	Shigenobu Bando	Aurélie Buhl
Pedro Adragão	Subhash Banerjee	John Bullinga
Walter Ageno	Alan Bank	Jose Walter Cabrera
Rajesh Aggarwal	Gonzalo Barón Esquivias	Alberto Caccavo
Sergio Agosti	Craig Barr	Shanglang Cai
Piergiuseppe Agostoni	Maria Bartlett	Sarah Caine
Francisco Aguilar	Vanja Basic Kes	Leonardo Calò
Julio Aguilar Linares	Giovanni Baula	Valeria Calvi
Luis Aguinaga	Steffen Behrens	Mauricio Camarillo Sánchez
Jameel Ahmed	Alan Bell	Rui Candeias
Allessandro Aiello	Raffaella Benedetti	Vincenzo Capuano
Paul Ainsworth	Juan Benezet Mazuecos	Alessandro Capucci
Jorge Roberto Aiub	Bouziane Benhalima	Ronald Caputo
Raed Al-Dallow	Jutta Bergler-Klein	Tatiana Cárdenas Rizo
Lisa Alderson	Jean-Baptiste Berneau	Francisco Cardona
Jorge Antonio Aldrete Velasco	Richard A. Bernstein	Francisco Carlos da Costa
Dimitrios Alexopoulos	Percy Berrospi	Darrieux
Fernando Alfonso Manterola	Sergio Berti	Yan Carlos Duarte Vera
Pareed Aliyar	Andrea Berz	Antonio Carolei
David Alonso	Elizabeth Best	Susana Carreño
Fernando Augusto Alves da Costa	Paulo Bettencourt	Paula Carvalho
José Amado	Robert Betzu	Susanna Cary
Walid Amara	Ravi Bhagwat	Gavino Casu
Mathieu Amelot	Luna Bhatta	Claudio Cavallini
Nima Amjadi	Francesco Biscione	Guillaume Cayla
Fabrizio Ammirati	Giovanni BISIGNANI	Aldo Celentano
Marianna Andrade	Toby Black	Tae-Joon Cha
Nabil Andrawis	Michael J. Bloch	Kwang Soo Cha
Giorgio Annoni	Stephen Bloom	Jei Keon Chae
Gerardo Ansalone	Edwin Blumberg	Kathrine Chalamidas
M. Kevin Ariani	Mario Bo	Krishnan Challappa
Juan Carlos Arias	Ellen Bøhmer	Sunil Prakash Chand
Sébastien Armero	Andreas Bollmann	Harinath Chandrashekar
Chander Arora	Maria Grazia Bongiorno	Ludovic Chartier
Muhammad Shakil Aslam	Giuseppe Boriani	Kausik Chatterjee
M. Asselman	D.J. Boswijk	Carlos Antero Chavez Ayala
Philippe Audouin	Jochen Bott	Aamir Cheema
Charles Augenbraun	Edo Bottacchi	Amjad Cheema
S. Aydin	Marica Bracic Kalan	Lin Chen
Ivaneta Ayryanova	Drew Bradman	Shih-Ann Chen
Emad Aziz	Donald Brautigam	Jyh Hong Chen
Luciano Marcelo Backes	Nicolas Breton	Fu-Tien Chiang
E. Badings	P.J.A.M. Brouwers	Francesco Chiarella
	Kevin Browne	Lin Chih-Chan

Yong Keun Cho
Jong-II Choi
Dong Ju Choi
Guy Chouinard
Danny Hoi-Fan Chow
Dimitrios Chrysos
Galina Chumakova
Eduardo Julián José Roberto
Chuquiure Valenzuela
Nicoleta Cindea Nica
David J. Cislowski
Anthony Clay
Piers Clifford
Andrew Cohen
Michael Cohen
Serge Cohen
Furio Colivicchi
Ronan Collins
Paolo Colonna
Steve Compton
Derek Connolly
Alberto Conti
Gabriel Contreras Buenostro
Gregg Coodley
Martin Cooper
Julian Coronel
Giovanni Corso
Juan Cosín Sales
Yves Cottin
John Covallesky
Aurel Cracan
Filippo Crea
Peter Crean
James Crenshaw
Tina Cullen
Harald Darius
Patrick Dary
Olivier Dascotte
Ira Dauber
Vicente Davalos
Ruth Davies
Gershan Davis
Jean-Marc Davy
Mark Dayer
Marzia De Biasio
Silvana De Bonis
Raffaele De Caterina
Teresiano De Franceschi
J.R. de Groot
José De Horta

