Secondary versus primary stroke prevention in atrial fibrillation

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Secondary versus Primary Stroke Prevention in Atrial Fibrillation: Insights From the Darlington Atrial Fibrillation Registry

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Background and Purpose

Although atrial fibrillation (AF) patients who suffered an acute stroke are at high risk for recurrence, many patients are untreated or treated suboptimally for stroke prevention.

To compare clinical outcomes of AF patients with *versus* without previous stroke in relation to guideline-adherent antithrombotic treatment (ATT) in a contemporary primary care population.

Methods

Community cohort of 105,000 patients from 11 general practices in Darlington, England was used to assess AF stroke prevention strategies against 2014 National Institute for Health and Care Excellence (NICE) guidelines.

Results

Overall, 2259 (2.15%) AF patients were identified, of which 18.9% constituted a secondary prevention cohort. For secondary prevention, ATT was guideline-adherent in 56.3%, 18.9% were over-treated and 24.8% under-treated; corresponding proportions for primary prevention were 49.5%, 11.7% and 38.8%, respectively.

One-year stroke rates were 8.6% and 1.6% for secondary and primary prevention, respectively ($p<0.001$); corresponding all-cause mortality rates were 9.8% and 9.4%, respectively ($p=0.79$).

On multivariable analysis, lack of ATT guideline adherence was associated with increased stroke risk for primary prevention (OR 2.95, 95% CI 1.26-6.90, $p=0.013$ for under-treatment); for secondary prevention, lack of guideline adherence was associated with

increased risk of recurrent stroke (OR 2.80, 95% CI 1.25-6.27, p=0.012 for over-treatment) and all-cause death (OR 2.75, 95% CI 1.33-5.69, p=0.006 for under-treatment).

Conclusions

Only approximately half of eligible AF patients are prescribed OAC in line with guidelines. Guideline-adherent ATT significantly reduces the risk of stroke amongst primary prevention patients, and both risk of recurrent stroke and death in patients with previous stroke.

One third of ischemic strokes and over 80% of cardioembolic strokes are related to atrial fibrillation (AF).[1] AF may also play a role in approximately a third of cryptogenic strokes, which account for 25% of all strokes.[2] AF-related strokes result in a larger area of brain infarction and greater disability and mortality compared to strokes of other etiologies.[3] However, AF remains frequently under-recognized in patients who suffer an acute stroke and it is often left untreated in those with recent AF-related stroke, despite high risk for stroke recurrence.[1]

AF-related strokes are highly preventable. A meta-analysis showed that oral anticoagulation (OAC) with vitamin K antagonists (VKAs), such as warfarin, reduces the risk of stroke in AF patients by 64% and mortality by 26%, compared to placebo, whereas aspirin did not significantly decrease stroke risk and had no impact on mortality.[4] Another meta-analysis demonstrated that non-VKA OACs (NOACs) may offer additional stroke and mortality risk reduction by 19% and 10% respectively, relative to warfarin.[5] Consequently, in line with current AF guidelines, OAC should be offered to all AF patients as a default practice unless a "truly low-risk" category is evident, i.e. those with a CHA_2DS_2-VASc score=0 for men or CHA_2DS_2-VASc=1 for women.[6]

Despite these recommendations, contemporary registry data show that more than half of AF patients with no stroke risk factors are anticoagulated, while at least a third of those at high risk of stroke do not receive OAC where indicated, but instead are prescribed antiplatelet monotherapy or remain untreated.[7] Importantly, lack of guideline adherence in antithrombotic treatment for stroke prevention in AF has been shown to increase stroke/thromboembolic and mortality rates compared to recommended therapy.[8–11]

In contrast to previous data on guideline-adherence for stroke prevention in AF predominantly implemented by cardiologists,[7–10] we present findings from 11 general practices in the United Kingdom (UK) serving the community cohort of 105,000 patients, of whom 2.15% (n=2259) had established AF diagnosis. Our objective was to assess clinical outcomes of community-based AF patients with *versus* without previous stroke in relation to guideline-adherent antithrombotic treatment for stroke prevention.

