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Title: Prior Stroke and TIA as Risk Factors for Subsequent Stroke in AF Patients: a Report from the GARFIELD-AF Registry

Short Title: Risk of Stroke after Stroke/TIA in AF

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ABSTRACT

BACKGROUND: It is not always possible to verify whether a patient complaining of symptoms consistent with transient ischemic attack (TIA) has had an actual cerebrovascular event.

RESEARCH QUESTION: To characterize the risk of cardiovascular events associated with history of stroke/TIA in patients with atrial fibrillation (AF).

STUDY DESIGN AND METHODS: This study investigated the clinical characteristics and outcomes of patients with a history of stroke/TIA among 52,014 patients enrolled prospectively in GARFIELD-AF registry. The diagnosis of stroke or TIA was not protocol defined but based on physicians' assessment. Patients' 1-year risk of death, stroke/systemic embolism (SE), and major bleeding was assessed by multivariable Cox regression.

RESULTS: At enrollment, 5617 (10.9%) patients were reported to have a history of stroke or TIA. Patients with stroke or TIA were older and had a greater burden of diabetes, moderate-to-severe kidney disease, and atherothrombosis and higher median CHA_2DS_2-VASc and HAS-BLED scores than those without history of stroke or TIA. After adjustment, prior stroke/TIA was associated with significantly higher risk for all-cause mortality (hazard ratio [HR], 1.26; 95% CI, 1.12–1.42), cardiovascular death (HR, 1.22; 95% CI, 1.01–1.48), non-cardiovascular death (HR, 1.39; 95% CI, 1.15–1.68), and stroke/SE (HR, 2.17; 95% CI, 1.80–2.63) than patients without history of stroke/TIA. In patients with a prior stroke alone higher risk was observed for all-cause mortality (HR, 1.29; 95% CI, 1.11–1.50), non-cardiovascular death (HR, 1.39; 95% CI, 1.10–1.77), and stroke/SE (HR, 2.29; 95% CI, 1.83–2.86). No significantly elevated risk of adverse events was seen for patients with history of TIA alone.

INTERPRETATION: A history of prior stroke or TIA is a strong independent risk factor for mortality and stroke/SE. This excess risk is mainly attributed to a history of stroke (with or without TIA), whereas history of TIA is a weaker predictor.

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Atrial fibrillation (AF) is an independent risk factor for death and stroke/systemic embolism (SE) and patients may also have an increased risk of bleeding, especially those taking antithrombotic drugs for stroke prevention.[1,2] Patients with a history of stroke or transient ischemic attack (TIA) have a higher risk of subsequent events including all-cause mortality, cardiovascular mortality, stroke/SE, and major bleeding complications.[3] This is reflected in conventional risk assessments for stroke in patients with AF (e.g. CHA_2DS_2-VASc, in which a history of stroke/TIA is assigned 2 points).[4,5]

Many physicians consider TIA and stroke along a broad continuum of risk for future stroke or other vascular diseases.[6] However, it is not always feasible to verify whether TIA represents an actual cerebrovascular event.[7,8] While stroke is usually associated with impaired neurological function and evidence of an infarcted area on brain imaging, there are no persistent symptoms that allow a definitive diagnosis of TIA. Only approximately half patients reporting TIAs have ischemic changes on magnetic resonance imaging, and fewer than half have related brain abnormalities on computed tomography.[6] However, in clinical practice brain imaging is usually not performed in patients reporting events that might be indicative for a TIA. Moreover, symptoms such as dizziness, light headedness, headache, incoordination, and disorientation are commonly attributed to TIA that is not confirmed.[6] For these patients the risk of subsequent events might be much lower than for those with a documented history of stroke.

Using data from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) the clinical characteristics, predicted risks (from conventional risk score and the GARFIELD-AF risk calculator), and 1-year adjusted hazard ratios (HRs) for all-cause

mortality, cardiovascular and non-cardiovascular death, stroke/SE, and major bleeding were

analyzed in patients with and without history of stroke and/or TIA.