Axel De La Briolle
Gilberto de la Pena Topete
Angelo Amato Vincenzo de
Paola
Weimar de Souza
A. de Veer
Luc De Wolf
Eric Decoulx
Sasalu Deepak
Pascal Defaye
Freddy Del-Carpio Munoz
Diana Delic Brkljacic
N. Joseph Deumite
Silvia Di Legge
Igor Diemberger
Denise Dietz
Pedro Dionísio
Qiang Dong
Fabio Rossi dos Santos
Elena Dotcheva
Rami Doukky
Anthony D'Souza
Simon Dubrey
Xavier Ducrocq
Dmitry Dupljakov
Mauricio Duque
Dipankar Dutta
Nathalie Duvilla
A. Duygun
Rainer Dziewas
Charles B. Eaton
William Eaves
L.A Ebels-Tuinbeek
Clifford Ehrlich
Sabine Eichinger-Hasenauer
Steven J. Eisenberg
Adnan El Jabali
Mahfouz El Shahawy
Mauro Esteves Hernandes
Ana Etxeberria Izal
Rudolph Evonich III
Oksana Evseeva
Andrey Ezhov
Raed Fahmy
Quan Fang
Ramin Farsad
Laurent Fauchier
Stefano Favale
Maxime Fayard
Jose Luis Fedele

Francesco Fedele
Olga Fedorishina
Steven R. Fera
Luis Gustavo Gomes Ferreira
Jorge Ferreira
Claudio Ferri
Anna Ferrier
Hugo Ferro
Alexandra Finsen
Brian First
Stuart Fischer
Catarina Fonseca
Luísa Fonseca Almeida
Steven Forman
Brad Frandsen
William French
Keith Friedman
Athena Friese
Ana Gabriela Fruntelata
Shigeru Fujii
Stefano Fumagalli
Marta Fundamenski
Yutaka Furukawa
Matthias Gabelmann
Nashwa Gabra
Niels Gadsbøll
Michel Galinier
Anders Gammelgaard
Priya Ganeshkumar
Christopher Gans
Antonio Garcia Quintana
Olivier Gartenlaub
Achille Gaspardone
Conrad Genz
Frédéric Georger
Jean-Louis Georges
Steven Georgeson
Evaldas Giedrimas
Mariusz Gierba
Ignacio Gil Ortega
Eve Gillespie
Alberto Giniger
Michael C. Giudici
Alexandros Gkotsis
Taya V. Glotzer
Joachim Gmehling
Jacek Gniot
Peter Goethals
Seth Goldberg
Ronald Goldberg

Britta Goldmann
Sergey Golitsyn
Silvia Gómez
Juan Gomez Mesa
Vicente Bertomeu Gonzalez
Jesus Antonio Gonzalez
Hermosillo
V́ctor Manuel González
López
Hervé Gorka
Charles Gornick
Diana Gorog
Venkat Gottipaty
Pascal Goube
Ioannis Goudevenos
Brett Graham
G. Stephen Greer
Uwe Gremmler
Paul G. Grena
Martin Grond
Edoardo Gronda
Gerian Grönefeld
Xiang Gu
Ivett Guadalupe Torres Torres
Gabriele Guardigli
Carolina Guevara
Alexandre Guignier
Michele Gulizia
Michael Gumbley
Albrecht Günther
Andrew Ha
Georgios Hahalis
Joseph Hakas
Christian Hall
Bing Han
Seongwook Han
Joe Hargrove
David Hargroves
Kenneth B. Harris
Tetsuya Haruna
Emil Hayek
Jeff Healey
Steven Hearne
Michael Heffernan
Geir Heggelund
J.A. Heijmeriks
Maarten Hemels
I. Hendriks
Sam Henein
Sung-Ho Her