Materials and Methods

Study Population

The design of the Darlington AF Registry has been described previously.[12] In brief, the study population comprised of 105,000 patients living in Darlington, County Durham, UK, registered at one of 11 general practices. All patients with the diagnosis of AF or atrial flutter and known vital status in March 2013 were eligible for inclusion.

Data Collection

Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) tool was used to collect data.[12,13] All general practices in Darlington were equipped with this electronic record interrogation software that allowed for data collection on demographics, details of AF diagnosis, patient stroke risk profile and antithrombotic treatment, and was primarily developed to facilitate decision making on stroke prevention therapies.

As the GRASP-AF tool does not collect data on clinical outcomes, separate searches of the database were performed to identify those patients who suffered acute stroke or died within 12 months. The Read Codes were used to identify different types of strokes, comorbidities,

current therapies and contraindications to treatment. All clinical events were manually reviewed and adjudicated.[12]

Definitions

Thromboembolic risk was assessed using the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category [female]).[14]

"Low-risk" patients were men with CHA_2DS_2-VASc=0 and women with CHA_2DS_2-VASc=1 (1 point for sex category only); "moderate-risk" were men with CHA_2DS_2-VASc=1; and "high-risk" were those with CHA_2DS_2-VASc score ≥2, irrespective of gender.

Antithrombotic treatment for stroke prevention was assessed against 2014 National Institute for Health and Care Excellence (NICE) guidelines.[6] Antithrombotic treatment was considered guideline-adherent when the following criteria were applicable:

- OAC in moderate to high-risk patients with no reported contraindications to OAC therapy
- no OAC in low-risk patients and those who refused treatment with OAC
- OAC + antiplatelet therapy in moderate to high-risk patients and acute vascular disease (i.e. recent acute myocardial infarction)

Lack of guideline adherence in antithrombotic treatment was considered as either over-treatment (OAC overuse) or under-treatment (OAC underuse). Specifically, under-treatment was defined as no OAC (but antiplatelet or no therapy) in moderate or high-risk patients and no reported contraindications or refusal to treatment. Over-treatment was defined as follows: OAC in low-risk patients or OAC + antiplatelet therapy in moderate to high-risk patients with no evidence of acute vascular disease (i.e. recent acute myocardial infarction); OAC in

patients with reported contraindications to anticoagulation; or antiplatelet agents in those who had reported contraindications to both OAC and antiplatelet therapy.

Of note, the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines differ with NICE recommendations on stroke risk requiring anticoagulation, i.e. OAC is recommended in patients with CHA_2DS_2-VASc score ≥2, while those with score 1 may be offered OAC, aspirin or even no stroke prophylaxis.[15]

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous parameters as mean and standard deviation (SD). Baseline characteristics, antithrombotic therapies and clinical outcomes were tabulated in relation to prior stroke history. Multivariable logistic regression analyses were performed to determine independent predictors for new/recurrent stroke and all-cause death after adjustment for the components of the CHA_2DS_2-VASc score (age assessed as a continuous variable) and guideline-adherent or non-adherent (over-treatment or under-treatment), antithrombotic treatment and AF duration. The multivariable analysis was performed separately for patients with prior stroke history (secondary prevention group) and those without previous stroke (primary prevention group). All statistical analyses were performed using IBM SPSS Statistics (version 21) software (Chicago, Illinois, USA). Statistical significance was set at a two-sided p-value of <0.05.

Results

Overall, 2259 (2.15%) AF patients were identified, of which 428 (18.9%) constituted a secondary prevention cohort. Patients with previous stroke were older, more often had comorbidities and were at higher risk of stroke (all patients had CHA_2DS_2-VASc score ≥2, mean score of 5.5, standard deviation [SD] of 1.28) as compared with those without prior stroke (CHA_2DS_2-VASc score ≥2 in 82.3%, mean score of 3.0, SD of 1.54) (Table 1).

Overall, <50% of patients were prescribed anticoagulation (46.4% VKAs and 1.4% NOACs), while 35.9% received antiplatelet therapy alone and 16.2% remained untreated (Table 1). Antithrombotic drug choice in relation to prior stroke history is summarized in Figure 1. Guideline-adherent antithrombotic treatment for stroke prevention was applied more frequently in the secondary *versus* primary prevention cohort (56.3% vs 49.5%, p=0.011). Over-treatment was more common in patients with prior stroke, whereas under-treatment was more frequent in subjects with no stroke history (Table 1, Figure 2).