Methods

GARFIELD-AF Registry

GARFIELD-AF is a prospective, observational, worldwide registry of 52,014 patients with

newly diagnosed AF who were enrolled in 35 countries between March 2010 and August

2016.[9] All patients were followed for a minimum 2 years. The design of the GARFIELD-AF

registry has been described previously.[9,10] Eligible patients aged >18 years with AF diagnosed

according to standard local procedures within the previous 6 weeks, and with at least one risk

factor for stroke as judged by treating physicians were consecutively enrolled.[9]

Ethics

The study was approved by independent ethics committee and hospital-based institutional

review board (details available in Supplementary Materials). The registry was conducted in

accordance with the principles of the Declaration of Helsinki, local regulatory requirements,

and International Conference on Harmonisation–Good Pharmaco-epidemiological and

Clinical Practice guidelines. Written informed consent was obtained from all study

participants. Confidentiality and anonymity of all patients recruited into this registry were

maintained.

Procedures and Outcome Measures

Baseline characteristics collected at inclusion in the registry included: medical history, care

setting, type of AF, date and method of diagnosis, symptoms, antithrombotic treatment

(vitamin K antagonists [VKAs], non-vitamin K antagonist oral anticoagulants [NOACs], and

antiplatelet [AP]), as well as all cardiovascular drugs.[9] The risks of stroke and bleed at enrollment were calculated by CHA_2DS_2-VASc and HAS-BLED risk scores, respectively. HAS-BLED scores were calculated excluding fluctuations in international normalized ratio. The risks of death, stroke/SE, and major bleeding were also assessed at baseline with the newly described and validated GARFIELD-AF risk calculator.[11]

Data were captured by electronic case report forms (eCRFs) and examined for completeness and accuracy by the coordinating center (Thrombosis Research Institute, London, UK). An audit and quality control program was implemented, including source document verification of 20% of all eCRFs, additional audit of critical variables, and an electronic audit trail for all data modifications.[12] Patient contact was conducted in the setting of an everyday practice patient visit, according to local standards. The diagnosis of previous cerebrovascular events was made on history taking; brain imaging was not required to establish the diagnosis of stroke or TIA. The present data were extracted from the study database in October 2017.

Definitions

A history of ischemic stroke was defined as a previous episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. History of TIA was defined as previous transient episode of neurologic dysfunction without acute infarction.[6] Vascular disease included any suspicion of coronary artery disease, with or without a history of acute coronary syndromes (ACS), and/or peripheral artery disease.

Statistical Analysis

The analysis was performed on all patients enrolled in GARFIELD-AF with available information on stroke/TIA history. Follow-up was truncated at 1 year after enrollment.

Continuous variables were expressed as median and interquartile range, whereas categorical variables were expressed as frequencies and percentages.

Occurrence of major clinical outcomes was described as number of events and event rate per 100 person-years with corresponding 95% confidence intervals (CIs). Event rates were estimated by Poisson model. Only the first occurrence of each event was taken into account. Relative risk for all-cause mortality was assessed by Cox proportional hazards model. Stroke/SE and major bleeding outcomes accounted for any death as competing risk according to Fine-Gray proportional subdistribution hazards model.[13–15] Similarly, for risk of cause-specific mortality, death from other causes was considered a competing event. Both a statistical test and a graphical examination based on Schoenfeld residuals were used to assess the proportional hazards assumption.[16] All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

Disposition of the 52,014 patients entered in GARFIELD-AF registry is depicted in Figure 1. In all, 5617 patients (10.9%) had prior stroke and/or TIA. Of these patients, 3362 reported stroke (59.9%), 1788 TIA (31.8%), and 467 stroke and TIA (8.3%; Table 1).

Compared with patients with no stroke/TIA, patients with prior stroke/TIA were slightly older and more likely to have history of diabetes, moderate-to-severe chronic kidney disease (CKD), major bleeding, dementia, and coronary artery disease, ACS, or carotid artery occlusion. Their baseline CHA_2DS_2-VASc, HAS-BLED, and GARFIELD-AF risk scores were also higher. Patients with history of TIA or stroke had similar baseline characteristics,

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although stroke patients were more likely male, Asian, and experienced prior SE and bleeding than TIA patients (Table 1).

Treatment

Antithrombotic prescriptions for stroke prevention (NOAC ± AP, VKA ± AP, and AP alone) were similar across all groups of patients regardless of stroke/TIA history, although patients without a history of stroke/TIA were less likely anticoagulated and more likely not to receive any antithrombotic medications (Table 2).

Outcome Events

Rates of all-cause mortality, cardiovascular and non-cardiovascular death, and stroke/SE were higher in patients with than without history of stroke/TIA at 1 year (Table 3). Higher rates of all major clinical events (except major bleeding) were also recorded in all three sub-groups of patients with stroke, TIA, and stroke and TIA compared with patients without a history of stroke/TIA.