Paul Hermany
Jorge Eduardo Hernández Del
Río
Yorihiko Higashino
Michael Hill
Tetsuo Hisadome
Eiji Hishida
Etienne Hoffer
Matthew Hoghton
Kui Hong
Suk keun Hong
Stevie Horbach
Masataka Horiuchi
Yinglong Hou
Jeff Hsing
Chi-Hung Huang
David Huckins
kathy Hughes
A. Huizinga
E.L. Hulsman
Kuo-Chun Hung
Gyo-Seung Hwang
Margaret Ikpoh
Davide Imberti
Hüseyin Ince
Ciro Indolfi
Shujiro Inoue
Didier Irles
Harukazu Iseki
C. Noah Israel
Bruce Iteld
Venkat Iyer
Ewart Jackson-Voyzey
Naseem Jaffrani
Frank Jäger
Martin James
Sung-Won Jang
Nicolas Jaramillo
Nabil Jarmukli
Robert J. Jeanfreau
Ronald D. Jenkins
Carlos Jerjes Sánchez
Javier Jimenez
Robert Jobe
Tomas Joen-Jakobsen
Nicholas Jones
Jose Carlos Moura Jorge
Bernard Jouve
Byung Chun Jung
Kyung Tae Jung

Werner Jung
Mikhail Kachkovskiy
Krystallenia Kafkala
Larisa Kalinina
Bernd Kallmünzer
Farzan Kamali
Takehiro Kamo
Priit Kampus
Hisham Kashou
Andreas Kastrup
Apostolos Katsivas
Elizabeth Kaufman
Kazuya Kawai
Kenji Kawajiri
John F. Kazmierski
P Keeling
José Francisco Kerr Saraiva
Galina Ketova
AJIT Singh Khaira
Aleksey Khripun
Doo-Il Kim
Young Hoon Kim
Nam Ho Kim
Dae Kyeong Kim
Jeong Su Kim
June Soo Kim
Ki Seok Kim
Jin bae Kim
Elena Kinova
Alexander Klein
James J. Kmetzo
G. Larsen Kneller
Aleksandar Knezevic
Su Mei Angela Koh
Shunichi Koide
Athanasios Kollias
J.A. Kooistra
Jay Koons
Martin Koschutnik
William J. Kostis
Dragan Kovacic
Jacek Kowalczyk
Natalya Koziolova
Peter Kraft
Johannes A. Kragten
Mori Krantz
Lars Krause
B.J. Krenning
F. Krikke
Z. Kromhout

Waldemar Krysiak
Priya Kumar
Thomas Kümler
Malte Kuniss
Jen-Yuan Kuo
Achim Küppers
Karla Kurrelmeyer
Choong Hwan Kwak
Bénédicte Laboulle
Arthur Labovitz
Wen Ter Lai
Andy Lam
Yat Yin Lam
Fernando Lanas Zanetti
Charles Landau
Giancarlo Landini
Estêvão Lanna Figueiredo
Torben Larsen
Karine Lavandier
Jessica LeBlanc
Moon Hyung Lee
Chang-Hoon Lee
John Lehman
Ana Leitão
Nicolas Lellouche
Malgorzata Lelonek
Radoslaw Lenarczyk
T. Lenderink
Salvador León González
Peter Leong-Sit
Matthias Leschke
Nicolas Ley
Zhanquan Li
Xiaodong Li
Weihua Li
Xiaoming Li
Christoh Lichy
Ira Lieber
Ramon Horacio Limon
Rodriguez
Hailong Lin
Gregory Y. H. Lip
Feng Liu
Hengliang Liu
Guillermo Llamas Esperon
Nassip Llerena Navarro
Eric Lo
Sergiy Lokshyn
Amador López
José Luís López-Sendón