Based on the Read Codes, general practitioners (GPs) reported contraindications to OAC therapy more frequently in patients with previous stroke (13.8%) compared to subjects without prior stroke (7.0%) (Table I, please see http://stroke.ahajournals.org).

One-Year Outcomes

After 12 months of follow-up the observed stroke rates were 8.6% (n=37) and 1.6% (n=30) for the secondary and primary prevention cohort, respectively (p<0.001). No difference was observed in the incidence of hemorrhagic strokes (0.2% in both groups) (Table 2). All-cause death rates were comparable in patients with prior stroke (9.8%, n=42) and those without previous stroke (9.4%, n=172). The causes of death were also similar in both groups, except

that in the secondary prevention cohort more patients died of non-cerebral bleeding (0.5%, n=2) compared with the primary prevention cohort (0.1%, n=1) (Table 2).

Clinical Outcomes in Relation to Guideline-Adherent Antithrombotic Therapy

In the primary prevention group, the 1-year stroke rates were similar in guideline-adherent (0.8%) and over-treated patients (0.5%), while the under-treated patients had an approximately four-fold higher stroke rate (3.1%). The corresponding event rates for 12-month all-cause mortality were 7.1%, 6.0% and 13.2%, respectively (Table 3).

In the secondary prevention cohort, the lowest rate of stroke recurrence, at 5.4%, was in patients receiving guideline recommended treatment, whereas the event rates for under- and over-treatment were 9.4% and 17.3%, respectively (p=0.011). There was no significant difference in all-cause mortality between guideline-adherent (6.6%) and over-treated patients (6.2%, p=0.88), while the mortality was 3-fold higher in the under-treated subjects (19.8%, p<0.001).

On multivariable logistic regression analysis (Table 4), non-adherence with guideline recommended antithrombotic treatment was associated with an increased risk of stroke in the primary prevention cohort (odds ratio [OR] 2.95, 95% confidence interval [CI] 1.26-6.90, p=0.013 for under-treatment), whereas in the secondary prevention cohort, non-adherence with guideline recommended antithrombotic treatment was associated with an increased risk of recurrent stroke (OR 2.80, 95% CI 1.25-6.27, p=0.012 for over-treatment) and all-cause death (OR 2.75, 95% CI 1.33-5.69, p=0.006 for under-treatment). No association was found between AF duration and outcome events.

As a sensitivity analysis, the impact of OAC therapy *per se* on clinical outcomes after completely excluding patients who denied treatment or had any contraindications is shown in the Supplementary Material (Table II and III, please see http://stroke.ahajournals.org). The results show broadly similar trends as our principal analysis, with an even more pronounced effect of OAC on outcomes.

Discussion

In this paper we provide antithrombotic treatment patterns in an unselected (i.e. consecutive all-comers) contemporary, community-based AF population. The main findings of this study are that despite a high thromboembolic risk, particularly amongst secondary prevention patients, only approximately 50% of AF patients in primary care were prescribed OAC in line with guidelines. Secondly, guideline-adherent antithrombotic treatment reduces the risk of stroke amongst primary prevention patients, and in those with prior stroke, there was a significant reduction in both recurrent stroke and mortality.

Several studies have found that guideline-adherent thromboprophylaxis in AF is associated with fewer stroke and lower mortality rates compared to non-guideline stroke prevention.[8–11] However, these studies assessed adherence to guidelines in patients managed solely by cardiologists[8–10] or internal medicine specialists.[11] Unlike in previous studies we present findings from a community-based AF cohort managed by primary care physicians, however it should be noted that the vast majority of strokes are diagnosed and managed in a hospital setting and specialist input is provided at that stage, unless AF was not present at the time of the event. Our analysis also provides novel data on the clinical implications of non-adherence with recommended antithrombotic treatment for stroke prevention in AF and how this affects

clinical outcomes in patients who have already suffered an acute stroke.