Unadjusted HR/sub-HRs (SHRs) for all-cause mortality, cardiovascular and non-cardiovascular death, and stroke/SE were significantly higher in patients with a history of stroke/TIA than in those without this complication. The same pattern was evident for stroke patients and those with stroke and TIA whereas for TIA subgroup unadjusted HR/SHRs for all-cause mortality and stroke/SE were marginally significantly higher than in patients without stroke/TIA (eTable 1).

After adjusting for baseline risk factors and anticoagulant treatment, patients with versus without stroke/TIA had higher HR/SHRs for all-cause mortality (HR, 1.26; 95% CI, 1.12–

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1.42), cardiovascular death (SHR, 1.22; 1.01–1.48), non-cardiovascular death (SHR,1.39; 95% CI, 1.15–1.68), and stroke/SE (SHR, 2.17; 95% CI, 1.80–2.63), but not major bleeding (Table 3 and Figure 2). History of stroke was associated with a greater than two-fold increase in the risk of recurrent stroke/SE over 1 year. These individuals also bore greater risk for all-cause mortality and non-cardiovascular mortality relative to patients without history of stroke/TIA.

Patients with history of stroke and TIA had the highest risk of all major adverse events including cardiovascular mortality, but not major bleeding. No significant excess risk of death by any cause was observed in patients with TIA compared with those without history of stroke/TIA. In these patients there was a non-significant 35% increase in the risk of stroke/SE (eTable 1 and Figure 2).

The risk of major bleeding was similar across all patient groups with or without history of stroke/TIA. There were numerically more intracranial bleeds in patients with history of stroke/TIA (n = 7; 0.12%) than without history of stroke/TIA (n = 17; 0.04%). These events were very rare across subgroups.

Discussion

History of stroke or stroke and TIA was associated with significantly higher rates of all-cause death and elevated risk of subsequent stroke/SE whereas history of TIA was not associated with significantly elevated risk for death or stroke/SE. After adjustment for a large variety of baseline characteristics and anticoagulant treatment, the 1-year risk of death and stroke/SE in patients with history of stroke/TIA or stroke, but not TIA, was persistently elevated compared

with patients without history of stroke/TIA. History of stroke and TIA was associated with the highest risk of subsequent major adverse events over 1-year follow-up.

These observations were reflected in the GARFIELD-AF risk score for death and stroke/SE at baseline, which only takes into account history of stroke and not TIA. The GARFIELD-AF risk score was developed using data on GARFIELD-AF cohort and externally validated in a large cohort of AF patients in USA.[11] In this study GARFIELD-AF risk score was lower for patients with history of TIA relative to those with history of stroke (who were determined as at intermediate risk) and history of stroke and TIA (who had worst prognosis and highest prevalence of comorbid disease).

Stroke and TIA should be considered separate entities. Brief, reversible stroke syndromes (referred to as TIAs) and acute ischemic stroke (resulting in infarcted areas in the brain and various degrees of clinical deficit) are different manifestations of a continuum of ischemic cerebral disease with the same risk factors and pathophysiology. Even among patients with previous stroke, there is a wide spectrum of symptom severity. Higher-risk TIA patients with symptoms of longer duration, worse severity, or associated morphological changes on brain imaging require emergent work-up and preventive treatment for subsequent stroke.[17]

Major differences exist in the reliability of diagnosis for TIA compared with stroke, especially outside the neurology setting and when TIA occurred far in the past. In the GARFIELD-AF registry, it is notable that overall only 1.7% of all patients and 10.6% of patients with history of TIA or stroke were enrolled by a neurologist. It is likely that a substantial number of TIAs may have been suspected, but a diagnosis was not confirmed methodically. Some physicians

may also misdiagnose TIA. Overall, the impact of prior stroke versus history of TIA on future adverse outcomes in AF patients remains poorly defined.

Clinical Implications

In unselected newly diagnosed AF patients history of previous stroke or TIA is strongly associated with elevated risk of subsequent stroke events and death over the first 1 year. However, this strong association is observable only in patients with history of stroke or stroke and TIA and not those with history of TIA. History of TIA carries no significantly higher risk for subsequent events compared with patients without history of stroke/TIA.