Adalberto Menezes Lorga
Filho
Richard S. Lorraine
Carlos Alberto Luengas
Robert Luke
Ming Luo
Steven Lupovitch
Philippe Lyrer
Changsheng Ma
Genshan Ma
Irene Madariaga
Koji Maeno
Dominique Magnin
Gustavo Maid
Sumeet K. Mainigi
Konstantinos Makaritsis
Rohit Malhotra
Rickey Manning
Athanasios Manolis
Helard Andres Manrique
Hurtado
Ioannis Mantas
Fernando Manzur Jattin
Vicky Maqueda
Niccolo Marchionni
Francisco Marin Ortuno
Antonio Martín Santana
Jorge Martinez
Petra Maskova
Norberto Matadamas
Hernandez
Katsuhiko Matsuda
Tillmann Maurer
Ciro Mauro
Erik May
Nolan Mayer
John McClure
Terry McCormack
William McGarity
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
Lluís 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 Prella
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
Hans Rickli
Werner Rieker
Tomas Ripolil Vera
Luiz Eduardo Ritt
Douglas Roberts
Ignacio Rodriguez Briones
Aldo Edwin Rodriguez
Escudero
Carlos Rodríguez Pascual
Mark Roman
Francesco Romeo
E. Ronner
Jean-Francois Roux
Nadezda Rozkova
Miroslav Rubacek
Frank Rubalcava
Andrea M. Russo
Matthieu Pierre Rutgers
Karin Rybak
Samir Said
Tamotsu Sakamoto
Abraham Salacata
Adrien Salem
Rafael Salguero Bodes
Marco A. Saltzman
Alessandro Salvioni
Gregorio Sanchez Vallejo
Marcelo Sanmartín Fernández
Wladimir Faustino Saporito
Kesari Sarikonda
Taishi Sasaoka
Hamdi Sati
Irina Savelieva
Pierre-Jean Scala
Peter Schellinger
Carlos Scherr
Lisa Schmitz
Karl-Heinz Schmitz
Bettina Schmitz
Teresa Schnabel
Steffen Schnupp
Peter Schoeniger
Norbert Schön
Peter Schwimmbeck
Clare Seamark

Greg Searles	Xiaofei Sun	Ernst Günter Vester
Karl-Heinz Seidl	H. Swart	Hubert Vial
Barry Seidman	Janko Szavits-Nossan	Jason Victory
Jaroslav Sek	Jens Taggeselle	Alejandro Villamil
Lakshmanan Sekaran	Yuichiro Takagi	Marc Vincent
Carlo SERRATI	Amrit Pal Singh Takhar	Anthony Vlastaris
Neerav Shah	Angelika Tamm	Jürgen vom Dahl
Vinay Shah	Katsumi Tanaka	Kishor Vora
Anil Shah	Tanyanan Tanawuttiwat	Robert B. Vranian
Shujahat Shah	Sherman Tang	Paul Wakefield
Vijay Kumar Sharma	Aylmer Tang	Ningfu Wang
Louise Shaw	Giovanni Tarsi	Mingsheng Wang
Khalid H. Sheikh	Tiziana Tassinari	Xinhua Wang
Naruhito Shimizu	Ashis Tayal	Feng Wang
Hideki Shimomura	Muzahir Tayebjee	Tian Wang
Dong-Gu Shin	J.M. ten Berg	Alberta L. Warner
Eun-Seok Shin	Dan Tesloianu	Kouki Watanabe
Junya Shite	Salem H.K. The	Jeanne Wei
Gerolamo Sibilio	Dierk Thomas	Christian Weimar
Frank Silver	Serge Timsit	Stanislav Weiner
Iveta Sime	Tetsuya Tobaru	Renate Weinrich
Tim A. Simmers	Andrzej R. Tomasiak.	Ming-Shien Wen
Narendra Singh	Mikhail Torosoff	Marcus Wiemer
Peter Siostrzonek	Emmanuel Touze	Preben Wiggers
Didier Smadja	Elina Trendafilova	Andreas Wilke
David W. Smith	W. Kevin Tsai	David Williams
Marcelo Snitman	Hung Fat Tse	Marcus L. Williams
Dario Sobral Filho	Hiroshi Tsutsui	Bernhard Witzenbichler
Hassan Soda	Tian Ming Tu	Brian Wong
Carl Sofley	Ype Tuininga	Ka Sing Lawrence Wong
Adam Sokal	Minang Turakhia	Beata Wozakowska-Kaplon
Yannie Soo Oi Yan	Samir Turk	Shulin Wu
Rodolfo Sotolongo	Wayne Turner	Richard C. Wu
Olga Ferreira de Souza	Arnljot Tveit	Silke Wunderlich
Jon Arne Sparby	Richard Tytus	Nell Wyatt
Jindrich Spinar	C Valadão	John (Jack) Wylie
David Springs	P.F.M.M. van Bergen	Yong Xu
Alex C. Spyropoulos	Philippe van de Borne	Xiangdong Xu
Dimitrios Stakos	B.J. van den Berg	Hiroki Yamanoue
Clemens Steinwender	C van der Zwaan	Takeshi Yamashita
Georgios Stergiou	M. Van Eck	Ping Yen Bryan Yan
Ian Stiell	Peter Vanacker	Tianlun Yang
Marcus Stoddard	Dimo Vasilev	Jing Yao
Anastas Stoikov	Vasileios Vasilikos	Kuo-Ho Yeh
Witold Streb	Maxim Vasilyev	Wei Hsian Yin
Ioannis Styliadis	Srikar Veerareddy	Yoto Yotov
Guohai Su	Mario Vega Miño	Ralf Zahn
Xi Su	Asok Venkataraman	Stuart Zarich
Wanda Sudnik	Paolo Verdecchia	Sergei Zenin
Kai Sukles	Francesco Versaci	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 ₂ DS 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