As expected, we observed higher one-year stroke rates in AF patients with *versus* without prior stroke. The magnitude of the stroke rate difference was six-fold higher in secondary *versus* primary prevention patients, thereby reflecting a very high thromboembolic risk among those with a previous stroke. Despite such high risk only about half of the patients with prior strokes were prescribed OAC in line with current NICE guidelines.[6]

More importantly, the lowest stroke recurrence was observed in patients who were guideline-adherent, while it was higher for under-treatment and unexpectedly highest for over-treatment. Although higher stroke rates for over-treatment compared to guideline-adherence may be surprising, the EORP-AF (EURObservational Research Programme Atrial Fibrillation) Pilot Registry also found a similar association between over-treatment and higher one-year incidence of thromboembolic events, defined as any of the following: stroke, TIA, acute coronary syndrome, coronary intervention, cardiac arrest, peripheral embolism or pulmonary embolism.[10] By contrast, other studies have not reported such an association[8,11] or have found a lower risk of thromboembolism for over-treatment.[9]

The possible explanation of "more is not better" is not straightforward and may include various contributing factors. First, in contrast to the present analysis, none of other studies considered the presence of contraindications to ATT or patient's declining therapy when defining adherence *versus* non-adherence to antithrombotic treatment.[8–11] Prior papers base OAC prescribing solely on thromboembolic risk (and thus, this assumes that 100% must be given OAC, no exceptions). Such an approach fails again to reflect real-life everyday clinical practice, by not taking into account an unselected population of consecutive patients as well

as many clinical- and patient-related factors affecting the final decision-making needed for OAC prescribing. In addition, only the present study and the EORP-AF registry corrected the definition of non-adherence for the presence of acute vascular disease.[10]

Second, although Gorin *et al.*[9] found significantly fewer event rates in over-treated patients and suggested that a more aggressive antithrombotic treatment (i.e. combination of OAC and antiplatelet therapy) may be advocated in selected AF patients, the authors used the older $CHADS_2$ score (Congestive Heart Failure, Hypertension, Age≥75, Diabetes, Stroke/TIA) which resulted in classifying some patients as "low-risk" (i.e. with $CHADS_2$=0) and thus over-treated, while in the present analysis many of them would be categorized as "high-risk" and consequently guideline-adherent. In addition, over-treated patients were significantly younger and had lower risk of stroke compared with those under-treated or guideline-adherent.[9] By contrast, in the present analysis over-treated *versus* guideline-adherent patients were at significantly lower risk of stroke in the primary prevention, while an opposite relation with a trend towards a higher thromboembolic risk was noted in the over-treated, secondary prevention cohort.

Third, unlike previous studies, we analyzed the population of AF patients with prior stroke, which are at the highest risk for stroke recurrence; 8.6% after one year of observation despite antithrombotic treatment. Indeed, our analysis did not show over-treatment to be associated with increased stroke rates in patients without prior stroke. Also, some physicians may consider that combination therapy (OAC + antiplatelets) was more effective and superior to OAC monotherapy for stroke prevention in patients with prior stroke. Our data suggest that despite such an "aggressive" antithrombotic treatment, the risk of stroke recurrence remains high. On the other hand, we may speculate that fear of bleeding complications while being

more aggressive with antithrombotic treatment results in suboptimal quality of anticoagulation. Indeed, for AF patients undergoing percutaneous coronary interventions and thus requiring combination OAC and antiplatelet therapy, the average time in therapeutic range (TTR) was only 52.6%, with an International Normalized Ratio (INR) of 1.6 to 2.6.[16] Consequently, instead of a decrease in stroke rates, an increase in both stroke and major bleeding rates were observed when compared to patients who were not receiving combination antithrombotic treatment.