Limitations

Although this analysis was based on a large cohort 52,014 patients of whom 66% were anticoagulated, with 1-year follow-up, it is recognized that the reliability of diagnosing prior TIA may be low. Both the diagnosis of TIA and the risk profile in patients with history of TIA could not be accurately determined in the absence of external validation such as brain imaging. However, limitation also represents a strength of the study, because it demonstrates the prognostic value of a diagnosis of TIA and stroke in the real-world.

Interpretation

In patients with AF, history of stroke or TIA was associated with higher risk of stroke/SE and death than in patients without history of stroke/TIA, despite similar rates of anticoagulation across groups. Patients with history of stroke or TIA were older and had higher CHA_2DS_2-VASc score as well as higher GARFIELD-AF risk score. This excess risk was mainly attributable to history of stroke or stroke and TIA. The weak predictive power of history of TIA may be due to low reliability of diagnosing TIA retrospectively. Our findings suggest

that history of TIA without stroke should be considered with caution for assessment of future risk in patients with newly diagnosed AF.

Author Contributions

W.H., J.P.B., A.J.C., D.A.F., K.A.A.F., S.Z.G., S.G., S.H., G.K., L.G.M., A.G.G.T., F.W.A.V., and A.K.K. contributed to the study design. A.J.C., D.A.F., and S.Z.G. contributed to data acquisition. S.V. and K.S.P. analyzed the data. All authors contributed to data interpretation. W.H. and J.P.B. drafted the manuscript. All authors critically reviewed and approved the final manuscript. R.H., S.D., and A.K. provided editorial support.

References

1.   Allender S, Scarborough P, Peto V, et al. European cardiovascular disease statistics, 2008 edition. Brussels: European Heart Network, 2008.

2.   Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162.

3.   Group SRiAFW. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology*. 2007;69:546–554.

4.   Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.

5.   Lip GY, Nieuwlaat R, Pisters R, et al. 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.

6.   Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089.

7.   Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke*. 2010;41:1367–1370.

8.   Ferro JM, Falcao I, Rodrigues G, et al. Diagnosis of transient ischemic attack by the nonneurologist. A validation study. *Stroke*. 1996;27:2225–2229.

9.   Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J*. 2012;163:13–19.

10.   Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One*. 2013;8:e63479.

11.   Fox KAA, Lucas JE, Pieper KS, et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open*. 2017;7:e017157.

12.   Fox KAA, Gersh BJ, Traore S, et al. Evolving quality standards for large-scale registries: the GARFIELD-AF experience. *Eur Heart J Qual Care Clin Outcomes*. 2017;3:114–122.

13.   Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.

14.   Bakoyannis G, Touloumi G. Practical methods for competing risks data: a review. *Stat Methods Med Res*. 2012;21:257–272.

15.   Huebner M, Wolkewitz M, Enriquez-Sarano M, et al. Competing risks need to be considered in survival analysis models for cardiovascular outcomes. *J Thorac Cardiovasc Surg*. 2017;153:1427–1431.

16.   Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.

17.   Amarenco P, Lavallee PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374:1533–1542.

Table 1. Baseline Characteristics of Patients According to their History of Stroke or TIA

Baseline Characteristic	No stroke/TIA (N = 46,053)	Stroke/TIA (N = 5617)	TIA (N = 1788)	Stroke (N = 3362)	Stroke + TIA (N = 467)
Sex male, n (%)	25,830 (56.1)	3025 (53.9)	912 (51.0)	1865 (55.5)	248 (53.1)
Age, median (IQR), years	70.0 (62.0; 78.0)	74.0 (67.0; 81.0)	74.5 (67.0; 81.0)	74.0 (67.0; 80.0)	76.0 (67.0; 82.0)
Age group, n (%)					
<65 years	14,522 (31.5)	1081 (19.2)	336 (18.8)	666 (19.8)	79 (16.9)
65-74 years	15,075 (32.7)	1772 (31.6)	558 (31.2)	1075 (32.0)	139 (29.8)
≥75 years	16,456 (35.7)	2764 (49.2)	894 (50.0)	1621 (48.2)	249 (53.3)
Ethnicity, n (%)					
Caucasian	28,276 (62.9)	3542 (64.8)	1351 (78.0)	1871 (57.0)	320 (71.1)
Hispanic/Latino	2998 (6.7)	390 (7.1)	130 (7.5)	226 (6.9)	34 (7.6)
Asian (not Chinese)	10,440 (23.2)	1043 (19.1)	129 (7.5)	864 (26.3)	50 (11.1)
Chinese	2308 (5.1)	363 (6.6)	75 (4.3)	256 (7.8)	32 (7.1)
Afro-Caribbean/Mixed/Other	939 (2.1)	126 (2.3)	46 (2.7)	66 (2.0)	14 (3.1)