Risk Factor	Univariate		Multivariate			
	HR (95% CI)	p value	Model 1 *		Model 2 †	
			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.

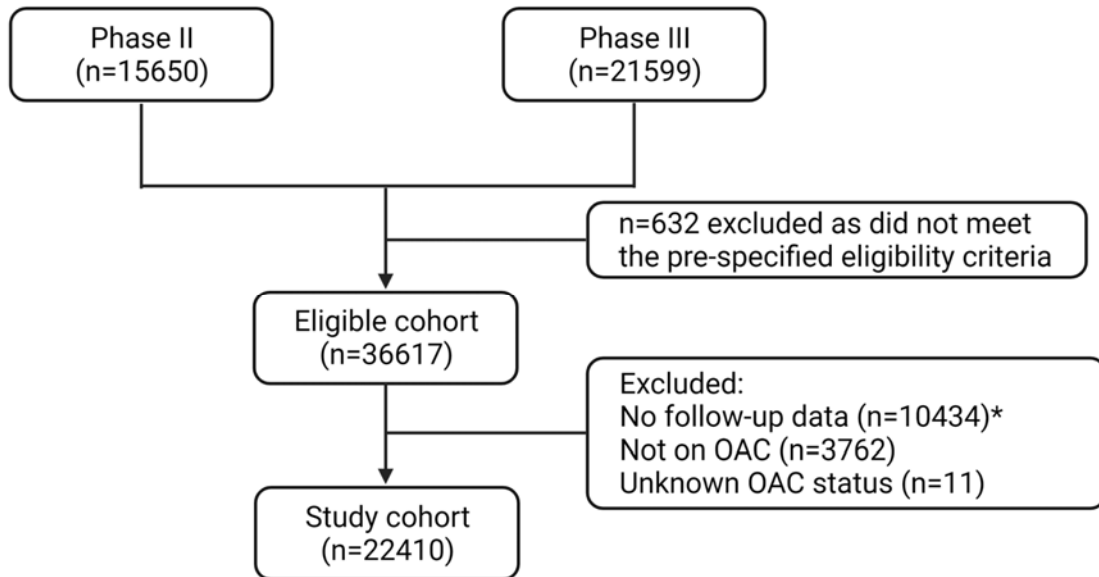
Table S4. Risk factors for residual risk of ischaemic stroke in VKA-treated patients with atrial fibrillation

Risk Factor	Univariate		Multivariate			
	HR (95% CI)	p value	Model 1 *		Model 2 †	
			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.