Nonetheless, despite stroke rates being three times higher in the over-treated versus guideline-adherent group, we have observed similar mortality rates in both treatment cohorts. This finding would suggest that even though a more aggressive antithrombotic regimen is not sufficient to protect against stroke recurrence in at very high risk of stroke AF patients, while many of these strokes are not fatal, reduction in all-cause mortality with antithrombotic therapy exceeds the reduction of stroke-related deaths only.[17]

Despite being at very high risk for stroke, some patients may have genuine contraindications to anticoagulation, as many stroke and bleeding risk factors do overlap.[18] In the present analysis, contraindications to OAC were reported in 13.8% and 7.0% of patients with *versus* without previous stroke, respectively. However, contraindications to OAC therapy are frequently not absolute and may be transient, and depend on individually-perceived lack of benefit from OAC prescription.[6] Indeed, a considerable variation in the rates of reported contraindications to OAC (ranging from 2.6% to 12.0%) was observed across 1857 general practices in England.[13] Contemporary registry data also show that approximately 50% of eligible AF patients are not offered OAC or have stroke prevention treatment discontinued due to physician's preference.[19,20] Many physicians have concerns with regard to prescribing

OAC to frail, elderly patients with many comorbidities, cognitive impairment and frequent falls[21] although the available data show that even these patients, including the very elderly (>85 years of age) also benefit from anticoagulation.[22,23]

Bleeding risk assessment scores, such as the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR ratios, age ≥65 years, drugs or alcohol)[6,24] were predominantly designed to 'flag up' patients at increased risk for bleeding to allow for correction of the reversible risk factors (e.g. uncontrolled hypertension, labile INR values, concomitant drugs, alcohol abuse, etc.)[25] but were by no means intended to withhold or preclude OAC therapy.[26] Importantly, the net clinical benefit of systemic anticoagulation, when balancing stroke risk reduction *versus* increased risk of bleeding, is still positive and even greater in patients at increased risk of bleeding.[27] Therefore, once the reasons for interrupting OAC therapy have been corrected, a change from one anticoagulant to another may seem more reasonable than complete withdrawal of OAC therapy, even in patients who have survived major bleeds or those with prior intracranial hemorrhage.[28,29] Similarly, in patients who have experienced an ischemic stroke despite being on OAC, a switch to a more effective anticoagulant to prevent a recurrent thromboembolic event, i.e. dabigatran 150 mg twice daily, could be considered.[30]

Foregoing anticoagulation may also result from patient's refusal to use OAC. However, this shared-decision making has to be based on detailed and clear explanation to a patient of their individual benefits and risks with OAC therapy.[31] One recent study showed that 12% of AF patients would refuse OAC even if it was 100% effective in preventing strokes, while those who accepted anticoagulation were willing to accept 4.4 major bleeds to prevent one stroke.[32]

Limitations and Strengths

A limitation of this study is that the analysis focused on the quantity but not quality of antithrombotic treatment. Despite having very precise data on various antithrombotics used as well as corrections made for antithrombotic drug uptake preceding the outcome events, neither INR nor TTR values were available. In addition, although the contraindications to, and reasons for patients declining, antithrombotic therapy were reported very precisely using Read codes, specific reasons for withholding or precluding OAC could not be identified. We could not establish the cause of death with certainty in 45 patients, as death certificates could not be retrieved. However, it is unlikely that any significant number of strokes were missed that way. It cannot be also excluded that some strokes were missed by being not coded, although this is also unlikely as stroke rates contribute to the stroke prevalence recording, which is linked to therapy reimbursement. Incorrect coding was addressed by a wide search of related conditions.

Although the cohort was a broad patient representation from 11 GP practices serving the population of over 100,000 patients, it was confined to one UK region, and therefore the results may not be representative of other primary care populations in different regions. Unfortunately, data on socio-demographic characteristics were not available for the purpose of this analysis. However, in contrast to previous studies, we used very precise and robust criteria for study endpoints employed in randomized clinical trials, with stroke confirmed by cerebral imaging and every outcome event was manually adjudicated. The usefulness of the GRASP-AF tool employed for diagnostic and data collection purposes has been also previously confirmed.[13]

Our definition of adherence to guidelines is different from previously published papers because we have analyzed the unselected cohort of consecutive all-comers and thus included

also those patients who declined OAC or had reported contraindications to therapy. Indeed, we aimed to assess the impact of guideline-adherence, rather than the specific impact of OAC therapy *per se* on clinical outcomes after completely excluding patients who denied treatment or had any contraindications. The results of the latter approach (broadly similar trends and showing even more pronounced effect of OAC on outcomes) have been summarized *as a sensitivity analysis.*

Summary

Despite a high thromboembolic risk profile, particularly amongst secondary prevention patients, only approximately 50% of AF patients in primary care are prescribed OAC in line with current guidelines. Guideline-adherent antithrombotic therapy significantly reduces the risk of stroke amongst primary prevention patients, but in those with prior stroke, there is also a significant reduction in both recurrent stroke and death rates.