Body mass index, median (IQR), kg/m²	27.0 (24.0; 31.0)	26.0 (24.0; 30.0)	27.0 (24.0; 31.0)	26.0 (23.0; 29.0)	27.0 (24.0; 31.0)
Pulse, median (IQR), bpm	84.0 (71.0; 106.0)	80.0 (70.0; 100.0)	82.0 (70.0; 100.0)	80.0 (69.0; 98.0)	80.0 (70.0; 106.5)
SBP, median (IQR), mm Hg	130.0 (120.0; 145.0)	133.0 (120.0; 146.0)	135.0 (120.0; 146.5)	133.0 (120.0; 146.0)	133.0 (120.0; 145.0)
DBP, median (IQR), mm Hg	80.0 (70.0; 89.0)	80.0 (70.0; 87.0)	80.0 (70.0; 86.0)	80.0 (70.0; 88.0)	80.0 (70.0; 86.0)
Type of AF, n (%)					
Permanent	5780 (12.6)	825 (14.7)	298 (16.7)	444 (13.2)	83 (17.8)
Persistent	6953 (15.1)	787 (14.0)	231 (12.9)	495 (14.7)	61 (13.1)
Paroxysmal	12,610 (27.4)	1646 (29.3)	463 (25.9)	1054 (31.4)	129 (27.6)
New onset (unclassified)	20,710 (45.0)	2359 (42.0)	796 (44.5)	1369 (40.7)	194 (41.5)
Medical history, n (%)					
Heart failure	10,458 (22.7)	1209 (21.5)	381 (21.3)	721 (21.5)	107 (22.9)
Coronary artery disease	9745 (21.2)	1392 (24.8)	443 (24.8)	810 (24.1)	139 (29.8)
Acute coronary syndromes	4155 (9.1)	697 (12.5)	238 (13.4)	384 (11.5)	75 (16.1)

Carotid occlusive disease	948 (2.1)	582 (10.5)	183 (10.4)	315 (9.5)	84 (18.6)
Vascular disease	6470 (14.1)	1121 (20.0)	360 (20.2)	631 (18.8)	130 (27.8)
Dementia	536 (1.2)	221 (4.0)	43 (2.4)	137 (4.1)	41 (8.8)
Venous thromboembolism	1173 (2.6)	176 (3.2)	70 (3.9)	80 (2.4)	26 (5.6)
History of systemic embolism	162 (0.4)	171 (3.1)	47 (2.6)	102 (3.1)	22 (4.8)
History of bleeding	996 (2.2)	308 (5.5)	74 (4.2)	193 (5.8)	41 (8.9)
Moderate to severe renal disease	4529 (11.1)	820 (16.6)	249 (15.7)	480 (16.3)	91 (22.2)
Hypertension	34,895 (76.0)	4451 (79.3)	1393 (78.0)	2668 (79.5)	390 (83.5)
Hypercholesterolemia	17,990 (40.3)	2832 (51.4)	964 (54.9)	1583 (48.0)	285 (62.2)
Diabetes mellitus	10,035 (21.8)	1406 (25.0)	419 (23.4)	841 (25.0)	146 (31.3)
Smoking status, n (%)					
Previous smoker	9842 (23.4)	1313 (25.6)	439 (26.7)	751 (24.5)	123 (28.9)
Current smoker	4722 (11.2)	446 (8.7)	142 (8.7)	279 (9.1)	25 (5.9)
Alcohol consumption, n (%)					
Light	12,913 (33.1)	1413 (29.5)	515 (34.0)	768 (26.7)	130 (32.7)