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Figure Legends

Figure 1 Antithrombotic Treatment in Relation to Prior Stroke History

OAC – oral anticoagulation

Figure 2 Antithrombotic Treatment in Relation to Guideline-Adherence and Prior Stroke History

Panel A Prior stroke history

Panel B No prior stroke history

OAC – oral anticoagulation

Table 1 Baseline Characteristics Overall and in the Primary and Secondary Prevention Groups

	All	Previous Stroke	No Previous Stroke	
n (%)	2259 (100)	428 (18.9)	1831 (81.1)	**P-value**
Demographics				
Females	1041 (46.1)	193 (45.1)	848 (46.3)	0.68
Age, years, mean [SD]	75.6 (12.2)	79.6 (9.6)	74.7 (12.6)	
<65 years	367 (16.2)	28 (6.5)	339 (18.5)	
65-74 years	554 (24.5)	93 (21.7)	461 (25.2)	
≥75 years	1338 (59.2)	307 (71.7)	1031 (56.3)	<0.001
Medical history				
Heart failure	514 (22.8)	106 (24.8)	408 (22.3)	0.27
Hypertension	1404 (62.2)	305 (71.3)	1099 (60.0)	0.001
Diabetes	490 (21.7)	120 (28.0)	370 (20.2)	0.001
Vascular disease	389 (17.2)	97 (22.7)	292 (15.9)	0.001
Acute myocardial infarction	152 (6.7)	41 (9.6)	111 (6.1)	0.008
Thromboembolic risk				
CHA_2DS_2-VASc, mean (SD)	3.5 (1.79)	5.5 (1.28)	3.0 (1.54)	
score=0	118 (5.2)	0	118 (6.4)	
score=1	206 (9.1)	0	206 (11.6)	
score≥2	1935 (85.7)	428 (100)	1507 (82.3)	<0.001
Antithrombotic treatment				
None	367 (16.2)	28 (6.5)	339 (18.5)	
Antiplatelets	812 (35.9)	136 (31.8)	676 (36.9)	
OAC	971 (43.0)	225 (52.6)	746 (40.7)	
OAC + antiplatelets	109 (4.8)	39 (9.1)	70 (3.8)	<0.001
Oral anticoagulation				
Contraindicated	187 (8.3)	59 (13.8)	128 (7.0)	<0.001
Declined	113 (5.0)	28 (6.5)	85 (4.6)	0.11
Antithrombotic therapy				
Guideline adherent	1147 (50.8)	241 (56.3)	906 (49.5)	0.011

Over-treatment	296 (13.1)	81 (18.9)	215 (11.7)	<0.001
Under-treatment	816 (36.1)	106 (24.8)	710 (38.8)	<0.001

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); OAC, oral anticoagulant; SD, standard deviation.

Table 2 One-year Outcomes Overall and in the Primary and Secondary Prevention Groups

	All	Previous Stroke	No Previous Stroke	
n (%)	2259 (100.0)	428 (18.9)	1831 (81.1)	**P-value**
Recurrent/new stroke*	67 (3.0)	37 (8.6)	30 (1.6)	<0.001
Ischemic	62 (2.7)	36 (8.4)	26 (1.4)	
Hemorrhagic	5 (0.2)	1 (0.2) [a]	4 (0.2) [a]	
Cause of death				
All-cause	214 (9.5)	42 (9.8) [a]	172 (9.4) [a]	0.79
Cardiovascular				
Cardiac death	14 (0.6)	3 (0.7) [a]	11 (0.6) [a]	
Heart failure	24 (1.1)	3 (0.7) [a]	21 (1.1) [a]	
Stroke	11 (0.5)	3 (0.7) [a]	8 (0.4) [a]	
PE or STE	3 (0.1)	1 (0.2) [a]	2 (0.1) [a]	
Intracranial bleeding	5 (0.2)	1 (0.2) [a]	4 (0.2) [a]	
Non-cardiovascular				
Bleeding non-cerebral	3 (0.1)	2 (0.5)	1 (0.1)	
Cancer	42 (1.9)	4 (0.9) [a]	38 (2.1) [a]	
Other	67 (3.0)	16 (3.7) [a]	51 (2.8) [a]	
Unknown	45 (2.0)	9 (2.1) [a]	36 (2.0) [a]	

Values in the same row not sharing the same subscript are significantly different at $p<0.05$

***** Confirmed by imaging (CT was predominantly used)

ATT, antithrombotic treatment; CT, computer tomography; PE, pulmonary embolism; STE, systemic thromboembolism.

Table 3 Event Rates at One-Year in Relation to Prior Stroke History, Thromboembolic Risk and Antithrombotic Guideline-Adherence

n (%)	**Under-treatment**	**Adherent treatment**	**Over-treatment**	P-value
Prior stroke history	n=106	n=241	n=81	
CHA_2DS_2-VASc, mean (SD)	5.5 (1.40) [a]	5.5 (1.26) [a]	5.9 (1.11) [a]	0.050
Recurrent stroke	10 (9.4) [a, b]	13 (5.4) [a]	14 (17.3) [b]	0.011
All-cause death	21 (19.8)	16 (6.6) [a]	5 (6.2) [a]	0.006
No prior stroke	n=710	n=906	n=215	
CHA_2DS_2-VASc, mean (SD)	3.1 (1.39) [a]	3.2 (1.51) [a]	2.4 (1.95) [b]	<0.001
New stroke	22 (3.1)	7 (0.8) [a]	1 (0.5) [a]	0.003
All-cause death	94 (13.2)	65 (7.1) [a]	13 (6.0) [a]	0.003

Values in the same row not sharing the same subscript are significantly different at $p<0.05$

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); SD, standard deviation.

Table 4 Multivariable Logistic Regression Analysis for New/Recurrent Stroke *and* Death in Relation to Prior Stroke History

	New Stroke		**Death**	
	OR (95% CI)	P value	OR (95% CI)	P value
Prior stroke history				
Age (per 1 y increase)	1.00 (0.97-1.04)	0.83	1.08 (1.04-1.13)	<0.001
Female sex	1.32 (0.63-2.74)	0.46	1.02 (0.49-2.12)	0.96
Hypertension	0.91 (0.43-1.95)	0.81	0.81 (0.38-1.72)	0.81
Diabetes	1.72 (0.83-3.56)	0.14	2.21 (1.08-4.52)	0.03
Heart failure	0.91 (0.39-2.12)	0.83	1.55 (0.73-3.30)	0.26
Vascular disease	0.89 (0.38-2.10)	0.80	1.52 (0.70-3.28)	0.29
ATT under-treatment	1.39 (0.58-3.30)	0.46	2.75 (1.33-5.69)	0.006
ATT over-treatment	2.80 (1.25-6.27)	0.01	0.66 (0.23-1.89)	0.44
No prior stroke				
Age (per 1 y increase)	1.07 (1.03-1.12)	0.002	1.11 (1.09-1.14)	<0.001
Female sex	2.29 (0.96-5.50)	0.06	1.32 (0.91-1.91)	0.15
Hypertension	0.79 (0.36-1.73)	0.56	0.97 (0.67-1.41)	0.88
Diabetes	2.11 (0.94-4.73)	0.07	1.31 (0.88-1.97)	0.19
Heart failure	1.38 (0.60-3.15)	0.44	2.11 (1.46-3.05)	<0.001
Vascular disease	2.12 (0.94-4.78)	0.07	3.28 (2.25-4.78)	<0.001
ATT under-treatment	2.95 (1.26-6.90)	0.01	1.36 (0.94-1.97)	0.10
ATT over-treatment	0.56 (0.07-4.57)	0.58	0.83 (0.43-1.61)	0.58

ATT, antithrombotic treatment; CI, confidence interval; OR, odds ratio; y, year