Moderate	3807 (9.8)	362 (7.6)	108 (7.1)	228 (7.9)	26 (6.5)
Heavy	926 (2.4)	98 (2.1)	26 (1..7)	65 (2.3)	7 (1.8)
CHA$_2$DS$_2$-VASc score, median (IQR)	3.0 (2.0; 4.0)	5.0 (4.0; 6.0)	5.0 (4.0; 6.0)	5.0 (4.0; 6.0)	6.0 (5.0; 6.0)
HAS-BLED score, median (IQR)*	1.0 (1.0; 2.0)	2.0 (2.0; 3.0)	2.0 (1.0; 2.0)	3.0 (2.0; 3.0)	3.0 (2.0; 3.0)
GARFIELD-AF score, median (IQR)					
Death	2.3 (1.2; 4.3)	3.7 (2.0; 6.6)	3.0 (1.7; 5.3)	4.0 (2.1; 7.1)	4.5 (2..4; 8.6)
Ischemic stroke/SE	0.9 (0.7; 1.3)	2.1 (1.3; 3.3)	1.0 (0.7; 1.5)	2.5 (1.9; 3.9)	2.7 (2.0; 4.4)
Major bleeding	0.9 (0.6; 1.3)	1.1 (0.8; 1.6)	1.1 (0.8; 1.6)	1.1 (0.8; 1.6)	1.3 (0.9; 1.9)
Specialty at diagnosis of AF, n (%)					
Cardiology	30,736 (66.7)	3198 (56.9)	992 (55.5)	1952 (58.1)	254 (54.4)
Geriatrics	138 (0.3)	62 (1.1)	20 (1.1)	33 (1.0)	9 (1.9)
Internal medicine	8164 (17.7)	1126 (20.1)	402 (22.5)	619 (18.4)	105 (22.5)
Neurology	271 (0.6)	597 (10.6)	115 (6.4)	450 (13.4)	32 (6.9)
Primary care/General practice	6744 (14.6)	634 (11.3)	259 (14.5)	308 (9.2)	67 (14.4)

Care setting at diagnosis of AF, n (%)					
Anticoagulation clinic	289 (0.6)	52 (0.9)	21 (1.2)	26 (0.8)	5 (1.1)
Emergency room	5091 (11.1)	578 (10.3)	218 (12.2)	315 (9.4)	45 (9.6)
Hospital	26,607 (57.8)	3534 (62.9)	994 (55.6)	2258 (67.2)	282 (60.4)
Office	14,066 (30.5)	1453 (25.9)	555 (31.0)	763 (22.7)	135 (28.9)

The risk factor "Labile INRs" not included in HAS-BLED score because not collected at baseline. Therefore maximum HAS-BLED score at baseline is 8 points (not 9). IQR: interquartile range; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Antithrombotic Initiated at Enrollment According to Patients' History of Stroke or TIA

	No Stroke/TIA (N = 46,053)	Stroke/TIA (N = 5617)	TIA (N = 1788)	Stroke (N = 3362)	Stroke + TIA (N = 467)
NOAC ± AP	12,490 (27.5)	1535 (27.8)	503 (28.7)	904 (27.3)	128 (28.0)
VKA ± AP	17,592 (38.7)	2503 (45.3)	815 (46.5)	1470 (44.4)	218 (47.6)
AP only	9539 (21.0)	1136 (20.6)	334 (19.1)	704 (21.3)	98 (21.4)
None	5811 (12.8)	346 (6.3)	100 (5.7)	232 (7.0)	14 (3.1)

VKA, Vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant; AP: antiplatelet.

Table 3. Hazard Ratios (HRs) for All-cause Mortality and Sub-hazard Ratios (SHRs) for Cause-specific Mortality, Stroke/SE, and Major Bleeding in Patients Stratified by History of Stroke or TIA

Outcome	History of Stroke/TIA	Events	Rate (95% CI)	Unadjusted HR/SHR[a] (95% CI)	Adjusted HR/SHR[a,b] (95% CI)
All-cause mortality	No	1791	4.1 (3.9-4.3)		
	Yes	330	6.2 (5.6-7.0)	1.53 (1.36-1.72)	1.26 (1.12-1.42)
CV mortality	No	671	1.5 (1.4-1.7)		
	Yes	124	2.3 (2.0-2.8)	1.52 (1.26-1.84)	1.22 (1.01-1.48)
Non-CV mortality	No	653	1.5 (1.4-1.6)		
	Yes	132	2.5 (2.1-3.0)	1.66 (1.38-2.00)	1.39 (1.15-1.68)
Stroke/SE	No	503	1.2 (1.1-1.3)		
	Yes	147	2.8 (2.4-3.3)	2.42 (2.01-2.90)	2.17 (1.80-2.63)
Major bleeding	No	354	0.8 (0.7-0.9)		
	Yes	55	1.0 (0.8-1.4)	1.28 (0.96-1.69)	1.04 (0.78-1.38)

[a]Reference group is patients with no history of stroke or TIA. [b]HRs and SHRs were adjusted for sex, age, ethnicity, type of AF, anticoagulant treatment, diabetes, hypertension, history of bleeding, congestive heart failure, vascular disease, moderate-to-severe renal disease, smoking status, and heavy alcohol consumption. CI, confidence interval; SE, systemic embolism.

eTable S1. Adjusted* Hazard Ratios (HRs) for All-cause Mortality and Sub-hazard Ratios (SHRs) for Cause-specific Mortality, Stroke/SE, and Major Bleeding over 1 Year in Patients Stratified by History of Stroke, TIA, and Stroke and TIA

Outcome	Parameter	Events	Rate (95% CI)	Unadjusted HR/SHR[a] (95% CI)	Adjusted HR/SHR[a,b] (95% CI)
All-cause mortality	No history of stroke or TIA	1791	4.1 (3.9–4.3)		
	History of TIA only	90	5.3 (4.3–6.5)	1.24 (1.00–1.53)	0.99 (0.80–1.22)
	History of stroke only	195	6.2 (5.4–7.1)	1.47 (1.27–1.70)	1.29 (1.11–1.50)
	History of stroke and TIA	45	10.5 (7.8–14.0)	2.44 (1.82–3.28)	1.77 (1.32–2.39)
CV mortality	No history of stroke or TIA	671	1.5 (1.4–1.7)		
	History of TIA only	36	2.1 (1.5–2.9)	1.32 (0.95–1.85)	1.04 (0.74–1.46)
	History of stroke only	69	2.2 (1.7–2.8)	1.37 (1.07–1.76)	1.19 (0..92–1.52)
	History of stroke and TIA	19	4.4 (2.8–6.9)	2.70 (1.71–4.26)	1.74 (1.08–2.79)
Non-CV mortality	No history of stroke or TIA	653	1.5 (1.4–1.6)		
	History of TIA only	34	2.0 (1.4–2.8)	1.26 (0.89–1.78)	1.02 (0.72–1.44)
	History of stroke only	78	2.5 (2.0–3.1)	1.59 (1.26–2.01)	1.39 (1.10–1.77)
	History of stroke and TIA	20	4.7 (3.0–7.2)	2.89 (1.86–4.52)	2.21 (1.41–3.48)

Stroke/SE	No history of stroke or TIA	503	1.2 (1.1–1.3)		
	History of TIA only	33	2.0 (1.4–2.8)	1.49 (1.05–2.12)	1.35 (0.95–1.92)
	History of stroke only	96	3.1 (2.5–3.8)	2.52 (2.03–3.13)	2.29 (1.83–2.86)
	History of stroke and TIA	18	4.2 (2.7–6.7)	3.13 (1.96–5.00)	2.55 (1.60–4.05)
Major bleeding	No history of stroke or TIA	354	0.8 (0.7–0.9)		
	History of TIA only	19	1.1 (0.7–1.8)	1.36 (0.86–2.16)	1.05 (0.66–1.67)
	History of stroke only	32	1.0 (0.7–1.4)	1.22 (0.85–1.75)	1.07 (0.74–1.54)
	History of stroke and TIA	4	0.9 (0.3–2.5)	1.08 (0.40–2.87)	0.78 (0.29–2.09)

[a]Reference group is patients with no history of stroke or TIA. [b]HRs and SHRs were adjusted for sex, age, ethnicity, type of AF, anticoagulant treatment, diabetes, hypertension, history of bleeding, congestive heart failure, vascular disease, moderate-to-severe renal disease, smoking status, and heavy alcohol consumption. CI, confidence interval; SE, systemic embolism.

Figure Legends

Figure 1. Flow chart for selection of study population and categorization of groups.

Figure 2. Adjusted* hazard ratios (HRs) for all-cause mortality and sub-hazard ratios (SHRs) for cause-specific mortality, stroke/SE, and major bleeding in patients stratified by history of stroke, TIA, and stroke and TIA. Reference group is patients with no history of stroke or TIA. *HRs and SHRs were adjusted for sex, age, ethnicity, type of AF, anticoagulant treatment, diabetes, hypertension, history of bleeding, congestive heart failure, vascular disease, moderate-to-severe renal disease, smoking status, and heavy alcohol consumption.